Respiratory Medicine
Series Editor: Sharon I.S. Rounds

Nicola A. Hanania
Amir Sharafkhaneh *Editors*

COPD

A Guide to Diagnosis and Clinical Management

Humana Press

Respiratory Medicine

Series Editor:
Sharon I.S. Rounds

For futher volumes:
http://www.springer.com/series/7665

Nicola A. Hanania • Amir Sharafkhaneh
Editors

COPD

A Guide to Diagnosis and Clinical Management

Humana Press

Editors
Nicola A. Hanania
Baylor College of Medicine
Section of Pulmonary and Critical Care Medicine
1504 Taub Loop
Houston, TX 77030, USA
hanania@bcm.tmc.edu

Amir Sharafkhaneh
Baylor College of Medicine
Michael E. DeBakey VA Medical Center
2002 Holcombe Blvd.
Houston, TX 77030, USA
amirs@bcm.tmc.edu

ISBN 978-1-58829-949-9 e-ISBN 978-1-59745-357-8
DOI 10.1007/978-1-59745-357-8
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2010935948

Printed on acid-free paper

Humana Press is part of Springer Science+Business Media (www.springer.com)

We dedicate this work to all our COPD patients who continue to teach us every day and to our primary care colleagues who are in the forefront of managing these patients.

Preface

Chronic obstructive pulmonary disease (COPD) affects millions of people across the world. Cigarette smoking and/or exposure to other noxious stimuli results in inflammation and damage to the airways and lung parenchyma, resulting in expiratory flow limitation. COPD is not only a major burden to our patients but is also costly and results in billions of dollars of direct and indirect costs annually. In recent years and with advancement of science, our understanding of COPD improved significantly. Current management guidelines consider COPD as a "…preventable and treatable…" condition. Recent studies clearly indicate that available pharmacological and non-pharmacological interventions may improve various clinical outcomes in patients with COPD.

This book was written to help clinicians who take care of patients with COPD including primary care providers and specialists. Primary care providers are in the forefront of delivering care to patients and play a vital role in managing various chronic diseases including COPD. A clear example of the role of primary care providers in improving patient care is the fight against atherosclerotic cardiac diseases. Every primary care provider is well aware of the long-term effects of hypertension and hypercholesterolemia. Even though both diseases are asymptomatic in overwhelming majority of the cases, primary care providers routinely check both blood pressure and cholesterol levels and treat their patients according to evidence-based guidelines in the hope to prevent cardiovascular morbidity and mortality. Indisputably, this approach resulted in decline in cardiovascular-related mortality. Unfortunately this is not the case with COPD, which remains undiagnosed and therefore untreated in more than 50% of the patients, and where mortality rose in last few decades. We hope that this book will help improve knowledge of the healthcare community caring for COPD patients and may improve its diagnosis and appropriate management.

With this goal in mind, a group of experts in this field took the task of developing this publication focusing on essential issues that all providers should be aware of. The first four chapters of the book cover major points about the systemic nature of COPD, the clinical and physiological assessments, and the outcome measures and prognostic markers. In the following section, various pharmacologic and non-pharmacological management strategies are reviewed based on available evidence. The final sections outline the non-pulmonary effects of COPD and their management. The authors of the book hope that it will provide an easy to read guide and thus improve management and care of patients with COPD.

We would like to thank all the contributors for their selfless effort in authoring a publication comprehensive and yet targeted to a very important audience. We also would like to thank Mr. Richard Lansing and Ms. Amanda Quinn from Springer for their assistance in the publication of this work. Last but not least, we would like to thank our wives and families for their support, patience, and understanding.

Houston, USA — Nicola M. Hanania, MD, MS
Houston, USA — Amir Sharafkhaneh, MD, PhD

Contents

Contributors

Sandra G. Adams, M.D.
Department of Medicine, Division of Pulmonary Diseases/Critical Care Medicine, University of Texas, Health Science Center at San Antonio and The South Texas Veterans Health Care System, San Antonio TX, USA

Paul Albert, M.D.
Division of Infection and Immunity,
The University Hospital Aintree, Liverpool, UK

Antonio Anzueto, M.D.
Department of Medicine, Division of Pulmonary Diseases/Critical Care Medicine, University of Texas, Health Science Center at San Antonio and The South Texas Veterans Health Care System, San Antonio TX, USA

Bianca Beghe, M.D., Ph.D.
Department of Cardiologic, Thoracic and Vascular Sciences,
University of Padova, Padova, Italy

Soo Borson, M.D.
University of Washington School of Medicine,
Seattle WA, USA

Jean Bourbeau, M.D.
Respiratory Epidemiology and Clinical Research Unit,
Montreal Chest Institute of the Royal Victoria, Hospital,
McGill University Health Centre, Montreal, Canada

Peter M.A. Calverley, M.D.
Division of Infection and Immunity,
The University Hospital Aintree, Liverpool, UK

Mario Cazzola, M.D.
Unit of Respiratory Diseases, Department of Internal Medicine,
University of Rome, Rome, Italy

Bartolome R. Celli, M.D.
Brigham and Women's Hospital, Harvard University,
Boston MA, USA

Kevin M. Chan, M.D.
Department of Internal Medicine, Division of Pulmonary
and Critical Care Medicine, University of Michigan, Ann Arbor MI, USA

Andrew C. Chang, M.D.
Department of Surgery, Section of Thoracic Surgery,
University of Michigan Health System, Ann Arbor MI, USA

Claudio F. Donner, M.D.
Mondo Medico di I.F.I.M. s.r.l., Multidisciplinary
and Rehabilitation Outpatient Clinic, Borgomanero, Italy

Leonardo M. Fabbri, M.D.
Department of Respiratory Diseases,
University of Modena and Reggio Emilia, Modena, Italy

Kalpalatha Guntupalli, M.D.
Section of Pulmonary and Critical Care Medicine,
Baylor College of Medicine, Houston TX, USA

Nicola A. Hanania, M.D., M.S.
Section of Pulmonary and Critical Care Medicine,
Baylor College of Medicine, Houston TX, USA

Max Hirshkowitz, Ph.D.
Michael E. DeBakey Veterans Administration Medical Center,
Baylor College of Medicine, Houston TX, USA

Mohammed Jamshidi, D.O, F.A.C.S., F.A.S.A.
Cardiovascular Institute, TriCity Medical Center,
Oceanside CA, USA

Charlie K. Lan, DO
Michael E. DeBakey VAMC,
Baylor College of Medicine, Houston TX, USA

Pierantonio Laveneziana, M.D.
Respiratory Investigation Unit, Department of Medicine,
Queen's University and Kingston General Hospital, Kingston, Canada

Fabrizio Luppi, M.D.
Department of Respiratory Diseases,
University of Modena and Reggio Emilia, Modena, Italy

Barry J. Make, M.D.
Division of Pulmonary Sciences and Critical, National Jewish
Medical and Research Center, University of Colorado School of Medicine,
Denver CO, USA

Fernando J. Martinez, M.D., M.S.
Department of Internal Medicine, Division of Pulmonary
and Critical Care Medicine, University of Michigan Ann Arbor MI, USA

Linda Nici, M.D.
Providence VAMC, Brown University, Providence RI, USA

Denis E. O'Donnell, M.D.
Respiratory Investigation Unit, Department of Medicine,
Queen's University and Kingston General Hospital, Kingston, Canada

Klaus F. Rabe, M.D.
Department of Pulmonology, Leiden University Medical Center,
Leiden, The Netherlands

Virginia Reichert, RN, NP
Department of Medicine,
NYU School of Medicine, Great Neck NY, USA

Stephen I. Rennard, M.D.
Department of Internal Medicine, University of Nebraska Medical Center,
Omaha NE, USA

E.P.A. Rutten, M.D.
Department of Respiratory Medicine, University Hospital Maastricht,
Horn, The Netherlands

Amir Sharafkhaneh, M.D.
Michael E. DeBakey Veterans Administration Medical Center,
Baylor College of Medicine, Houston TX, USA

Hossein Sharafkhaneh, M.D., Ph.D.
Michael E. DeBakey Veterans Administration Medical Center,
Baylor College of Medicine, Houston, TX, USA

Arunabh Talwar, M.D.
Department of Medicine, Division of Pulmonary and Critical Care Medicine,
North Shore University Hospital, Manhasset, NY, USA

Justin Travers, M.D.
Respiratory Investigation Unit, Department of Medicine,
Queen's University and Kingston General Hospital, Kingston, Canada

Jørgen Vestbo, M.D., FRCP
Department of Cardiology and Respiratory Medicine, Hvidovre Hospital,
Hvidovre, Denmark

E.F.M. Wouters, M.D., Ph.D.
Department of Respiratory Medicine, University Hospital Maastricht,
Maastricht, The Netherlands

Richard Zu Wallack, M.D.
University of Connecticut, St. Francis Hospital, Hartford, CT, USA

1

The Multiple Components of COPD

Leonardo M. Fabbri, Fabrizio Luppi, Bianca Beghe, and Klaus F. Rabe

Key Points:

- Tobacco smoking affects multiple organ systems resulting in numerous so-called tobacco-related diseases, including various chronic respiratory diseases, mainly chronic obstructive pulmonary disease (COPD).
- Smokers with stable COPD have a chronic inflammation of the entire tracheobronchial tree characterized by an increased number of macrophages and CD8 T lymphocytes in the airway wall and of neutrophils in the airway lumen, leading to a progressive and not fully reversible airflow limitation, as measured by the forced expiratory volume in 1 second (FEV_1).
- The inflammatory mediators involved in COPD have not been clearly defined, but it is now apparent that many lipid mediators, inflammatory peptides, reactive oxygen and nitrogen species, chemokines, cytokines, and growth factors are involved in orchestrating the complex inflammatory process that results in small airway fibrosis and alveolar destruction. Many proteases are also involved in the inflammatory process and are responsible for the destruction of elastin fibers in the lung parenchyma, which is the hallmark of emphysema.
- CD8+ T lymphocytes from the bronchial mucosa of patients with COPD predominantly express the chemokine receptor CXCR3 and produce gamma interferon (IFN-γ), suggesting that these cells elaborate type I cytokines.
- Recent research suggests that inflammation is not confined to the lungs: inflammatory cells and mediators are detectable in the bloodstream and may have systemic effects in different areas of the body. This may account for the observation that patients with COPD also present with systemic symptoms and comorbid conditions.
- Long-term smoke exposure can result in systemic oxidants–antioxidants imbalance and low-grade systemic inflammatory response. Although most of the smoking-induced changes are reversible after quitting, some inflammatory mediators like C-reactive protein (CRP) are still significantly raised in ex-smokers up to 10–20 years after quitting, suggesting ongoing low-grade inflammatory response persisting in former smokers.
- Considering the systemic nature of the inflammatory response to cigarette smoke, there is increasing evidence that lung abnormalities may be responsible for the chronic comorbidities that develop along with COPD, particularly

Supported by: A.R.C.A. (Associazione per la Ricerca e la Cura dell'Asma); Consorzio Ferrara Ricerche, A.S.T.M.P. (Associazione per lo Studio de Tumori e delle Malattie Polmonari).

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_1,

chronic heart failure (CHF), coronary and peripheral vascular diseases, and the metabolic syndrome.
- Comorbidities are highly likely to affect health outcomes in COPD, and COPD patients are more likely to die of cardiovascular complications or cancer than of respiratory failure.

Keywords Bronchitis • chronic diseases • chronic heart failure • emphysema • inflammation • metabolic syndrome • osteoporosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a major and growing cause of morbidity and mortality [1, 2]. COPD is characterized by progressive and not fully reversible airflow limitation, as measured by the forced expiratory volume in 1 second (FEV_1). The airflow limitation is associated with a chronic inflammatory process in the airways and lung parenchyma in response to noxious particles or gases, in particular, tobacco smoking [1, 2].

The chronic inflammatory process in COPD is characterized by infiltration of the airways by neutrophils, macrophages, and CD8+ T cells [3, 4]. Such features of inflammation in COPD are likely driven by various cellular pathways, including pro-inflammatory cytokines and mediators of oxidative stress released locally or systemically [5, 6]. More than airway inflammation, a systemic inflammation has also been observed in COPD, with the detection of increased levels of cytokines and inflammatory mediators, particularly from the endothelium, that can cause lung and airways injury [5, 7–9].

The presence of systemic inflammation in COPD has been linked to a variety of complications, including weight loss [7, 10], cachexia [11], osteoporosis [12, 13], and cardiovascular diseases [14, 15]. Moreover, elevation of acute-phase proteins in COPD patients suggests that individuals with increased systemic inflammatory markers, such as fibrinogen or C-reactive protein (CRP), experience an accelerated decline in lung function and are at increased risk of hospitalization for COPD [16, 17].

The aim of the present chapter is to discuss the pathophysiology of COPD, its multiple components, risk factors, systemic consequences, and comorbidities based on current knowledge.

Structural Changes

In COPD, the structural changes occurring in both the large and small airways and in the lung parenchyma may be related to the characteristic clinical manifestations and lung function changes of the disease, e.g., symptoms (i.e., chronic cough and sputum production), airflow limitation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale [18].

Inflammation of the submucosal glands and hyperplasia of goblet cells may contribute to symptoms, such as chronic sputum production, although these pathological abnormalities are not present in all patients with chronic sputum and may be present in subjects without symptoms. The various pathological changes in the central airways

Table 1.1 Causes of airflow limitation in chronic obstructive pulmonary disease (COPD) (Adapted from [1]).

Irreversible	• Fibrosis and narrowing of airways • Loss of elastic recoil due to alveolar destruction • Destruction of alveolar support that maintains patency of small airways
Reversible	• Accumulation of inflammatory cells, mucus, and plasma exudate in bronchi • Smooth muscle contraction in peripheral and central airways • Dynamic hyperinflation during exercise

responsible for the symptoms of chronic cough and sputum production may continue to be present throughout the course of the disease. Thus, these pathological changes may be present either on their own or in combination with the changes in the peripheral airways and lung parenchyma described below.

Fixed or poorly reversible expiratory airflow limitation is the hallmark functional abnormality of COPD. Several pathological characteristics may contribute to airflow limitation (Table 1.1). Airway remodeling and emphysema are most likely responsible for the fixed, poorly reversible component of airflow limitation, whereas airway smooth muscle contraction, airway inflammation, and intraluminal accumulation of mucus and plasma exudate may be responsible for the small part of airflow limitation that is still reversible either spontaneously or with treatment.

The early decline in lung function in COPD is correlated with inflammatory changes in the peripheral airways, similar to those that occur in the central airways: exudate of fluid and cells in the airway wall and lumen, goblet and squamous cell metaplasia of the epithelium, oedema of the airway mucosa due to inflammation, and excess mucus in the airways due to goblet cell metaplasia. The most characteristic change in the peripheral airways of patients with COPD is airway narrowing. Inflammation initiated by cigarette smoking and other risk factors leads to repeated cycles of injury and repair of the walls of the peripheral airways. Injury is caused either directly by inhaled toxic particles and gases such as those found in cigarette smoke, or indirectly by the action of inflammatory mediators; this injury then initiates repair processes. Although airway repair is only partly understood, it seems likely that disordered repair processes can lead to tissue remodeling with altered structure and function. Cigarette smoke may impair lung repair mechanisms, thereby further contributing to altered lung structure [19]. Even normal lung repair mechanisms can lead to airway remodeling because tissue repair in the airways, as elsewhere in the body, may involve scar tissue formation. Inflammatory changes such as airway oedema and mucus hypersecretion also contribute to airway narrowing in COPD. So does loss of elastic recoil, but fibrosis of the small airways plays the largest role [18].

The relative contribution of airway remodeling and emphysema to airflow limitation is not known. Indeed, there is still no consensus on whether the fixed airflow limitation in COPD is mainly due to inflammation and scarring in the small airways or predominantly due to loss of support to the airways resulting from loss of alveolar walls due to emphysema. In general, the studies assessing the lung function in relation to airway and pulmonary structure have shown a relatively poor relationship between macroscopic emphysema and the severity of airways obstruction as measured with spirometry. However, the relative contribution of airway narrowing/fibrosis and emphysema to airflow limitation may depend on the severity of COPD. Bronchiolar abnormalities may contribute more significantly to mild–moderate chronic airflow limitation. When

only subjects with less severe COPD are considered, several indices of bronchiolar inflammation correlate with the degree of airflow obstruction. Indeed the most consistent relationship between lung function and airway and pulmonary structure found in subjects with severe COPD is between severe emphysema and severe airflow limitation. The most important factor is emphysema and loss of elastic recoil. Most studies in advanced COPD find that the best reflection of the severity of airflow limitation is the extent of pulmonary emphysema. Thus, although both the destruction of alveolar attachments to the outer wall of the peripheral airways and the loss of lung elastic recoil produced by emphysema have been implicated in the pathogenesis of peripheral airways obstruction, direct measurements of peripheral airways resistance show that the structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD. Thus, when COPD becomes moderate or severe, loss of elastic recoil becomes overwhelmingly important and may mask the effects of bronchiolar disease on chronic airflow limitation [18].

Advanced COPD is also associated with gas exchange abnormalities, i.e., hypoxemia and, later on, hypercapnia. Abnormal gas exchange may be due to several factors, such as alveolar hypoventilation, altered gas transfer, inequalities in ventilation–perfusion (V/Q) ratio, and right–left blood shunting. Several studies have demonstrated a negative relationship between single breath or steady-state carbon monoxide transfer factor (TLCO) and the degree of emphysema [20, 21]. In COPD, regardless of the stage of disease and the presence or absence of emphysema, V/Q inequality is generally accepted to be the major mechanism that impairs gas exchange and leads to arterial hypoxemia. Impaired V/Q relationships may be caused by multiple pathological changes in different lung structures, including the airways, parenchyma, and pulmonary vasculature. Bronchiolar lesions are associated with V/Q mismatching, as indicated by a significant correlation between bronchiolar inflammation and the distribution of ventilation. Low V/Q units in the lungs may represent areas with a partially blocked airway. Destruction of the lung surface area by emphysema reduces the diffusing capacity and interferes with gas exchange [20]. The severity of pulmonary emphysema appears to be related to the overall inefficiency of the lung as a gas exchanger. This is reflected by the good correlation between the diffusing capacity of carbon monoxide per liter of alveolar volume (TLCO/VA) and the severity of macroscopic emphysema. Reduced ventilation due to loss of elastic recoil in emphysematous lung together with loss of the capillary bed and generalized inhomogeneity of ventilation due to the patchy nature of these changes leads to areas of V/Q mismatching which result in arterial hypoxemia. Of the four classic mechanisms determining hypoxemia and/or hypercapnia – alveolar hypoventilation, alveolar-end capillary diffusion limitation to oxygen, increased intrapulmonary shunt, and ventilation–perfusion mismatching – the last is by far the most common intrapulmonary determinant of hypoxemia in COPD. The role of shunt is almost negligible, even in the most life-threatening conditions, and diffusion limitation is conspicuously absent. Hypercapnia can be induced by ventilation–perfusion imbalance and/or alveolar hypoventilation, the latter being predominant during exacerbations.

Pulmonary hypertension develops late in the natural history of patients with COPD, is usually associated with the development of severe hypoxemia ($P_aO2 < 8$ KPa or 60 mmHg), and is often hypercapnia as well. It represents the main cardiovascular complication associated with the development of right ventricular hypertrophy (cor pulmonale). Several factors are known to contribute to the development of pulmonary hypertension in patients with COPD, i.e., (1) thickening of pulmonary vessel walls and reduction of lumen; (2) hypoxia, which causes pulmonary vascular smooth muscle to

contract and further reduces the lumen; (3) impaired endothelium-dependent vasodilation (reduction of nitric oxide (NO) synthesis or release in response to hypoxaemia); (4) abnormal secretion of vasoconstrictor peptides such as endothelin-1; (5) destruction of the capillary bed, which further increases the pressure required to perfuse the pulmonary circulation.

Cor pulmonale is defined as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease." This is a pathological definition and the clinical diagnosis and assessment of right ventricular hypertrophy is difficult in life. The prevalence and natural history of cor pulmonale in COPD are not yet clear. Pulmonary hypertension and reduction of the vascular bed due to emphysema can lead to right ventricular hypertrophy and right heart failure. Right heart failure is associated with venous stasis and thrombosis that may result in pulmonary embolism and further compromise the pulmonary circulation.

Pulmonary Inflammation

COPD is associated with inflammation of the central and peripheral airways, lung parenchyma, and pulmonary vessels. In the central airways, the characteristics of inflammation are (1) an increased number of mononuclear cells, particularly macrophages and CD8+ T lymphocytes, associated in a few cases with neutrophils, eosinophils, and mast cells in the airway mucosa; (2) an increased number of neutrophils and, in a few cases, eosinophils in bronchoalveolar lavage (BAL) fluid; (3) infiltration of submucosal glands by neutrophils; (4) hyperplasia of goblet cells and enlarged mucous glands; (5) metaplasia of airway epithelium that is otherwise well preserved; and (6) no change in the structure of the lamina reticularis of the basement membrane. The contribution of these pathological abnormalities to airflow limitation and gas exchange abnormalities remains unclear. However, as airflow limitation progresses, the number of T lymphocytes and macrophages increases in the submucosa, and the number of CD8+ T lymphocytes also increases significantly [3, 4, 22, 23].

Peripheral airways show pathological abnormalities similar to those in the central airways: (1) an increased number of mononuclear cells in the airway mucosa; (2) a significant increase in lymphocytes and particularly in the number of CD8+ T lymphocytes as airflow limitation progresses [3, 22, 23]; (3) an increased number of neutrophils in the airway fluid; and (4) metaplasia of airway epithelium with hyperplasia of goblet cells. In addition, peripheral airways show (1) increased intra-luminal mucus and exudate; (2) increased mass of smooth muscle; (3) fibrosis, distortion, and obliteration of airway walls; and (4) loss of alveolar attachments to the bronchiolar walls.

In the lung parenchyma, the characteristic pathological abnormalities are (1) panlobular emphysema and centrilobular emphysema in various combinations [24]; (2) paraseptal emphysema; and (3) loss of vascular bed linked to emphysema [25].

Patients with COPD may have a significant reversibility of airflow limitation in response to bronchodilators and/or glucocorticosteroids [26–30]. These patients have the same pathologic abnormalities as COPD patients, but may also have some pathological features of asthma, namely, a small but significant increase of eosinophils in BAL fluid and increased thickness of the reticular layer of the basement membrane [27]. Moreover, in COPD with partial reversibility of airflow limitation, the bronchodilator response is associated with increased exhaled NO and sputum eosinophilia [31].

Inflammatory Mediators

Migration and activation of inflammatory cells is regulated by cytokines and chemokines, small proteins secreted by a variety of structural cells, such as epithelial cells, endothelial cells, smooth muscle cells, and fibroblasts, as well as by inflammatory cells. Chemokines are a family of more than 40 small (8–11 kDa) cytokines that have been defined primarily by their ability to mediate leukocyte chemotaxis. Chemokines are divided into four major families on the basis of the spacing of the most amino terminal of four conserved cysteine residues, i.e., the C, CC, CXC, and CX3C families, where X represents any amino acid [32].

Bronchopulmonary inflammation of COPD is characterized by CD8+ T lymphocytes, Tc1 cells and neutrophils. Recent reports demonstrate that T cells from the bronchial mucosa of patients with COPD predominantly express the chemokine receptor CXCR3 [33–35] and produce gamma interferon (IFN-γ), suggesting that these cells elaborate type I cytokines [36].

CXCR3 binds three highly potent, inflammation-inducible CXC chemokine agonists: IFN-γ-inducible protein 10 (CXCL10/IP-10), a monokine induced by IFN-γ, and IFN-inducible T-cell α-chemoattractant (CXCL11/I-TAC) [36]. CD8+ cells are potent producers of IFN-γ in COPD. IFN-γ causes emphysema with alveolar enlargement, enhanced lung volumes, enhanced pulmonary compliance, and macrophage- and neutrophil-rich inflammation when inducibly targeted, in a transgenic fashion, to the adult mouse lung [37]. Prominent protease and antiprotease alterations have also been noted in mice: the induction and activation of matrix metalloproteinase (MMP)-12 and cathepsins B, H, D, S, and L; the elaboration of MMP-9; and the selective inhibition of secretory leukocyte proteinase inhibitor. Therefore, IFN-γ causes emphysema and alterations in pulmonary protease/antiprotease balance when expressed in pulmonary tissues [37].

Several chemokines involved in neutrophil chemotaxis belong to the CXC family, of which interleukin-8 (IL-8, CXCL8) is the most prominent member relevant in COPD. IL-8 levels are markedly elevated in the sputum and BAL fluid of patients with COPD and correlate with the extent of neutrophilic inflammation and disease severity. The blocking of IL-8 reduces the chemotactic response of neutrophils to sputum from COPD patients in vitro [38]. IL-8 activates human neutrophils by binding to two G-protein-coupled receptors, designated CXCR1 and CXCR2. CXCR1 is selectively activated by two chemokine ligands, IL-8 and granulocyte chemoattractant protein (CXCL6/GCP2), the binding of which is coupled to activation and degranulation. CC chemokines are also thought to be involved in COPD. Increased expression of monocyte chemoattractant protein 1 (CCL2/MCP-1) and its cognate receptor CCR2 has been demonstrated in macrophages and epithelial cells from patients with COPD [39]. CCL2/MCP-1 may play a role in recruitment of blood monocytes to the lungs of COPD patients [40]. Elastin fragments generated at the diseased sites are potent chemoattractants for monocytes in the lung in pulmonary emphysema [41]. Furthermore, an increase in the number of dendritic cells in the airways of patients with COPD has been observed and could be explained by the interaction of CCL20 with CCR6 on pulmonary dendritic cells [42]; in particular, the number of dendritic cells in epithelium and adventitia of small airways in patients with COPD increases significantly with disease severity.

Tumor necrosis factor-α (TNF-α) is also present in high concentrations in the sputum of COPD patients and is detectable in bronchial biopsy specimens. TNF-α can induce IL-8 expression in airway cells by activation of the transcription factor NF-κB [43].

In COPD, alveolar macrophages and neutrophils play a central role in the destruction of lung parenchyma [44, 45]. Various proteases break down connective tissue components, particularly elastin, in lung parenchyma to produce emphysema [46].

Three MMPs degrade elastin: MMP-2, MMP-9, and MMP-12. Elevated MMP-9 was found in homogenates of lung removed from patients undergoing lung volume reduction surgery, meaning that the samples were from an advanced stage of emphysema [47]. These lung homogenates revealed MMP-9-related elastolytic and gelatinolytic activity and significant elevations in MMP-9, with no significant increase in neutrophil elastase by ELISA [48]. There is also an increase in the activity of MMP-9 and MMP-2 in the lung parenchyma of patients with emphysema. The role of MMP-9 in the pathogenesis of emphysema is likely to be complex. α_1-Antitrypsin can be cleaved by MMP-9. Increased chemotactic activity in BAL fluid is associated with the development of smoking-related emphysema [McCrea, 1994 #188], and potentiation of IL-8 by MMP-9 could amplify the alveolar inflammation and destruction in smokers who develop emphysema [49].

Oxidative stress may also have an important role in COPD. In smokers and in COPD patients, there is an oxidant–antioxidant imbalance in favor of oxidants [6]. Smoking produces a decrease in alveolar and lung glutathione (GSH) metabolism, widely recognized as a central feature of COPD [50]. The severity of airway obstruction, as measured by FEV_1 in smokers with COPD, correlates negatively with the concentration of GSH in BAL fluid: the higher the concentration of GSH, the lower the FEV_1 [51]. Patients with acute exacerbations of COPD show increased production of superoxide anion by their peripheral blood neutrophils compared with stable patients. Products of lipid peroxidation are significantly increased in plasma or BAL fluid from healthy smokers and from patients with acute exacerbations of COPD, compared with healthy nonsmokers [51]. Smoking also produces a fall in the plasma antioxidant capacity, a global measure of systemic oxidative stress [50]. There are few measurements of GSH in the lung epithelial lining fluid (ELF) from smokers and patients with COPD. The GSH concentration in BAL fluid from patients with COPD is similar to that in chronic smokers with no airflow obstruction. This emphasizes the effects of smoking on GSH metabolism rather than reflecting the disease severity in the COPD patients. The relevance of these studies is not known. It is possible that GSH concentrations in BAL are influenced by the recent smoking of these patients.

Exposure to cigarette smoke is reported to induce goblet cell metaplasia and mucus production [52], but the mechanism is unknown. Mucin synthesis in airways has been reported to be regulated by the epidermal growth factor receptor (EGFR) system. In particular, the exposure of airway epithelial cells to cigarette smoke upregulates EGFR expression and activates EGFR tyrosine phosphorylation, causing mucin synthesis in epithelial cells [53]. The mechanisms by which cigarette smoke induces EGFR activation are not completely defined [53]. However, it has been observed that cigarette smoke is able to transactivate EGFR and thereby stimulate the transmembrane metalloproteinase TNF-α converting enzyme, the ADAM ("A Disintegrin And Metalloproteinase") 17. This metalloproteinase is able to cleave transmembrane amphiregulin, a ligand for the EGFR. The binding of amphiregulin to EGFR then triggers the receptor's activation [54]. Cigarette smoke can also cause neutrophil migration into the airways [55]. Neutrophils are also increased in the bronchial glands [56]. In vivo and in vitro studies show that these neutrophils can stimulate goblet cell degranulation [57]. Purified neutrophil elastase has been shown to be a potent secretagogue for goblet cells in vitro [58]. However, it is not clear whether this molecule is responsible for the effect of neutrophils on degranulation, since the cells themselves release little or no elastase in vitro, even after activation with a variety of molecules (IL-8, leukotriene B_4, TNF-α). Rather, the activation of neutrophils causes a translocation of elastase from the azurophilic granules to the cell surface [59]. However, in a guinea pig model, the elastase inhibitor ICI 200355 inhibited the neutrophil-dependent goblet cell degranulation seen after the

tracheal instillation of neutrophil chemoattractants [60].These results confirmed the role of neutrophil elastase in degranulation, but the question of how elastase exerts its effect still remains, since neutrophil activators and chemoattractants do not appear to promote its release [61]. The potential role of elastase in goblet cell degranulation implies a direct interaction between neutrophils and goblet cells. Some experimental evidence suggests a direct interaction between neutrophils and goblet cells in the airway epithelium, involving ICAM-1, CD11b, or CD18 cells [61]. These leukocyte adhesion receptors play an important role in inflammation via their regulatory effects on leukocyte adhesion, transmigration, and function [62].

Systemic Inflammation

Recent research suggests that inflammation is not confined to the lungs: inflammatory cells and mediators generated in the lungs may enter the bloodstream and may have systemic effects on other susceptible areas of the body. This may account for the observation that patients with COPD also present with systemic symptoms and comorbid conditions, including muscle weakness, weight loss, cardiovascular disease, osteoporosis, hypertension, depression, cognitive decline, sleep disorders, sexual dysfunction, and possibly diabetes [8, 13] (Fig. 1.1).

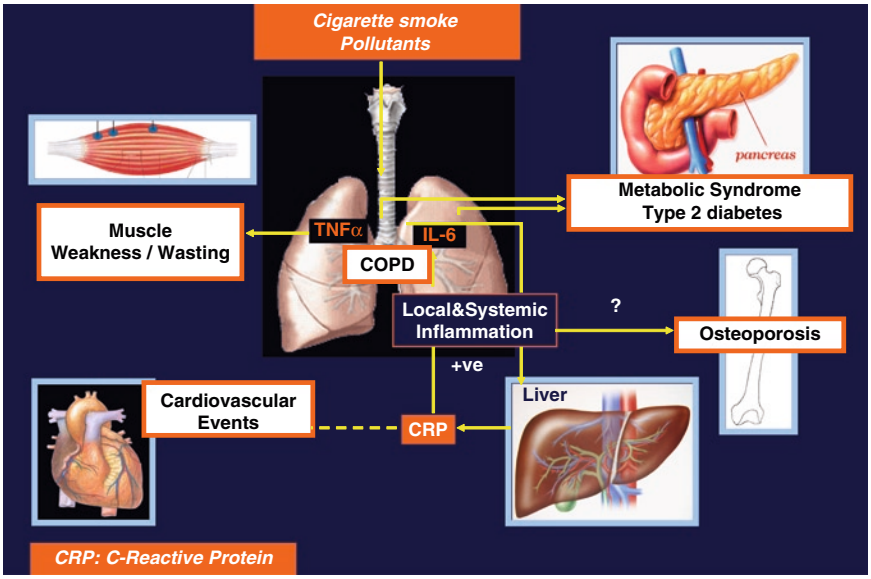


Fig. 1.1. The central role of inflammation in co-morbidity associated with chronic obstructive pulmonary disease (*COPD*). Inflammation appears to play a central role in the pathogenesis of COPD and other conditions that are increasingly being recognized as systemic inflammatory diseases. As part of the chronic inflammatory process, TNF-α receptor polymorphisms are associated with increased severity of disease possibly due to enhanced TNF-α effects. Also, CRP levels can be increased directly by TNF-α and other cytokines, and elevated CRP and fibrinogen may be crucial in the pathogenesis of cardiovascular disease. Reactive oxygen species (*ROS*) released as a result of COPD may enhance the likelihood of developing cardiovascular disease, diabetes, and osteoporosis. *TNF-α* tumor necrosis factor-alpha, *CRP* C reactive protein, *ROS* reactive oxygen species

In recognition of the systemic component of COPD, the 2004 ATS/ERS *Standards for Diagnosis and Treatment of Patients with COPD* were the first guidelines to acknowledge that assessment of severity should ideally include systemic symptoms, such as weight loss and muscle wasting [2]. Patients with COPD have higher baseline levels of several circulating inflammatory markers [63]. The reasons are not clear, and it remains unknown whether the systemic inflammation is a primary or secondary phenomenon. Specific subsets of patients with COPD have been identified, and those with increased resting energy expenditure and decreased fat-free mass have more marked elevation of stable-state CRP and lipopolysaccharide binding protein [64]. Furthermore, those with higher levels of systemic inflammation lack a response to nutritional supplementation [65], raising the possibility that this may be an associated phenomenon rather than cause and effect. CRP levels in serum are raised in COPD patients independent of cigarette smoking, and they are reduced in COPD patients who use inhaled glucocorticosteroids [66]. There is also a genetic influence on CRP levels in COPD [67], and CRP is considered a strong and independent predictor of COPD outcomes in individuals with airflow limitation [17]. CRP is also associated with impaired energy metabolism, impaired functional capacity, distress due to respiratory symptoms [64], and lower quadriceps strength [68]. In the presence of exacerbated respiratory symptoms, CRP levels in plasma may help to establish the diagnosis of a COPD exacerbation [69].

Changes have also been noted in various inflammatory cells in peripheral blood, including neutrophils and lymphocytes [70]. Patients with COPD have increased numbers of neutrophils in the lungs, increased activation of neutrophils in peripheral blood and an increase in TNF-α and soluble TNF-R. It has been suggested that this indicates the importance of a TNF-α/neutrophil axis in maintaining the COPD phenotype [43]. The central role of TNF-α in lung inflammation is not only supported by animal models [43] but has also been implicated in the COPD phenotype with low body mass index [71]. Cytokine production by macrophages is enhanced by hypoxia in vitro [72], and thus the inverse correlation between arterial oxygen tension and circulating TNF-α and solubleTNF-R may be the result of systemic hypoxia [72]. It is tempting therefore to assume that TNF inhibition would be as beneficial in COPD as it has been in other inflammatory conditions, such as rheumatoid arthritis and Crohn's disease [13]. However, this was also hypothesized for congestive heart failure (CHF). TNF-α is believed to play a key role in the pathogenesis of CHF, and raised levels are associated with higher mortality in CHF [73]. However, studies using TNF-α blockade have shown no benefit and possibly an increase in mortality for reasons that are not clear [74], suggesting that it is not a simple cause and effect. Finally, both an increase in CD8+ cells [75–78] and an increase in CD4+ cells [79] have been reported in patients with COPD [75–78], highlighting the difficulties in conducting peripheral blood studies in this disease [79].

Systemic Consequences and Comorbidities

Considering the systemic nature of the inflammatory response to irritants, particularly cigarette smoke, there is increasing evidence that lung abnormalities may be responsible not only for respiratory symptoms, e.g., dyspnoea, but also for the chronic comorbidities that develop along with COPD, particularly chronic heart failure (CHF), coronary and peripheral vascular diseases, and the metabolic syndrome [8, 13]. Comorbidities are highly likely to affect health outcomes in COPD, and COPD patients are more likely to die of cardiovascular complications or cancer than of respiratory failure [80].

Progressive respiratory failure accounts for approximately one third of COPD-related mortality; therefore, factors other than progression of lung disease must play a substantial role. The most common comorbidities that have been described in association with COPD are hypertension, diabetes, coronary artery disease [81, 82], CHF [83], pulmonary infections, cancer [84], and pulmonary vascular disease [80]. The number of preexisting comorbidities in patients with COPD is associated with increased in-hospital mortality [82]. Comorbid conditions that have been associated with an increased mortality risk in COPD patients include chronic renal failure, cor pulmonale [85], and pulmonary vascular disease [86]. Underlying heart diseases have not been consistently associated with a higher mortality risk. However, since COPD is frequently underreported, it is difficult to make an accurate estimate of how comorbid conditions influence COPD mortality or, conversely, how COPD affects the outcome of other diagnoses [80].

There is a growing body of evidence to indicate that persistent low-grade systemic inflammation is present in stable COPD. Low-grade systemic inflammation has been implicated in the pathogenesis of cardiovascular events and chronic myopathy of the skeletal muscle. Since COPD patients suffer from excess morbidity and mortality related to cardiovascular events, it has been suggested that systemic inflammation may be the common link [13].

Chronic Heart Failure

CHF and COPD are two commonly encountered conditions in clinical practice. CHF accounts for their frequent coexistence. The prevalence of COPD ranges from 20% to 32% in patients with CHF [15, 87]. FEV_1 is as good a predictor of cardiovascular mortality as serum cholesterol [88]. Ischemic heart disease, and not respiratory failure, is the leading cause of death in COPD patients, with only a small fraction dying of respiratory failure [87]. The relationship between COPD and cardiovascular events remains unclear. Patients with COPD are not at increased risk for hypertension or left ventricular hypertrophy; however, they consistently show evidence of low-grade systemic inflammation that plays an increasingly recognized role in the pathogenesis of atherosclerosis [87]. Patients with severe COPD are 2.18–2.74 times more likely to have elevated or highly elevated circulating CRP levels than control subjects [89]. A working hypothesis to account for the high prevalence of systolic dysfunction in patients with COPD is that low-grade systemic inflammation accelerates the progression of coronary atherosclerosis, which ultimately results in ischemic cardiomyopathy. Such a hypothesis fits the clinical observation of a high incidence of left ventricular wall motion abnormalities noted in patients with COPD and left ventricular dysfunction [87].

Diabetes

Type II diabetes mellitus is a disorder with an increased incidence in COPD. Systemic inflammation may also explain why patients with COPD have an increased risk of developing type II diabetes [90]. Some aspect of inflammation can predict the development of diabetes and glucose disorders [91, 92], and fibrinogen, circulating white blood cell count, and lower serum albumin predict the development of type II diabetes [92]. Furthermore, patients with noninsulin-dependent diabetes mellitus have increased circulating levels of TNF-α, IL-6, and CRP [93], which are also risk factors for cardiovascular events in both sexes [94, 95].

The roles of circulating cytokines in the pathogenesis of diabetes and insulin resistance have received increasing interest. Adipose tissue secretes numerous adipokines, which markedly influence lipid and glucose/insulin metabolism [13]. Sonnenberg et al. [96] proposed that TNF-α might be a mediator of the diabetic process. As described above, this cytokine acts via its receptor to activate the nuclear transcription factor NF-κB, leading to cytokine production, upregulation of adhesion molecules and increasing oxidative stress. Indeed, this latter effect together with TNF-α may provide a stimulating pathway that interferes with glucose metabolism and insulin sensitivity [13]. This concept is supported by several clinical and experimental observations. It is known that TNF-α expression is increased in patients with weight gain and insulin resistance [97]. Perhaps this represents a modulating effect, as TNF-α stimulates lipolysis [98] but TNF-α levels are associated with hyperinsulinemia and insulin resistance [99]. Other studies have also confirmed that an acute-phase response (CRP) is increased in obesity and associated with insulin resistance [100]. Furthermore, adiponectin levels are reduced in obesity and associated with insulin resistance and hyperinsulinemia [101]. However, the most direct supporting data for this putative axis come from the obese, insulin-resistant mouse, in which TNF-α inhibition improves insulin sensitivity [97]. These observations support the concept that inflammation, as reflected in acute-phase proteins, is in some way intimately associated with the development of glucose intolerance and insulin resistance.

Atherosclerosis

As atherosclerosis is the most common cause of coronary and peripheral artery disease worldwide, the epidemiology and clinical consequences of peripheral arterial disease are closely associated with classic risk factors for atherosclerosis, including cigarette smoking.

Pai et al. [94] assessed the risk of coronary heart disease and related it to the circulating levels of several inflammatory markers. They found that high levels of CRP and IL-6 are significantly related to an increased risk in both males and females.

CRP is a type I acute-phase protein that possesses the ability to bind to bacteria, subsequently facilitating the binding of complement necessary for bacterial killing and/or phagocytosis. The protein can increase during an inflammatory process. TNF-α, IL-1, and IL-6 stimulate CRP synthesis by inducing hepatic gene expression [102], implicating TNF-α at the core of the process. Macrophages have receptors for CRP, and CRP can increase cytokine production [103, 104]. These features may be central to atheroma production. CRP may deposit directly onto the arterial wall during atherogenesis, possibly via the Fcγ receptor [105], facilitating monocyte adherence through the production of the monocyte chemokine MCP-1. Further activation can result in production of other pro-inflammatory cytokines and differentiation of the monocytes into macrophages. In the presence of oxidized low-density lipoproteins, CRP can facilitate the production of foam cells, which are the building blocks of atherosclerotic plaques.

A study by Smeeth et al. [106] indicated that the risk of a myocardial infarct or cerebrovascular event is increased greatly within the first 3 days after an "acute systemic respiratory tract infection," defined by the authors as pneumonia, acute bronchitis, "chest infections," or influenza. These events are accompanied by a well-recognized acute inflammatory response and cytokine production. Indeed, in patients with COPD, not only is the baseline CRP > 3 mg/L in almost half of the patients, but the further rise during an acute exacerbation [107] is also associated with a rise in fibrinogen [108],

increasing the prothrombotic risk. This may well account for the increased risk of vascular events in COPD and particularly the increased mortality within a few months of hospital admission for an acute exacerbation [109].

Osteoporosis

The risk of osteoporosis with steroid use is well known, but patients with COPD have an increased risk even in the absence of steroid use. McEvoy et al. [110] observed that vertebral fractures were present in up to 50% of steroid-naive males with COPD. A more recent study by Bolton et al. [107] confirmed that osteopenia is a feature of COPD and associated with an increase in circulating TNF-α. Postmenopausal osteoporosis is related to high serum levels of TNF-α and IL-6 [111]. It is known that macrophages can differentiate into osteoclasts in the presence of marrow mesenchymal cells. Marrow mesenchymal cells release the cytokine RANK ligand (RANKL), a member of the TNF-α superfamily. TNF-α and IL-1 enhance this process and can induce RANKL expression in marrow stromal cells and synergize with RANKL in osteoclastogenesis [112]; osteoclast formation can also be induced by IL-6 independent of RANKL [113]. However, other inflammatory conditions, such as rheumatoid arthritis [114] and periodontal disease [115], have T cells induced to produce RANKL, and it is therefore likely that a similar process occurs in COPD.

The role of pro-inflammatory cytokines may therefore be central to the osteoporosis associated with inflammatory disease. In support of this concept is the study reported by Gianni et al. [111], who confirmed that raloxifene is able to decrease TNF-α transcription and serum levels while increasing bone density. Again, these data support a close association between the pro-inflammatory process and osteopenia.

Muscle Wasting

In patients with COPD, peripheral muscle dysfunction is clearly evidenced by the significant reduction in both strength and endurance in the ambulatory muscles of these patients in comparison with healthy subjects [116]. Other studies have shown several morphological, structural, and biochemical abnormalities that could contribute to the dysfunction [116].

Low body mass index, older age, and low arterial oxygen tension have been shown to be significant independent predictors of mortality in COPD [117, 118]. More specifically, loss of fat-free mass adversely affects respiratory and peripheral muscle function, exercise capacity, and health status. Both weight loss and loss of fat-free mass appear to be the result of a negative energy balance and are seen more commonly in emphysema [119]. In starvation and nutritional imbalance there is an adaptive reduction in resting energy requirements [120]. In contrast, as in cachexia, increased resting energy expenditure has been noted in many COPD patients, linked to systemic inflammation [121, 122]. Furthermore, nutritional intake is also generally adequate (although not during acute exacerbations). While there is no universally agreed upon definition of cachexia, accelerated loss of skeletal muscle in the context of a chronic inflammatory response is a characteristic feature [123] not limited to COPD. Patients with cachexia display preferential loss of fat-free mass, enhanced protein degradation [124], and poor responsiveness to nutritional interventions [125, 126]. In addition, cachectic patients exhibit changes in the metabolism of proteins, lipids, and carbohydrates that are thought to be related to systemic rather than local inflammation [125, 127]. Thus, muscle wasting in COPD displays similarities to the cachexia seen in CHF, renal failure,

AIDS and cancer, among others. Cachexia in these conditions is not only associated with reduced survival [126, 128] but is also related to poor functional status and health-related quality of life [123]. Common findings in all these conditions include increased levels of circulating pro-inflammatory molecules, including TNF-α, IL-1, IL-6, IL-8, and IFN-γ, and reduced levels of anabolic hormones, including insulin-like growth factors and testosterone [123].

TNF-α plays a central role in the muscle wasting and weight loss seen in COPD. It has several direct effects (anorexia, altered levels of circulating hormones and catabolic cytokines, and altered end organ sensitivities to them) that could promote muscle wasting [129], predominantly via the ubiquitin pathway. This process is mediated by NF-κB, a transcription factor that is inactive when bound to its inhibitor but that can be activated by inflammatory cytokines, including TNF-α [130]. In muscle cells, NF-κB can interfere with skeletal muscle differentiation and repair via inhibition of MyoD expression [131].

Conclusions

COPD can no longer be considered a disease only of the lungs. It is associated with a wide variety of systemic consequences, most notably systemic inflammation. A better understanding of its origin, consequences, and potential therapy should prove to be of great relevance and lead to better care of the patients suffering from this devastating disease.

Acknowledgements We thank M. McKenney for scientific assistance with the manuscript, and E. Veratelli for her scientific secretarial assistance.

References

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J (2007) Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176(6):532–555
2. Celli BR, Snider GL, Heffner J, Tiep B, Ziment I, Make B, Braman S, Olsen G, Philips Y (1995) Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 152(5 Pt 2):S77–S121
3. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Pare PD (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350(26):2645–2653
4. Cosio MG, Saetta M, Agusti A (2009) Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med 360(23):2445–2454
5. Barnes PJ, Shapiro SD, Pauwels RA (2003) Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J 22(4):672–688
6. MacNee W (2005) Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2(1):50–60
7. Agusti AG (2005) Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2(4):367–370, discussion 371–2
8. Barnes PJ, Celli BR (2009) Systemic manifestations and comorbidities of COPD. Eur Respir J 33(5):1165–1185
9. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF (2007) Systemic effects of smoking. Chest 131(5):1557–1566

10. Vermeeren MA, Creutzberg EC, Schols AM, Postma DS, Pieters WR, Roldaan AC, Wouters EF (2006) Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med 100(8):1349–1355
11. Rutten EP, Franssen FM, Engelen MP, Wouters EF, Deutz NE, Schols AM (2006) Greater whole-body myofibrillar protein breakdown in cachectic patients with chronic obstructive pulmonary disease. Am J Clin Nutr 83(4):829–834
12. Sabit R, Bolton CE, Edwards PH, Pettit RJ, Evans WD, McEniery CM, Wilkinson IB, Cockcroft JR, Shale DJ (2007) Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175:1259–1265
13. Sevenoaks MJ, Stockley RA (2006) Chronic obstructive pulmonary disease, inflammation and co-morbidity–a common inflammatory phenotype? Respir Res 7:70
14. Rutten FH, Cramer MJ, Zuithoff NP, Lammers JW, Verweij W, Grobbee DE, Hoes AW (2007) Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease. Eur J Heart Fail 9(6–7):651–659
15. Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuithoff NP, Lammers JW, Hoes AW (2005) Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ 331(7529):1379
16. Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG (2001) Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164(6):1008–1011
17. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG (2007) C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175(3):250–255
18. Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM (2001) Cellular and structural bases of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163(6):1304–1309
19. Global Initiative for Asthma (2002) Update of the NHLBI/WHO workshop report: global strategy for asthma management and prevention. Issued January 1995. National Institutes of Health, National Heart Lung and Blood Institute, Bethesda, MD, Document no. 02–3659
20. Gould GA, MacNee W, McLean A, Warren PM, Redpath A, Best JJ, Lamb D, Flenley DC (1988) CT measurements of lung density in life can quantitate distal airspace enlargement – an essential defining feature of human emphysema. Am Rev Respir Dis 137(2):380–392
21. McLean A, Warren PM, Gillooly M, MacNee W, Lamb D (1992) Microscopic and macroscopic measurements of emphysema: relation to carbon monoxide gas transfer. Thorax 47(3):144–149
22. ÓShaughnessy TC, Ansari TW, Barnes NC, Jeffery PK (1997) Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV1. Am J Respir Crit Care Med 155(3):852–857
23. Saetta M, Di Stefano A, Turato G, Facchini FM, Corbino L, Mapp CE, Maestrelli P, Ciaccia A, Fabbri LM (1998) CD8+ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157(3 Pt 1):822–826
24. Guerassimov A, Hoshino Y, Takubo Y, Turcotte A, Yamamoto M, Ghezzo H, Triantafillopoulos A, Whittaker K, Hoidal JR, Cosio MG (2004) The development of emphysema in cigarette smoke-exposed mice is strain dependent. Am J Respir Crit Care Med 170(9):974–980
25. Baraldo S, Saetta M, Cosio MG (2003) Pathophysiology of the small airways. Semin Respir Crit Care Med 24(5):465–472
26. Anthonisen NR, Wright EC (1986) Bronchodilator response in chronic obstructive pulmonary disease. Am Rev Respir Dis 133(5):814–819
27. Chanez P, Vignola A, ÓShaughnessy T, Enander I, Li D, Jeffery P, Bousquet J (1997) Corticosteroid reversibility in COPD is related to features of asthma. Am J Respir Crit Care Med 155:1529–1534
28. Enright P, Quanjer P (2007) Don't diagnose mild COPD without confirming airway obstruction after an inhaled bronchodilator. COPD 4(2):89–90

29. Gross NJ (1986) COPD: a disease of reversible air-flow obstruction. Am Rev Respir Dis 133(5):725–726
30. Perez-Padilla R, Hallal PC, Vazquez-Garcia JC, Muino A, Maquez M, Lopez MV, de Oca MM, Talamo C, Valdivia G, Pertuze J, Jardim J, Menezes AM (2007) Impact of bronchodilator use on the prevalence of COPD in population-based samples. COPD 4(2):113–120
31. Papi A, Romagnoli M, Baraldo S, Braccioni F, Guzzinati I, Saetta M, Ciaccia A, Fabbri LM (2000) Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 162(5):1773–1777
32. Zlotnik A, Yoshie O (2000) Chemokines: a new classification system and their role in immunity. Immunity 12(2):121–127
33. Grumelli S, Corry DB, Song LZ, Song L, Green L, Huh J, Hacken J, Espada R, Bag R, Lewis DE, Kheradmand F (2004) An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. PLoS Med 1(1):e8
34. Panina-Bordignon P, Papi A, Mariani M, Di Lucia P, Casoni G, Bellettato C, Buonsanti C, Miotto D, Mapp C, Villa A, Arrigoni G, Fabbri LM, Sinigaglia F (2001) The C-C chemokine receptors CCR4 and CCR8 identify airway T cells of allergen-challenged atopic asthmatics. J Clin Invest 107(11):1357–1364
35. Saetta M, Mariani M, Panina-Bordignon P, Turato G, Buonsanti C, Baraldo S, Bellettato CM, Papi A, Corbetta L, Zuin R, Sinigaglia F, Fabbri LM (2002) Increased expression of the chemokine receptor CXCR3 and its ligand CXCL10 in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 165(10):1404–1409
36. Donnelly LE, Barnes PJ (2006) Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease. Trends Pharmacol Sci 27(10):546–553
37. Wang Z, Zheng T, Zhu Z, Homer RJ, Riese RJ, Chapman HA Jr, Shapiro SD, Elias JA (2000) Interferon gamma induction of pulmonary emphysema in the adult murine lung. J Exp Med 192(11):1587–1600
38. Beeh KM, Kornmann O, Buhl R, Culpitt SV, Giembycz MA, Barnes PJ (2003) Neutrophil chemotactic activity of sputum from patients with COPD: role of interleukin 8 and leukotriene B4. Chest 123(4):1240–1247
39. de Boer WI, Sont JK, van Schadewijk A, Stolk J, van Krieken JH, Hiemstra PS (2000) Monocyte chemoattractant protein 1, interleukin 8, and chronic airways inflammation in COPD. J Pathol 190(5):619–626
40. Maus UA, Koay MA, Delbeck T, Mack M, Ermert M, Ermert L, Blackwell TS, Christman JW, Schlondorff D, Seeger W, Lohmeyer J (2002) Role of resident alveolar macrophages in leukocyte traffic into the alveolar air space of intact mice. Am J Physiol Lung Cell Mol Physiol 282(6):L1245–L1252
41. Hunninghake GW, Davidson JM, Rennard S, Szapiel S, Gadek JE, Crystal RG (1981) Elastin fragments attract macrophage precursors to diseased sites in pulmonary emphysema. Science 212(4497):925–927
42. Demedts IK, Bracke KR, Van Pottelberge G, Testelmans D, Verleden GM, Vermassen FE, Joos GF, Brusselle GG (2007) Accumulation of dendritic cells and increased CCL20 levels in the airways of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175(10):998–1005
43. Mukhopadhyay S, Hoidal JR, Mukherjee TK (2006) Role of TNFalpha in pulmonary pathophysiology. Respir Res 7:125
44. Sibille Y, Reynolds HY (1990) Macrophages and polymorphonuclear neutrophils in lung defense and injury. Am Rev Respir Dis 141(2):471–501
45. Hunninghake GW, Crystal RG (1983) Cigarette smoking and lung destruction. Accumulation of neutrophils in the lungs of cigarette smokers. Am Rev Respir Dis 128(5):833–838
46. La Rocca G, Anzalone R, Magno F, Farina F, Cappello F, Zummo G (2007) Cigarette smoke exposure inhibits extracellular MMP-2 (gelatinase A) activity in human lung fibroblasts. Respir Res 8:23
47. Atkinson JJ, Senior RM (2003) Matrix metalloproteinase-9 in lung remodeling. Am J Respir Cell Mol Biol 28(1):12–24

48. Ohnishi K, Takagi M, Kurokawa Y, Satomi S, Konttinen YT (1998) Matrix metalloproteinase-mediated extracellular matrix protein degradation in human pulmonary emphysema. Lab Invest 78(9):1077–1087
49. Van den Steen PE, Proost P, Wuyts A, Van Damme J, Opdenakker G (2000) Neutrophil gelatinase B potentiates interleukin-8 tenfold by aminoterminal processing, whereas it degrades CTAP-III, PF-4, and GRO-alpha and leaves RANTES and MCP-2 intact. Blood 96(8):2673–2681
50. Peltoniemi MJ, Rytila PH, Harju TH, Soini YM, Salmenkivi KM, Ruddock LW, Kinnula VL (2006) Modulation of glutaredoxin in the lung and sputum of cigarette smokers and chronic obstructive pulmonary disease. Respir Res 7:133
51. MacNee W, Rahman I (2001) Is oxidative stress central to the pathogenesis of chronic obstructive pulmonary disease? Trends Mol Med 7(2):55–62
52. Hegab AE, Sakamoto T, Nomura A, Ishii Y, Morishima Y, Iizuka T, Kiwamoto T, Matsuno Y, Homma S, Sekizawa K (2007) Niflumic acid and AG-1478 reduce cigarette smoke-induced mucin synthesis: the role of hCLCA1. Chest 131(4):1149–1156
53. Takeyama K, Jung B, Shim JJ, Burgel PR, Dao-Pick T, Ueki IF, Protin U, Kroschel P, Nadel JA (2001) Activation of epidermal growth factor receptors is responsible for mucin synthesis induced by cigarette smoke. Am J Physiol Lung Cell Mol Physiol 280(1):L165–L172
54. Lemjabbar H, Li D, Gallup M, Sidhu S, Drori E, Basbaum C (2003) Tobacco smoke-induced lung cell proliferation mediated by tumor necrosis factor alpha-converting enzyme and amphiregulin. J Biol Chem 278(28):26202–26207
55. Nishikawa M, Kakemizu N, Ito T, Kudo M, Kaneko T, Suzuki M, Udaka N, Ikeda H, Okubo T (1999) Superoxide mediates cigarette smoke-induced infiltration of neutrophils into the airways through nuclear factor-kappaB activation and IL-8 mRNA expression in guinea pigs in vivo. Am J Respir Cell Mol Biol 20(2):189–198
56. Saetta M, Turato G, Facchini FM, Corbino L, Lucchini RE, Casoni G, Maestrelli P, Mapp CE, Ciaccia A, Fabbri LM (1997) Inflammatory cells in the bronchial glands of smokers with chronic bronchitis. Am J Respir Crit Care Med 156(5):1633–1639
57. Takeyama K, Agusti C, Ueki I, Lausier J, Cardell LO, Nadel JA (1998) Neutrophil-dependent goblet cell degranulation: role of membrane-bound elastase and adhesion molecules. Am J Physiol 275(2 Pt 1):L294–L302
58. Sommerhoff CP, Nadel JA, Basbaum CB, Caughey GH (1990) Neutrophil elastase and cathepsin G stimulate secretion from cultured bovine airway gland serous cells. J Clin Invest 85(3):682–689
59. Owen CA, Campbell MA, Sannes PL, Boukedes SS, Campbell EJ (1995) Cell surface-bound elastase and cathepsin G on human neutrophils: a novel, non-oxidative mechanism by which neutrophils focus and preserve catalytic activity of serine proteinases. J Cell Biol 131(3):775–789
60. Tokuyama K, Kuo HP, Rohde JA, Barnes PJ, Rogers DF (1990) Neural control of goblet cell secretion in guinea pig airways. Am J Physiol 259(2 Pt 1):L108–L115
61. Nadel JA (2000) Role of neutrophil elastase in hypersecretion during COPD exacerbations, and proposed therapies. Chest 117(5 Suppl 2):386S–389S
62. Liles WC, Dale DC, Price TH, Gaviria JM, Turner T, Saoud J, Frumkin LR (2000) Inhibition of in vivo neutrophil transmigration by a novel humanized anti-CD11/CD18 monoclonal antibody. Cytokines Cell Mol Ther 6(3):121–126
63. Gan WQ, Man SF, Senthilselvan A, Sin DD (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59(7):574–580
64. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM (2006) Raised CRP levels mark metabolic and functional impairment in advanced COPD. Thorax 61(1):17–22
65. Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF (2000) Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161(3 Pt 1):745–752

66. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR (2006) C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax 61(1):23–28
67. Hersh CP, Miller DT, Kwiatkowski DJ, Silverman EK (2006) Genetic determinants of C-reactive protein in COPD. Eur Respir J 28(6):1156–1162
68. Yende S, Waterer GW, Tolley EA, Newman AB, Bauer DC, Taaffe DR, Jensen R, Crapo R, Rubin S, Nevitt M, Simonsick EM, Satterfield S, Harris T, Kritchevsky SB (2006) Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. Thorax 61(1):10–16
69. Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, Vessey RS, Wedzicha JA (2006) Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 174(8):867–874
70. Sauleda J, Garcia-Palmer FJ, Gonzalez G, Palou A, Agusti AG (2000) The activity of cytochrome oxidase is increased in circulating lymphocytes of patients with chronic obstructive pulmonary disease, asthma, and chronic arthritis. Am J Respir Crit Care Med 161(1):32–35
71. Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, Shale DJ (2001) Inflammatory response and body composition in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164(8 Pt 1):1414–1418
72. Takabatake N, Nakamura H, Abe S, Inoue S, Hino T, Saito H, Yuki H, Kato S, Tomoike H (2000) The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alpha system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161(4 Pt 1):1179–1184
73. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL (2001) Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation 103(16):2055–2059
74. Coletta AP, Clark AL, Banarjee P, Cleland JG (2002) Clinical trials update: renewal (renaissance and recover) and attach. Eur J Heart Fail 4(4):559–561
75. de Jong JW, van der Belt-Gritter B, Koeter GH, Postma DS (1997) Peripheral blood lymphocyte cell subsets in subjects with chronic obstructive pulmonary disease: association with smoking, IgE and lung function. Respir Med 91(2):67–76
76. Domagala-Kulawik J, Hoser G, Dabrowska M, Chazan R (2007) Increased proportion of Fas positive CD8+ cells in peripheral blood of patients with COPD. Respir Med 101(6):1338–1343
77. Glader P, von Wachenfeldt K, Lofdahl CG (2006) Systemic CD4+ T-cell activation is correlated with FEV1 in smokers. Respir Med 100(6):1088–1093
78. Kim WD, Kim WS, Koh Y, Lee SD, Lim CM, Kim DS, Cho YJ (2002) Abnormal peripheral blood T-lymphocyte subsets in a subgroup of patients with COPD. Chest 122(2):437–444
79. Koch A, Gaczkowski M, Sturton G, Staib P, Schinkothe T, Klein E, Rubbert A, Bacon K, Wassermann K, Erdmann E (2007) Modification of surface antigens in blood CD8+ T-lymphocytes in COPD: effects of smoking. Eur Respir J 29(1):42–50
80. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, Davey Smith G, Upton M, Hawthorne V, Sin DD, Man SF, Van Eeden S, Mapel DW, Vestbo J (2006) The natural history of chronic obstructive pulmonary disease. Eur Respir J 27(3):627–643
81. Holguin F, Folch E, Redd SC, Mannino DM (2005) Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest 128(4):2005–2011
82. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD (2005) COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanent Medical Care Program. Chest 128(4):2068–2075
83. Sin DD, Wu L, Anderson JA, Anthonisen NR, Buist AS, Burge PS, Calverley PM, Connett JE, Lindmark B, Pauwels RA, Postma DS, Soriano JB, Szafranski W, Vestbo J (2005) Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. Thorax 60(12):992–997, Epub 2005 Oct 14

84. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357(9255):539–545
85. Naeije R (2005) Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2(1):20–22
86. Naeije R, Vizza D (2005) Current perspectives modern hemodynamic evaluation of the pulmonary circulation. Application to pulmonary arterial hypertension and embolic pulmonary hypertension. Ital Heart J 6(10):784–788
87. Le Jemtel TH, Padeletti M, Jelic S (2007) Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol 49(2):171–180
88. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM (1996) Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. Bmj 313(7059):711–715, discussion 715–6
89. Sin DD, Man SF (2003) Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 107(11):1514–1519
90. Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, Speizer FE, Barr RG, Camargo CA Jr (2004) Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. Diab Care 27(10):2478–2484
91. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP (2001) The relation of markers of inflammation to the development of glucose disorders in the elderly: the cardiovascular health study. Diabetes 50(10):2384–2389
92. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G (1999) Markers of inflammation and prediction of diabetes mellitus in adults (atherosclerosis risk in communities study): a cohort study. Lancet 353(9165):1649–1652
93. Pickup JC, Mattock MB, Chusney GD, Burt D (1997) NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia 40(11):1286–1292
94. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB (2004) Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 351(25):2599–2610
95. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR (2002) Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 347(20):1557–1565
96. Sonnenberg GE, Krakower GR, Kissebah AH (2004) A novel pathway to the manifestations of metabolic syndrome. Obes Res 12(2):180–186
97. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM (1996) IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 271(5249):665–668
98. Porter MH, Cutchins A, Fine JB, Bai Y, DiGirolamo M (2002) Effects of TNF-alpha on glucose metabolism and lipolysis in adipose tissue and isolated fat-cell preparations. J Lab Clin Med 139(3):140–146
99. Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG (1999) Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. J Clin Endocrinol Metab 84(1):272–278
100. Tamakoshi K, Yatsuya H, Kondo T, Hori Y, Ishikawa M, Zhang H, Murata C, Otsuka R, Zhu S, Toyoshima H (2003) The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 27(4):443–449
101. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA (2001) Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 86(5):1930–1935
102. Albert MA (2000) The role of C-reactive protein in cardiovascular disease risk. Curr Cardiol Rep 2(4):274–279

103. Ballou SP, Lozanski G (1992) Induction of inflammatory cytokine release from cultured human monocytes by C-reactive protein. Cytokine 4(5):361–368
104. Zahedi K, Tebo JM, Siripont J, Klimo GF, Mortensen RF (1989) Binding of human C-reactive protein to mouse macrophages is mediated by distinct receptors. J Immunol 142(7):2384–2392
105. Devaraj S, Du Clos TW, Jialal I (2005) Binding and internalization of C-reactive protein by Fcgamma receptors on human aortic endothelial cells mediates biological effects. Arterioscler Thromb Vasc Biol 25(7):1359–1363
106. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P (2004) Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 351(25):2611–2618
107. Stockley RA, ÓBrien C, Pye A, Hill SL (2000) Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 117(6):1638–1645
108. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, Jeffries DJ, Meade TW (2000) Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. Thromb Haemost 84(2):210–215
109. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J (2002) Mortality after hospitalization for COPD. Chest 121(5):1441–1448
110. McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM, Niewoehner DE (1998) Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157(3 Pt 1): 704–709
111. Gianni W, Ricci A, Gazzaniga P, Brama M, Pietropaolo M, Votano S, Patane F, Agliano AM, Spera G, Marigliano V, Ammendola S, Agnusdei D, Migliaccio S, Scandurra R (2004) Raloxifene modulates interleukin-6 and tumor necrosis factor-alpha synthesis in vivo: results from a pilot clinical study. J Clin Endocrinol Metab 89(12):6097–6099
112. Cenci S, Weitzmann MN, Roggia C, Namba N, Novack D, Woodring J, Pacifici R (2000) Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha. J Clin Invest 106(10):1229–1237
113. Kudo O, Sabokbar A, Pocock A, Itonaga I, Fujikawa Y, Athanasou NA (2003) Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. Bone 32(1):1–7
114. Kong YY, Feige U, Sarosi I, Bolon B, Tafuri A, Morony S, Capparelli C, Li J, Elliott R, McCabe S, Wong T, Campagnuolo G, Moran E, Bogoch ER, Van G, Nguyen LT, Ohashi PS, Lacey DL, Fish E, Boyle WJ, Penninger JM (1999) Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. Nature 402(6759):304–309
115. Teng YT, Nguyen H, Gao X, Kong YY, Gorczynski RM, Singh B, Ellen RP, Penninger JM (2000) Functional human T-cell immunity and osteoprotegerin ligand control alveolar bone destruction in periodontal infection. J Clin Invest 106(6):R59–R67
116. Couillard A, Prefaut C (2005) From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. Eur Respir J 26(4):703–719
117. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350(10): 1005–1012
118. Schols AM, Slangen J, Volovics L, Wouters EF (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157(6 Pt 1):1791–1797
119. Engelen MP, Schols AM, Lamers RJ, Wouters EF (1999) Different patterns of chronic tissue wasting among patients with chronic obstructive pulmonary disease. Clin Nutr 18(5):275–280
120. Schols AM (2003) Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. Eur Respir J Suppl 46:81s–86s

121. Baarends EM, Schols AM, Westerterp KR, Wouters EF (1997) Total daily energy expenditure relative to resting energy expenditure in clinically stable patients with COPD. Thorax 52(9):780–785
122. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF (1996) Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 51(8):819–824
123. Kotler DP (2000) Cachexia. Ann Intern Med 133(8):622–634
124. Morrison WL, Gibson JN, Scrimgeour C, Rennie MJ (1988) Muscle wasting in emphysema. Clin Sci (Lond) 75(4):415–420
125. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF (1995) Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med 152(4 Pt 1): 1268–1274
126. Tisdale MJ (1997) Biology of cachexia. J Natl Cancer Inst 89(23):1763–1773
127. Debigare R, Cote CH, Maltais F (2001) Peripheral muscle wasting in chronic obstructive pulmonary disease. Clinical relevance and mechanisms. Am J Respir Crit Care Med 164(9):1712–1717
128. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ (1997) Wasting as independent risk factor for mortality in chronic heart failure. Lancet 349(9058):1050–1053
129. Stewart CE, Newcomb PV, Holly JM (2004) Multifaceted roles of TNF-alpha in myoblast destruction: a multitude of signal transduction pathways. J Cell Physiol 198(2):237–247
130. Reid MB, Li YP (2001) Tumor necrosis factor-alpha and muscle wasting: a cellular perspective. Respir Res 2(5):269–272
131. Gordon JN, Green SR, Goggin PM (2005) Cancer cachexia. Qjm 98(11):779–788

2

Clinical Assessment of COPD

Jørgen Vestbo

Key Points:

- Chronic obstructive pulmonary disease (COPD) should be suspected in any patient aged 40 years or more with symptoms of cough, sputum production, or breathlessness and/or a history of exposure to risk factors, in particular smoking. When seeing patients with respiratory symptoms or smokers – think of COPD
- Do spirometry
- Exclude differential diagnoses, perform chest x-ray
- Assess functional impairment, by interview and even better by testing
- When possible, standardize your questioning
- Consider further physiological testing or imaging
- Calculate BMI, it has prognostic value

Keywords COPD • diagnosis • breathlessness • symptoms

Diagnosis and Differential Diagnosis

The current definition of chronic obstructive pulmonary disease (COPD) is "A preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" [1].

According to guidelines, COPD should be suspected in any patient aged 40 years or more with symptoms of cough, sputum production, or breathlessness and/or a history of exposure to risk factors, in particular smoking [2, 3]. Smoking is well known for causing COPD but the list of risk factors for developing COPD is long and include both host factors and environmental exposures, most often interacting [4, 5]. This should especially be taken into account outside Europe and the USA where exposure to risk factor other than smoking seems to play a larger role. A list of the currently accepted and suggested risk factors is shown in Table 2.1; risk factors marked with an asterisk have the most literature supporting their role.

Guidelines usually state that a suspected diagnosis of COPD is confirmed by spirometry with the well-known – but perhaps still questioned – post-bronchodilator ratio (FEV_1/FVC) of <0.7. There are, however, a number of differential diagnosis that need to be taken into account, as listed in Table 2.2.

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_2,

Table 2.1 Risk factors for chronic obstructive pulmonary disease (COPD)*.

External
Smoking*
Socioeconomic status*
Occupation*
Biomass fuel exposure*
Internal
Genetic factors*
Gender
Chronic mucus hypersecretion
Other
Airway hyper-responsiveness*
Elevated IgE
Asthma*
Environmental pollution
Perinatal events and childhood respiratory illness
Recurrent bronchopulmonary infections
Diet

IgE immunoglobulin E
In an attempted descending order, *risk factors with strongest evidence to support

Table 2.2 Most important differential diagnoses to chronic obstructive pulmonary disease (COPD).

Respiratory
Chronis asthma
Bronchiectasis
Obliterative bronchiolitis
Diffuse panbronchiolitis
Tuberculosis
Non-respiratory
Congestive heart failure
Recurrent pulmonary embolism

The most difficult clinical problem will often be distinguishing COPD from persistent poorly reversible asthma, especially in older patients. In general, it is easy to distinguish asthma from COPD, in particular in young and middle-aged patients where history will often suffice and where demonstration of a significant bronchodilator response is diagnostic of asthma. However, in older patients with significant previous cigarette exposure and only modest reversibility to a bronchodilator, the diagnosis can be difficult. In specialist clinics, measurements of NO in exhaled air, cell differentials and mediators in induced sputum, and typical features such as fragmented surface epithelium, presence of eosinophils and thickened basement membrane in mucosal biopsies can all be used, but most often a more pragmatic approach is needed. Treatment response to inhaled corticosteroids will often be the indicator of the presence of asthma or COPD to the clinician but the evaluation by treatment has never really been examined properly in prospective studies.

For most of the other differential diagnoses, the combination of a good clinical assessment together with simple investigations will usually resolve any uncertainty; often a chest radiograph will be helpful.

In the middle-aged and elderly, congestive heart failure is an important differential diagnosis. In many text books, fine basilar inspiratory crackles on auscultation is referred to as a good sign of heart failure but often minor abnormalities can be found in COPD as well. In this case, a chest radiograph is often helpful showing a dilated heart and flow shift indicating heart failure. Spirometry will more often show volume restriction than airflow restriction but particularly in more severe cases airflow limitation secondary to heart failure can be seen.

A diagnosis of bronchiectasis is often helped by a history of large volumes of sputum. It can sometimes be seen on a plain chest radiograph but often a diagnostic high-resolution computed tomography (HRCT) scan is required for diagnosis. Caution in interpreting bronchiectasis on an HRCT scan as absence of regular COPD is warranted as the two diseases often coexist.

Tuberculosis is an important differential diagnosis in high-prevalence countries and a chest radiograph is important. Obstructive bronchiolitis is seen much less frequently than COPD, is more frequent in younger patients and is often associated with rheumatoid arthritis or extensive fume exposure but smoking may be causative as well. An HRCT scan, preferably with expiration scans, is needed. Diffuse panbronchiolitis is rare and not smoking-related; HRCT is needed for diagnosis.

When differential diagnoses have been excluded, a post-bronchodilator FEV_1/FVC ratio <0.7 confirms the diagnosis of COPD. Again, caution is required when using this fixed cut-off value. The normal value for the FEV_1/FVC ratio is age-dependent and whereas a ratio <0.7 is clearly abnormal in a 40-year old it is close to the expected value for an 80-year old. Thus, COPD is likely to be under-diagnosed in younger adults and "over-diagnosed" in the elderly; whether this is truly over-diagnosis or actually abnormality associated with excess risk (like arterial hypertension associated with age) is currently unknown. If spirometry is requested on the basis of breathlessness this dilemma is usually trivial. However, an increasing number of more affluent patients are being diagnosed in health programmes or as a result of screening and have no symptoms. In this case, liberal use of the diagnostic label of COPD is unlikely to be very helpful in those with borderline abnormal spirometry.

Once a diagnosis of COPD is established it is recommended that staging takes place. According to guidelines, classification of the severity of the disease is based on FEV_1 expressed in per cent of predicted value as shown in Table 2.3. In addition to problems arising from the use of different reference values, or lack of locally derived reference values in certain ethnic population groups, it is well-known that composite scores including lung function, symptoms, body weight and exercise tolerance have better

Table 2.3 Severity grading of chronic obstructive pulmonary disease (COPD) according to GOLD [1].

Stage I:	Mild $FEV_1/FVC < 0.70$	$FEV_1 \geq 80\%$ predicted
Stage II:	Moderate $FEV_1/FVC < 0.70$	$50\% \leq FEV_1 < 80\%$ predicted
Stage III:	Severe $FEV_1/FVC < 0.70$	$30\% \leq FEV_1 < 50\%$ predicted
Stage IV:	Very severe $FEV_1/FVC < 0.70$	$FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

predictive value than FEV_1 alone; a good example of such a score is the BODE index [6]. If such a score is not used in its suggested form, several of the variables should nevertheless be registered, see later.

Symptoms in COPD

The most common symptoms seen in COPD are breathlessness, cough and fatigue. There is no good correlation between lung function and symptoms of COPD, not even the standardized scoring of breathlessness correlates well with FEV_1; the important message being that a simple physiological measure can never substitute a symptom history.

Breathlessness

Breathlessness is the most significant symptom in COPD and it is associated with significant disability, poor quality-of-life and poor prognosis.

Although the degree of breathlessness in a single patient can be difficult to understand – let alone explain, properly – we understand a lot about the mechanisms underlying the sensation of breathlessness in COPD [7]. Breathlessness is defined as an awareness of increased or inappropriate respiratory effort and is assumed to relate to an awareness of the motor command to breathe. The terms used to describe breathlessness may vary with the stimulus used to provoke it and despite the increased time for expiration many COPD patients describe the sensation of breathlessness as one of inspiratory difficulty [8]. The intensity of breathlessness is best related to changes in end-expiratory lung volumes during exercise and this fact probably explains the need to look at changes in measurements other than FEV_1 and FVC for characterizing COPD patients' disability or for assessing effects of treatment. For this purpose, measurements of inspiratory capacity (IC) may be better suited (see Chap. 3).

In early stages of COPD, patients often modify their behaviour in order to cope with the sensation of breathlessness. Patients avoid climbing stairs, get help with cleaning and shopping, and to the author it has always been a mystery how otherwise well-functioning subjects can ascribe increasing breathlessness associated with ordinary tasks as being merely the results of "age." However, with increasing severity of COPD, breathlessness becomes an unavoidable symptom and in severe and very severe COPD there is rarely any time when patients are asymptomatic. In very severe COPD, the patient is usually breathless on minimal exertion but due to the poor correlation between FEV_1 and breathlessness some patients may have surprisingly high levels of activity, even in late-stage COPD.

The degree of breathlessness can be measured using a number of different scales and questionnaires. The simple MRC dyspnoea scale [9] is a useful tool but as it was originally developed for assessing breathlessness in epidemiological surveys in the workplace, it is relatively insensitive to changes. However, a slightly modified version of the MRC Questionnaire, as shown in Table 2.4, has been translated into numerous languages, is easy and quick to use and it relates well to measures of health status and has additional predictive value to that of FEV_1 when it comes to predicting resource utilization and mortality [10].

The baseline and transitional dyspnoea indices of Mahler et al. [11] are much more specific and more susceptible to change but in addition they are much more time-consuming to use for clinicians; its main role lies in evaluating interventions with a supposed effect on breathlessness. The Borg category scale, as shown in Table 2.5, is

Table 2.4 The Medical Research Council dyspnoea scale (Modified).

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying or walking up a slight hill
2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking 100 m or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Table 2.5 The Borg scale.

0 Nothing at all
0.5 Very, very slight (just noticeable)
1 Very slight
2 Slight (light)
3 Moderate
4 Somewhat severe
5 Severe (heavy)
6
7 Very severe
8
9
10 Very, very severe (almost maximal)
Maximal

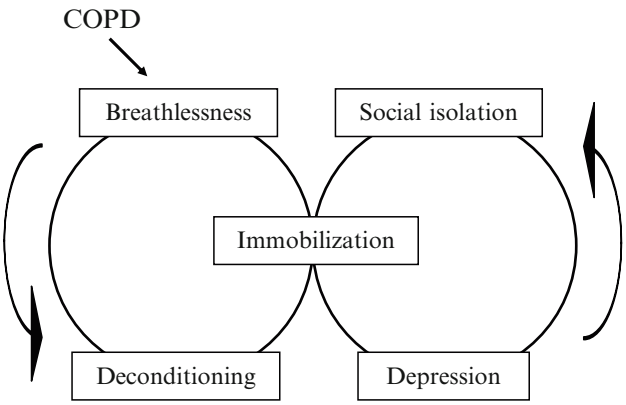


Fig. 2.1. The impact of breathlessness in chronic obstructive pulmonary disease (*COPD*)

often used in the exercise laboratory as it measures short-term changes in perceived intensity during a particular task, e.g., during shuttle walk testing. It is simple and easy to explain. As an alternative, visual analogue scales can be used; however, like the Borg scale, this approach is for use in task-specific situations and cannot be used for assessing the degree of breathlessness associated with usual daily tasks.

Although there is an increasing focus on systemic manifestations of COPD (see later), breathlessness is a major cause of deconditioning and subsequent muscle wasting in COPD. This has profound effects on the life of COPD patients as illustrated in Fig. 2.1.

Cough and Sputum Production

Cough is a respiratory defence mechanism protecting the airways and cough is the major method of clearing excess mucus production [12]. In COPD patients, cough as a symptom is almost as common as breathlessness and may actually precede the onset of breathlessness [8]. Cough is usually worse in the morning but seldom disturbs the patient's sleep; it can, nevertheless, be disabling because of the embarrassment felt by many patients when they have bursts of productive cough on social occasions and may contribute to the isolation often imposed on patients due to breathlessness (see Fig. 2.1). The actual role of cough and phlegm on the natural history of COPD has been debated for decades. Currently, most epidemiological studies seem to show that the symptoms of chronic bronchitis do not increase the risk of developing COPD in smokers with normal lung function [13]. However, the presence of these same symptoms in patients with severe and very severe COPD predict both a more rapid decline in lung function and more frequent acute exacerbations of COPD [14, 15].

In patients with more severe COPD, cough syncopy is frequent. It arises from the acute increase in intrathoracic pressure during cough, producing a transient reduction in venous return and cardiac output. A similar mechanism is thought to be the explanation for cough fractures.

Cough is difficult to measure. Questionnaires exist but their validity is questionable and devices for direct measurement of cough are still in the development stage.

Wheezing

Wheezing is generally seen as an asthma symptom but frequently occurs in COPD as well. However, nocturnal wheeze is uncommon in COPD and suggests the presence of asthma and/or heart failure [2, 3].

Fatigue

Fatigue is frequently reported by COPD patients. It is a ubiquitous and multifactorial symptom not to be confused with simple physical exhaustion due to breathlessness but is more an awareness of a decreased capacity for physical and mental activity due to lack of resources needed to perform the activity in question. Fatigue has been identified as a serious consequence in a number of chronic conditions and will undoubtedly be a focus of attention in the future characterization of COPD. No standardized measurement scales for fatigue in COPD exist.

Other Symptoms

Chest pain is a common complaint in COPD, mostly secondary to muscle pain. However, it should be noted that ischaemic heart disease is frequent in any population of heavy smokers and COPD patients may be at particular risk. Acid reflux occurrence is also frequent in COPD.

Ankle swelling may result from immobility secondary to breathlessness or as a result of right heart failure. Anorexia and weight loss often occur as the disease advances and should be mirrored by measurements of body mass index (BMI) and body composition (see later). Psychiatric morbidity is high in COPD, reflecting the social isolation, the neurological effects of hypoxaemia and possibly the effects of systemic inflammation; this is described in more detail in Chap. 17. Sleep quality is impaired in advanced disease [16] and this may contribute to neuropsychiatric comorbidity.

Assessment of the Patient Suspected of COPD

History

An accurate history, not least for the purpose of excluding differential diagnoses, should include family history of heart and lung diseases, childhood diseases (atopic and infectious), environment in which the subject grew up including exposures to fumes gas and dust, education and occupational experiences.

Most patients are, or have been, smokers with cigarette smoking dominating. Depending on the environment, patients may underestimate their tobacco use when confronted with questions on life-time smoking habits. Calculation of pack-years of smoking provides a useful estimate of smoking intensity (1 pack-year is equivalent to 20 cigarettes smoked per day for 1 year – or ten cigarettes smoked per day for 2 years) but additional information is needed on debut of smoking and inhalation habits. Objective verification of smoking status can be helpful and is often used in smoking cessation programmes, most often using exhaled breath carbon monoxide or urinary nicotine measurement.

Occupational exposures to organic dust and fumes contribute to the accelerated decline in the lung function characteristic of COPD [4, 5]. The evidence for outdoor as well as indoor pollution is much weaker except for areas where indoor burning of biomass fuel has lead to more extensive exposure.

Finally, a social history is needed in most COPD patients. Often the carer for the patient will have the same age and possibly other chronic diseases and the need for social support may depend on this. Also, the smoking habits of the family may determine the outcome of smoking cessation intervention.

Physical Signs

Not surprisingly, it is difficult to come up with standardized guidance for a disease that spans from almost normal health to terminal disease. The physical signs in patients with COPD will invariably depend on the severity of disease. A physical examination will in general be a poor tool for detecting mild or moderate COPD, and the reproducibility of physical signs have been shown to be very variable. In contrast, physical signs are more specific and sensitive for severe COPD.

Patients with mild and moderate disease appear normal in clinic and usually have done little to reduce their normal daily activities. Patients with severe COPD, and indeed very severe COPD, will appear breathless just from entering the clinic room, and even a short history will often be sufficient to realize that they are distressed. These patients will often appear to have a “barrel chest.” This used to be ascribed to emphysema, but more likely it represents the visible component of hyperinflation, where patients, in order to meet the ventilatory demands, increase their end-expiratory lung volume. Patients will often sit leaning forward with their arms resting on a table in front of them or on some other stationary object in order to use the ribcage and larger muscles to function as inspiratory muscles. Often, these patients often use pursed-lips breathing, presumably to avoid small airways collapse during tidal breathing.

The general stature of the patients should be observed. Weight loss, especially when there is clear muscle atrophy, can be a sign of severe disease, emphysematous-type COPD and likely a systemic effect of COPD, possibly due to systemic inflammation.

The patient’s breathing should also be observed. Use of accessory muscles indicates severe disease. Percussion of the chest is of little, if any, use in patients with COPD.

A tympanic percussion note is not specific for pulmonary hyperinflation and it is dubious if clinicians can use percussion for estimation of diaphragmatic motion.

On auscultation, patients with COPD generally have a noisy chest although patients with significant emphysema in a stable state can have remarkably few chest sounds. Although significant research has been carried out on chest sounds, it is unclear to this author if it should have any impact on the daily management of patients with COPD where the value of auscultation is generally limited – except in cases where comorbidities or complications may be detected this way; e.g., as unilateral wheeze in cases of endobronchial tumour, or decreased chest sounds on one side due to pneumothorax. Auscultation of the heart is an essential part in the physical examination of COPD patients. Severe COPD is associated with tachycardia at rest and with increasing severity of disease the risk of atrial fibrillation increases. Ventricular gallop rhythm, increases in the pulmonary second heart sound and murmurs of pulmonary or tricuspid insufficiency can all be signs of cor pulmonale.

A raised JVP, hepatomegaly and peripheral oedema have all been considered as signs of pulmonary hypertension and cor pulmonale. However, these signs are not specific for cor pulmonale as a raised JVP may result from increased intrathoracic pressure secondary to dynamic hyperinflation and hepatomegaly may be illusive due to downward displacement of the liver by the diaphragm in the hyperinflated chest. Finally, peripheral oedema can be the result of both altered renal function as a result of hypoxaemia and the result of simple inactivity.

Body Habitus

Weight, or rather BMI, has been shown to be a very strong predictor of prognosis with rapidly increasing risk of dying when BMI falls, even within the normal range [17, 18]. Some studies indicate that measures of fat-free mass can add further information [19]; the easiest and cheapest way of measuring body composition is by using measurements of body impedance. Measures of skin-fold thickness or mid-thigh diameter may also be useful but currently these methodologies have not been validated to the extent of body impedance. A BMI <20 kg/m^2 will denote a subject at risk as will a fat-free mass index <15 kg/m^2 in women and <17 kg/m^2 in men.

Lung Function Tests

The role of lung function tests COPD is crucial for diagnosis, assessment of severity, prognosis and for monitoring the course of the disease. The physiologic assessment of the COPD patient is described in detail in Chap. 3.

Arterial Blood Gases

In stable state, there is a general relationship between reductions in FEV_1 and arterial oxygen tension (P_aO_2), whereas arterial carbon dioxide tension (P_aCO_2) usually remains within the normal range until FEV_1 falls below 1.0–1.2 l (<30% of predicted) and even then large variations are found. Measurement of arterial blood gases with the patient breathing room air is recommended for assessing patients with moderate or severe COPD. Often, a practical approach is to initially measure arterial oxygen saturation ($SatO_2$) by means of pulse oximetry. If $SatO_2$ is <92%, arterial gases should be measured.

Exercise Testing

Exercise capacity can be assessed in different ways, but outside the physiology laboratorium; either a 6 min walk test or incremental shuttle walk testing is used. The correlation between lung function and exercise capacity is poor in the individual patient but in groups there are clear correlations, particularly with measures that reflect hyperinflation such as IC. As mentioned earlier, breathlessness during exercise can be measured easily using either a Borg scale (Table 2.5) or a visual analogue scale. During exercise, the severity of breathlessness is closely related to ventilation and to the severity of dynamic hyperinflation. Many, but not all, patients will desaturate during exercise and the extent of arterial desaturation is related to both TL_{CO} and resting blood gases.

Assessing exercise capacity is of particular value in patients whose breathlessness appears to be out of proportion to simple spirometric measures; it can also provide information of value for assessing cardiac disease through aligning the exercise test with a cardiac exercise test used for assessing ischaemic heart disease. Exercise testing is also usually done before and after pulmonary rehabilitation and is increasingly being used to assess the value of other interventions, including pharmacological treatments, see Chap. 3. In parallel with exercise testing, tests of muscle strength may be applied. Simple measures, e.g., quadriceps muscle strength, have been shown to be of value in COPD [20].

Blood Tests

Blood tests are often of little use in COPD but can be used for identifying polycythaemia in patients with severe COPD as this is associated with risk of subsequent vascular events, and there is some evidence to suggest that venesection may improve exercise tolerance as well as mental capacity. As in other chronic diseases, anaemia can occur as a systemic consequence and is generally a marker of poor prognosis; anaemia associated with COPD is usually normochromic and normocytic, characteristic of the anaemia of chronic disease. There is no indication for assessing blood biochemistry routinely in COPD patients and although there is a growing research interest in markers of systemic inflammation in COPD, data so far available are difficult to implement in clinical practice.

α_1-Antitrypsin levels should be measured in all patients aged <50 years, and in those with a family history of emphysema at an early age.

Radiology

There are no specific features of COPD on a plain chest radiograph. A radiological diagnosis of "emphysema" on a plain chest radiograph is usually based on lung overinflation and should be reported as such. Overinflation of the lungs results in low diaphragms, an increase in the retrosternal airspace and an obtuse costophrenic angle on the postero-anterior or lateral chest radiograph. The vascular changes associated with emphysema can often be seen on a plain chest radiograph by a reduction in the size and number of pulmonary vessels, particularly at the periphery of the lung, vessel distortion and areas of transradiancy; however, assessment of vascular loss in emphysema is very dependent on the quality of the radiograph.

Computed tomography (CT) can be used for the detection and quantification of emphysema, either using semiquantitative visual assessment of low-density areas on the CT scan or by using measures of lung density to quantify areas of low x-ray attenuation. Several studies have shown that visual evaluation of the CT scan can locate areas

of macroscopic emphysema in post mortem or resected lungs. The use of HRCT with thin slices does not improve the detection of mild emphysema; however, HRCT can be used to distinguish between the various types of emphysema.

More quantitative approaches to assessing macroscopic emphysema have been employed [21, 22]. They use the original virtue of the CT-scanner as a densitometer. As emphysema develops, alveolar wall mass decreases and this leads to a decreased CT lung density. Initial experiences suggest that this can be used to measure progression of emphysema, although the radiation involved precludes its use as a frequent measure of disease progression.

Magnetic resonance (MR) scanning using hyperpolarised gases such as Helium is still in its pioneering phase.

Electrocardiography and Echocardiography

Routine electrocardiography is not required in the assessment of patients with COPD unless cardiac comorbidities are suspected, including atrial fibrillation. ECG is an insensitive technique in the diagnosis of cor pulmonale.

Echocardiography can be used to assess the right ventricle and for the detection of pulmonary hypertension. In addition, it provides an opportunity to check for cardiac comorbidity, particularly in patients with breathlessness out of proportion to the findings on general examination and from pulmonary function testing.

Assessment of the Patient with Acute Exacerbation of COPD

This issue is dealt with in detail in Chap. 12 and has been reviewed recently [23].

Summary

COPD should be suspected in any patient aged 40 years or more with symptoms of cough, sputum production, or breathlessness and/or a history of exposure to risk factors, in particular smoking. Spirometry is needed for both diagnosis and staging, although other parameters such as breathlessness, exercise tolerance and body mass and/or body composition should be included in the staging procedure.

In the assessment of patients suspected of COPD, several differential diagnoses should be considered. Assessment can usually be done using fairly simple clinical tools, although advanced imaging seems to be a promising tool for the near future.

References

1. Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS (2001) Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:1256–1276, Updated guideline available on www.goldcopd.com (last accessed 7 February 2007)
2. National Collaborating Centre for Chronic Conditions (2004) Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 59(Suppl 1):1–232
3. Celli BR, MacNee W (2004) ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23:932–946

4. Anto JM, Vermeire P, Vestbo J, Sunyer J (2001) Epidemiology of chronic obstructive pulmonary disease. Eur Respir J 17:982–994
5. Annesi-Maesano I (2006) Epidemiology of chronic obstructive pulmonary disease. Eur Respir Mon 11:41–70
6. Celli BR, Cote CG, Marin JM et al (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012
7. Calverley PMA (1995) Ventilatory control and dyspnea. In: Calverley PMA, Pride NB (eds) Chronic Obstructive Pulmonary Disease. Chapman and Hall, London, pp 205–242
8. O'Donnell DE, Bertley JC, Chan LKL, Webb KA (1997) Qualitative aspects of exertional breathlessness in chronic airflow limitation. Am J Respir Crit Care Med 155:109–115
9. Medical Research Council Committee on Research into Chronic Bronchitis (1966) Instructions for Use of the Questionnaire on Respiratory Symptoms. W.J. Holman, Dawlish
10. Vestbo J (1993) Predictors of mortality, COPD morbidity, and cancer. With special reference to respiratory symptoms, lung function, and occupational exposure to cement dust. Dan Med Bull 40:1–16
11. Mahler DA, Weinberg DH, Wells CK, Feinstein AR (1984) The measurement of dyspnea: contents, interobserver agreement and physiologic correlates of two new clinical indices. Am Rev Respir Dis 145:467–470
12. Smith JA, Calverley PM (2004) Cough in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 17:393–398
13. Vestbo J, Lange P (2002) Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 166:329–332
14. Vestbo J, Prescott E, Lange P, The Copenhagen City Heart Study Group (1996) Association of chronic mucus hypersecretion with FEV_1 decline and COPD morbidity. Am J Respir Crit Care Med 153:1530–1535
15. Vestbo J, Hogg JC (2006) Convergence of the epidemiology and pathology of COPD. Thorax 61:86–88
16. Calverley PMA, Brezinova V, Douglas NJ et al (1982) The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis 126:206–210
17. Schols AM, Slangen J, Volovics L, Wouters EFM (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797
18. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP (1999) Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:1856–1861
19. Vestbo J, Prescott E, Almdal T et al (2006) Body mass, fat free body mass and prognosis in COPD patients from a random population sample. Am J Respir Crit Care Med 173:79–83
20. Swallow EB, Reyes D, Hopkinson NS et al (2006) Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax 62(2):115–120. doi:10.1136/thx.2006.062026
21. Müller NL, Staples CA, Miller RR, Abboud RT (1988) 'Density mask'. An objective method to quantitate emphysema using computed tomography. Chest 94:782–787
22. Coxson HO, Rogers RM, Whittall KP et al (1999) A quantification of lung surface area in emphysema using computed tomography. Am J Respir Crit Care Med 159:851–856
23. Vestbo J (2006) Clinical assessment, staging and epidemiology of chronic obstructive pulmonary disease exacerbations. Proc Am Thor Soc 3:252–256

3

Physiologic Assessment of COPD

Justin Travers, Pierantonio Laveneziana,
and Denis E. O'Donnell

Key Points:

- The pattern of pathophysiological abnormality in COPD is heterogeneous, highly variable, and unique to each individual.
- The standard criterion for a COPD diagnosis is a FEV_1/FVC ratio of less than 0.7 after the administration of a bronchodilator; however, alternative criteria have been recently proposed.
- The FEV_1 does not provide information about the extent of expiratory flow limitation (EFL) or dynamic lung hyperinflation (DH) and correlates poorly with measures of disability such as dyspnoea, health status, and exercise capacity.
- The presence of EFL can be detected by comparing tidal and maximal flow-volume loops, by the negative expiratory pressure technique, by manual compression of the abdomen, by the forced oscillation technique or by invasively using an esophageal balloon catheter.
- The inspiratory capacity (IC) is a simple measure of DH which correlates better with symptoms and exercise performance than the FEV_1.
- Exercise testing provides information about functional capacity and prognosis not available from resting pulmonary function testing.
- Six-minute walk and shuttle walk tests are simple to perform and useful tests of functional disability; however, the formal laboratory cardiopulmonary exercise test (CPET) has several advantages including the ability to assess DH and EFL during exercise.
- Currently the high-intensity exercise endurance protocol appears to be the most responsive exercise test for the evaluation of the efficacy of therapeutic interventions in COPD.
- There is interest in developing a composite score to accurately reflect COPD severity that incorporates several dimensions of the disease.

Keywords Dynamic lung hyperinflation • dyspnoea • expiratory flow limitation • inspiratory capacity

Introduction

COPD is an inflammatory disease involving the small and large airways, the lung parenchyma, and its vasculature. The pattern of pathophysiological abnormality is heterogeneous, highly variable, and unique to each individual. No single measurement

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_3,

adequately characterizes the full extent of the physiological impairment in any given patient. However, by using a variety of validated tests we are now in a position to uncover the pathophysiological diversity in individual patients with COPD with a fair degree of precision. The purpose of this review is to evaluate the clinical utility of the various physiological tests conducted during both rest and exercise for the diagnosis and modern management of COPD.

Making the Diagnosis

COPD is a heterogeneous disorder with the consistent feature of airflow obstruction that is not fully reversible [1]. The presence of airflow obstruction cannot be reliably determined from clinical history, physical examination, and radiologic imaging [2, 3]; so, pulmonary function testing is essential for diagnosis [1, 4]. The hallmark of airflow obstruction is a reduced ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC). The FEV_1 is preferred over other measures of expiratory air flow such as the peak expiratory flow rate (PEFR) or values calculated from the flow volume loop as it is less effort dependent and more reproducible [5].

The criterion for a diagnosis of COPD used by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a FEV_1/FVC ratio of less than 0.7 after the administration of a bronchodilator [1]. There is however a significant overlap between the FEV_1/FVC ratios of individuals with COPD and those of healthy individuals and the choice of 0.7 as a cut-off is somewhat arbitrary. For example, the FEV_1/FVC ratio declines with age, so COPD may be misdiagnosed in a proportion of healthy older adults [6]. By contrast, some individuals with advanced COPD may have a normal ratio, although in this case the FEV_1 and FVC are both reduced [4].

The forced expiratory maneuver in COPD is often incomplete. The expiratory time required to completely empty the lungs in severe COPD is often markedly prolonged reflecting the slow time constant for lung emptying of many alveolar units. Moreover dynamic airway compression during maximal expiration may cause respiratory discomfort forcing the patient to stop before standard end-of-test criteria are met. When this occurs the FVC underestimates vital capacity (VC) to an uncertain degree. To counter this uncertainty, the forced expiratory volume in 6 s (FEV_6) [7] has been proposed to be used in place of the FVC with appropriate adjustment of the reference ranges [8]. The FEV_6 could be an easier test for patients to perform [9], however, it may slightly reduce the sensitivity of spirometry in detecting airflow obstruction, especially in older individuals and those with mild COPD [10]. For diagnostic purposes, a FEV_1/FEV_6 ratio of 0.73 has been proposed as the equivalent of the standard FEV_1/FVC ratio of 0.7 [8]. Further studies to determine the appropriate cut points for the diagnosis of COPD are required before the FEV_6 can be recommended in place of the FVC for the diagnosis of COPD.

An alternative approach to the problem of FVC variability is to use the (slow) vital capacity (VC) as the denominator for the ratio [4]. This gives a more accurate measure of vital capacity but requires an additional measurement to be made and so may not be practical for mass screening.

An alternative to the current GOLD criteria for the diagnosis of airflow obstruction that may reduce the potential for overdiagnosis of older individuals is to define airflow obstruction as a FEV_1/FVC ratio below the lower limit of predicted normal (LLN) adjusted for age, gender, and height [4]. Although, by this definition, 5% of the apparently healthy population will be diagnosed as having COPD, this approach probably

identifies fewer subjects as having COPD than the use of a fixed FEV_1/FVC ratio. A LLN-based approach can also be used with the FEV_6 or the VC as the denominator in the ratio. In principle, all programmable spirometers could calculate the LLN if suitable reference equations were available. However, appropriate reference equations with post-bronchodilator spirometry in a variety of age groups are not available for many populations. While the merits of the various diagnostic criteria continue to be debated, the majority of patients with COPD will be accurately identified regardless of the method chosen.

Many studies have evaluated the practicalities of screening at-risk individuals for COPD in a community or primary care setting [11–13]. Although concerns have been raised about the accuracy of spirometry in this setting and post-bronchodilator measurements may not be available, screening is able to find cases at a relatively low cost. The value of finding cases has been questioned as the diagnostic label does not appreciably increase smoking cessation rates [14]. Symptomatic individuals however may be offered effective treatment and education, interventions that, unlike smoking cessation, may not alter the rate of FEV_1 decline but have significant impact on morbidity. In a recent study, around 50% of individuals diagnosed with COPD through screening received new treatment as a result of the diagnosis [15].

Evaluation of Disease Severity

An ideal measure of COPD severity would reflect impairment in the domains of morbidity, activity limitation, and participation restriction. The FEV_1 provides some information on severity of airway obstruction and has for many years been used as a measure of COPD severity but relates poorly to these domains.

Measurement of Airway Function

The most studied and validated measure of expiratory airflow is the FEV_1. This simple measurement provides a reproducible and relatively effort-independent measure of the degree of airways narrowing during expiration. The GOLD classification of COPD severity is based on FEV_1 in combination with the presence or absence of respiratory failure [1]. Arbitrary FEV_1 post-bronchodilator predicted values of >80%, 50–80%, 30–50%, and <30% define the boundaries of mild, moderate, severe, and very severe COPD, respectively. In COPD, however, the FEV_1 is prone to measurement artifacts related to volume history and gas compression. The FEV_1 gives no information about the extent of expiratory flow limitation or dynamic lung hyperinflation and correlates poorly with measures of disability such as dyspnoea, health status, and exercise capacity [16–22]. This poor statistical correlation is borne out of clinical observation where patients with the same measured FEV_1 (expressed as a percentage of predicted) may vary greatly in their level of disability; patients may deteriorate clinically, either acutely (e.g., during exacerbations) or chronically, while preserving spirometric FEV_1. Moreover, patients may achieve considerable improvements in symptoms and exercise endurance as a result of interventions such as bronchodilators, oxygen therapy, or exercise training, with little or no change in the FEV_1 [23–25]. FEV_1 expressed as a percent of predicted has been shown to predict mortality in COPD [26–28].

The pathophysiologic hallmark of COPD is the development of expiratory flow limitation (EFL). EFL is said to be present when the expiratory flows generated during

spontaneous tidal breathing represent the maximal possible flow rates that can be generated at that operating lung volume [29]. Under conditions of EFL, expiratory flow rates are independent of expiratory muscle effort and are determined by the static lung recoil pressure and the resistance of the airways upstream from the flow-limiting segment [29, 30]. The presence of EFL at rest (or during exercise) is an attractive alternative to the FEV_1 in assessing COPD severity as EFL shows a stronger correlation with dyspnoea than FEV_1 [31].

Measurement of EFL is not currently as straightforward as measurement of FEV_1. The presence of EFL can be suspected by comparing tidal and maximal flow-volume loops. If the tidal loop extends to, or beyond, the maximal loop, EFL may be present [32, 33] (Fig. 3.1). Unfortunately, this comparison is not always reliable [34]. The presence or absence of EFL may be measured by the negative expiratory pressure technique (NEP) [35], manual compression of the abdomen [36] or invasively by using an esophageal balloon catheter [37]. The forced oscillation technique (FOT)

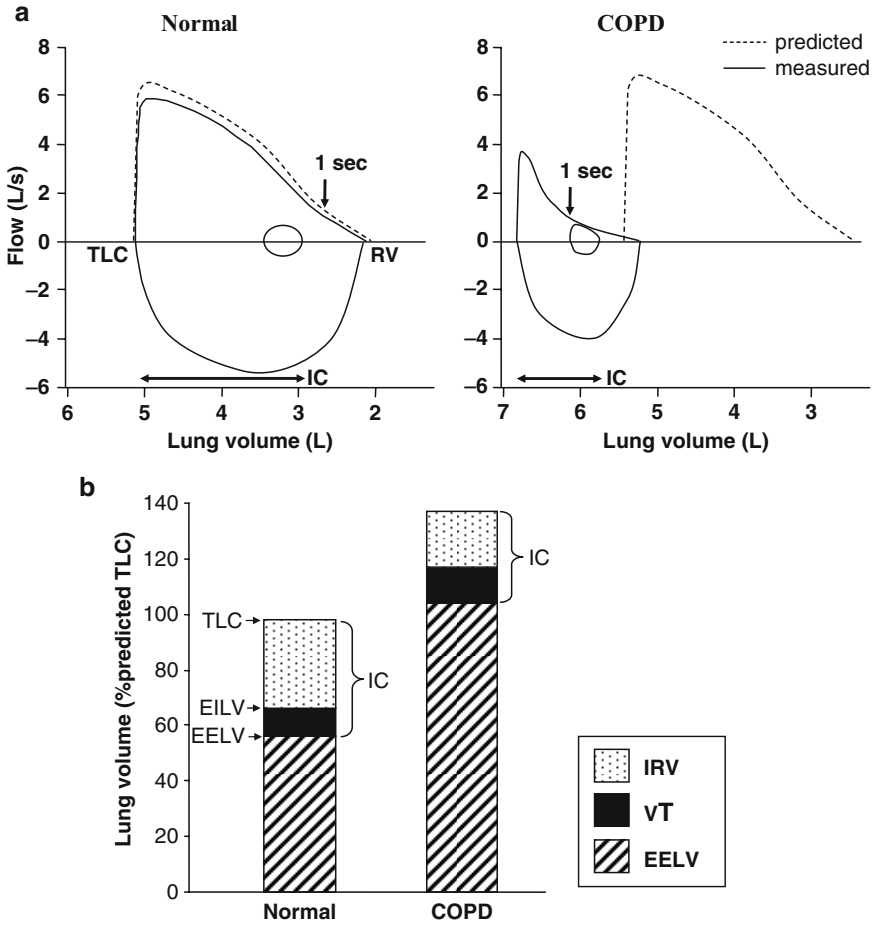


Fig. 3.1. (**a**) Maximal and tidal flow-volume loops in a healthy subject and in a patient with COPD. The patient exhibits markedly reduced FEV_1, expiratory flow limitation and lung hyperinflation, i.e., reduced IC. (**b**) Lung volume compartments in the same patient. Note the marked lung hyperinflation, with reduced IC compared with normal. See text for abbreviations (With permission from Reference [152])

shows promise as a noninvasive tool to detect EFL [38]. Although requiring further validation, multiple breaths can be measured over time allowing EFL to be continuously monitored using the FOT. Several other measures of expiratory air flow can be derived from analysis of the flow-volume loop. These measures include the maximal mid-expiratory flow ($FEF_{25–75\%}$) and the forced expiratory flow at 25%, 50%, or 75% of FVC. Interpretation of these tests can be difficult as they are less reproducible than the FEV_1 and the normal range is wider. The maximal mid-expiratory flow depends on FVC, which varies with expiratory time in subjects with COPD. An abnormal result has poor specificity for symptoms or mortality risk and the predictive value of these measures is unlikely to be as good as the FEV_1 [39].

Another measure is the peak expiratory flow rate (PEFR) which can be measured by the patient using a relatively inexpensive portable peak flow meter. The measured value reflects patient effort (fullness of inhalation, expiratory muscle effort) as well as airways resistance. In COPD, some of the PEFR may be produced by compression of the central airways from positive intrathoracic pressure rather than from air flow past the flow-limiting segments of the bronchial tree. The PEFR correlates with mortality in COPD, and retains prognostic value after adjustment for FEV_1 [40]. This may be because it is a measure of a patient's vigor as well as of pulmonary function.

Measures of airways resistance derived at plethysmography or using FOT correlate less well with relevant patient outcomes than other measures.

Measurement of Lung Hyperinflation

The relaxation volume of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of chest wall. In COPD, static lung hyperinflation refers to the increase in functional residual capacity (FRC) above the predicted normal value (Fig. 3.1) and is primarily due to emphysema, which increases lung compliance. In the presence of EFL, end-expiratory lung volume (EELV) is also dynamically determined and varies with the time constant for emptying of the respiratory system, the inspired tidal volume, and the expiratory time available [41]. Dynamic lung hyperinflation (DH) refers to an increase in EELV above the statically determined value. In flow-limited patients, EELV is a continuous dynamic variable that depends on the prevailing level of EFL and breathing pattern.

The assessment of lung volumes is relevant to COPD severity as lung hyperinflation, which commonly accompanies EFL in COPD patients, results in negative mechanical and sensory consequences and contributes importantly to dyspnoea and activity limitation [42–46]. Assessment of absolute lung volumes is however more difficult in COPD patients than in other groups. Gas dilution methods will underestimate FRC as they do not measure the volume of trapped gas or bullae. Plethysmography is generally more accurate; however, it may overestimate intra-thoracic gas volume (ITGV) by about 60 mL in patients with COPD in addition to the overestimation arising from patients using a panting frequency over 60 breaths/min, hiatal hernias, and other sources of intrathoracic gas [47–49]. Plethysmography relies on adding inspiratory capacity (IC) to ITGV to give total lung capacity (TLC); however, IC depends on the degree of DH. In subjects with severe COPD, exertion prior to plethysmography can cause further DH which will result in an underestimation of IC and TLC unless the technician waits for the DH to settle to resting levels prior to testing.

A simpler measure is the IC which can be measured at spirometry in a primary care setting and does not require determination of absolute lung volumes. A reduced resting IC can indicate the presence of lung hyperinflation in the setting of EFL [50]. The IC

represents the operating limits for tidal volume expansion during the exercise and correlates well with symptoms and exercise performance [23, 46, 51, 52] more so than the FEV_1. Moreover, a severely reduced IC/TLC ratio (i.e., <25%) has recently been shown to be an independent predictor of poor survival in COPD [53]. Improvements in IC during recovery from an acute exacerbation of COPD mirror the improvement in dyspnoea even though FEV_1 changes little [43]. However, if TLC and FRC rise in parallel, the IC may be unaltered despite significant lung hyperinflation [23, 54–56]. In this case, absolute lung volumes should be measured. Despite this limitation, the IC provides useful complementary information to that of the FEV_1 regarding the nature and degree of respiratory impairment in individuals with COPD.

Lung hyperinflation can also be detected by a variety of radiographic techniques [57–61]. The methodology for radiographic lung volume measurement (taken at TLC) is not standardized and is rarely used in clinical practice. Future refinements in high-resolution computed tomography scanning promise to facilitate identification of regional distribution patterns of air space distention and lung volume quantification in COPD patients.

No standardized stratification system currently exists for assessment of severity of resting lung hyperinflation. We recommend specifying the volume measured, TLC, EELV, or residual volume (RV), and the value as a percent of predicted normal. Values above 120% of predicted normal or values that exceed the upper limit of predicted normal are considered abnormal.

Measurement of Gas Transfer

Another dimension of COPD is the degree of pulmonary alveolar and vascular destruction caused by the pathologic process of emphysema. While this process leads to loss of pulmonary elastic recoil and parenchymal support for collapsible airways resulting in EFL and to static hyperinflation, it also adversely affects gas exchange due to reduction in alveolar surface area, reduction in the number of pulmonary capillary beds, and increased ventilation-perfusion mismatching. These factors result in a reduction in the diffusing capacity of the lung for carbon monoxide (DL_{CO}). A reduced DL_{CO} in the presence of airflow obstruction and the absence of a restrictive pattern suggests emphysema [4, 62, 63] whereas a normal or elevated DL_{CO} in the presence of airflow obstruction and the absence of a restrictive pattern suggests an alternate COPD phenotype such as asthma, pure chronic bronchitis, or pure small airways disease. Relevant to many COPD patients, the DL_{CO} may be underestimated by up to 5% in smokers due to an increased partial pressure of carbon monoxide in the blood reducing the gradient for the diffusion of carbon monoxide [64]. A low DL_{CO} is predictive of oxyhemoglobin desaturation during exercise [65, 66], presumably because oxygen uptake is limited by the rate of gas transfer in the setting of the reduced pulmonary capillary transit time of exercise. A low DL_{CO} is associated with a greater severity of baseline dyspnoea and explains a large proportion of the variability in the severity of baseline dyspnoea between COPD patients [67]. A low DL_{CO} is also associated with a greater degree of DH and dyspnoea during exercise among patients with a similar FEV_1 [46].

Testing Airway Reversibility

The FEV_1 is the best-studied measurement used to evaluate airway reversibility with bronchodilators. Standard reversibility testing measures the short-term change in FEV_1 following administration of a bronchodilator, usually 400 mcg of salbutamol via a spacer device. An increase in FEV_1 and/or FVC by 12% and 200 mL compared

with baseline is likely to indicate airways reversibility rather than random variation of the measurement [4]; however, the use of these criteria to define reversibility is arbitrary as no evidence-based definition of reversibility currently exists. The magnitude of bronchodilator response in any given patient will vary with time and will depend on the type and dosage of bronchodilator used [68]. The majority of COPD patients will show positive bronchodilator reversibility at some stage [69, 70]. The change in FEV_1 immediately following bronchodilator therapy is poorly predictive of longer-term improvements in symptoms and exercise endurance [23, 71, 72]. A single spirometric assessment will not reliably predict the long-term spirometric response to treatment [70, 73, 74]. FEV_1 and FVC (or IC) bronchodilator responses can occur independent of each other [75, 76]. Patients with resting EFL and/or severe lung hyperinflation demonstrate the greatest lung volume response to bronchodilators [50, 55, 56, 75–78].

Bronchodilator therapy does not necessarily abolish resting EFL, especially in more severe diseases, but changes the conditions under which it occurs [50]. An alternative way to assess the bronchodilator response is to measure maximal mid-expiratory flow rates. This is theoretically attractive because tidal breathing usually occurs at these mid-lung volumes; so, an improvement in $FEF_{25–75\%}$ should alleviate a constraint on tidal breathing. At least two studies have assessed the utility of this measure with disappointing results [79, 80]. The FVC changes post-bronchodilator and so the post-bronchodilator $FEF_{25–75\%}$ is not strictly comparable with the pre-bronchodilator $FEF_{25–75\%}$. It is possible to perform a volume correction (i.e., to account for bronchodilator-induced lung deflation) of the $FEF_{25–75\%}$ slope on the maximal flow volume curve. When this is done, bronchodilators have been shown to consistently increase volume-corrected $FEF_{25–75\%}$ [77, 81]. A reduction in the RV and EELV following bronchodilator provides indirect evidence of improved small airway function as a consequence of reduced airway closure and correlates well with changes in the $FEF_{25–75\%}$.

COPD Versus Asthma

The magnitude of bronchodilator response has been used as a criterion for dividing individuals with airflow obstruction into the diagnostic categories of asthma and COPD. The value of this approach is uncertain. A very large bronchodilator response, for example, an improvement in FEV_1 of greater than 400 mL, is suggestive of asthma [5]; however, most individuals with airflow obstruction will show a smaller response. Here spirometry cannot distinguish asthma with limited reversibility from COPD and indeed both conditions may coexist. Marked diurnal peak flow variability or variability of other indices of airflow obstruction over time is suggestive of asthma. A negative methacholine challenge provides evidence against concomitant asthma. The decision to pursue asthma-related management, such as allergen testing and avoidance, in subjects with COPD is primarily based on the clinical history.

Airway reversibility may also be assessed by a trial of steroids but the utility of this test is uncertain. An initial steroid response is unusual in the absence of an acute bronchodilator response and does not predict a reduction in the long-term rate of FEV_1 decline with inhaled steroids [82].

The changes in other pulmonary function tests following a bronchodilator have been examined. Changes in the forced inspiratory volume in 1 s (FIV_1) were more predicative of symptomatic benefit from bronchodilator therapy than other measures in one study [83]. The change in IC following bronchodilator (Fig. 3.2) is the most predictive resting spirometric measure of exertional dyspnoea and exercise endurance [77].

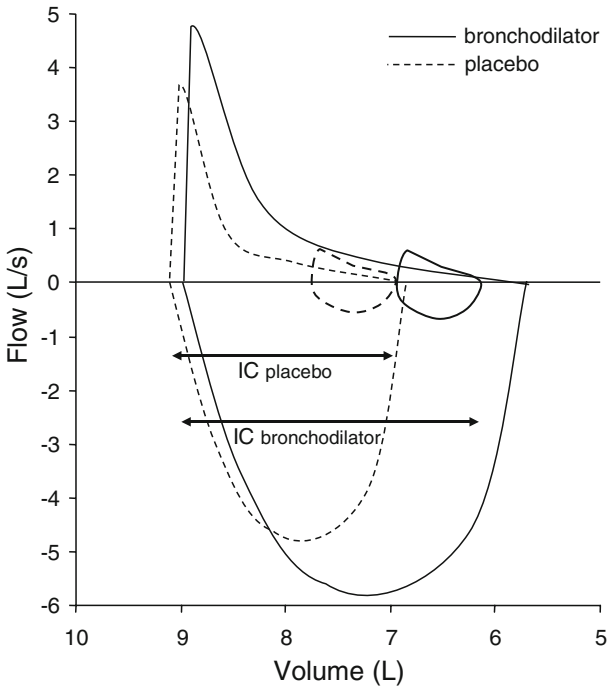


Fig. 3.2. In a typical patient with severe COPD, maximal expiratory flows increased from placebo (*dashed lines*) after a bronchodilator (*solid lines*) in association with a decrease in EELV, as reflected by an increase in IC. Tidal volume (*inner small loops*) was positioned at a lower operating lung volume and inspiratory reserve volume was increased after bronchodilator compared with placebo. Results for this patient are representative of those presented in the reviewed clinical trials evaluating both short- and long-acting bronchodilators in moderate-to-severe COPD (With permission from Reference [152])

The degree of bronchodilator reversibility of itself does not predict mortality in COPD [68, 84]; it is the post-bronchodilator FEV_1 or the "ceiling" of pulmonary function that is predictive [84].

Evaluation of Exercise Performance

Traditional resting spirometric measurements are poorly predictive of the important symptoms of exercise capacity and exertional dyspnoea in COPD patients [19, 85]. A direct assessment of exercise performance is therefore an important part of the assessment of the functional severity of COPD. Measuring exercise capacity assesses the ability of the individual to increase ventilation and cardiac output in response to the demands of exercise as well as the degree of peripheral muscular conditioning, motivation, and the intensity of exertional symptoms. Deficiencies in any of these factors are associated with increased mortality in COPD; it is, therefore, not surprising that exercise capacity is a good predictor of mortality [86].

Field Tests

Measurement of exercise capacity can be accomplished through field tests, activity monitors, and cardiopulmonary exercise testing (CPET). Observation of the patient walking along the corridor or climbing a flight of stairs provides useful qualitative information.

The number of stairs climbed before stopping correlates well with peak oxygen uptake ($V'O_2$) [87]. Supervised timed walking distances, such as the 12-min walk test or the more convenient 6-min walk test (6MWT) tests, have been used extensively as a measure of functional disability [88], to prescribe an exercise program and to assess outcome following rehabilitation. Concurrent measurements of dyspnoea intensity using validated scales enhance the value of this test. The 6 MW distance may be a better predictor of mortality in COPD than FEV_1 [89]. There are some limitations of the utility of the 6MWT. The pace of walking and the power output are not controlled during the test; so, the distance achieved is highly dependent on patient motivation. There is a learning effect and so two familiarization tests should be conducted prior to performing a baseline test [90] and care must be taken to standardize the instruction and encouragement of the patient [91]. Test reproducibility is relatively poor [92]. It is difficult to obtain metabolic data during a standard hallway 6MWT; however, metabolic data may be readily obtained if the test is modified for the treadmill [93]. The degree to which the 6MWT accurately reflects functional disabilities during the activities of daily living in the home or in the workplace is not known and needs further study. However, the 6MWT is a simple, inexpensive test that provides a useful evaluation of functional disability in COPD.

Recently, shuttle walk tests have received increasing attention [94, 95]. The incremental shuttle walk test is externally paced and requires an incremental increase in walking speed each minute, to a point at which the test is terminated because of breathlessness or the inability to sustain the required walking speed. The endurance shuttle walk test is performed at a constant pace. There is evidence that these tests are reliable and responsive to COPD interventions such as exercise training, pulmonary rehabilitation, and the administration of supplemental oxygen [96–99]. The endurance shuttle walking test may be more sensitive to detect the effects of therapeutic intervention than the incremental shuttle walk test [98]. The incremental shuttle walk test has the advantage that relationship between $V'O_2$ and walking speed is close to linear so provides an accurate estimate of peak $V'O_2$ [95, 97, 100]. Like the 6MWT, it is unclear how shuttle walk test results translate into everyday activities.

Cardiopulmonary Exercise Tests

Increasingly, functional exercise assessment is conducted in the setting of formal CPET in the laboratory. This more rigorous approach to the measurement of the physiological and perceptual responses to exercise has several advantages.

It provides an accurate assessment of the patient's exercise capacity (i.e., peak $V'O_2$).

It measures the perceptual responses to a quantifiable dyspneogenic stimulus (i.e., $V'O_2$, ventilation, power output).

It provides insights into pathophysiological mechanisms of dyspnoea in a given patient (e.g., excessive ventilation, dynamic hyperinflation, arterial oxygen desaturation).

It can identify other coexisting conditions that contribute to dyspnoea and exercise limitation (i.e., cardiac disorders, intermittent claudication, musculoskeletal problems).

Standardized comparisons of perceptual responses to measurable dyspnoea-provoking stimuli allow an accurate assessment of symptom responses to therapeutic interventions.

Standard cardiopulmonary exercise testing measures the following physiological responses: $V'O_2$, carbon dioxide output ($V'CO_2$), minute ventilation (V'_E), breathing pattern, arterial oxygen saturation, heart rate, oxygen pulse, and blood pressure (Fig. 3.3). It is important to record the intensity of dyspnoea, leg discomfort, and other

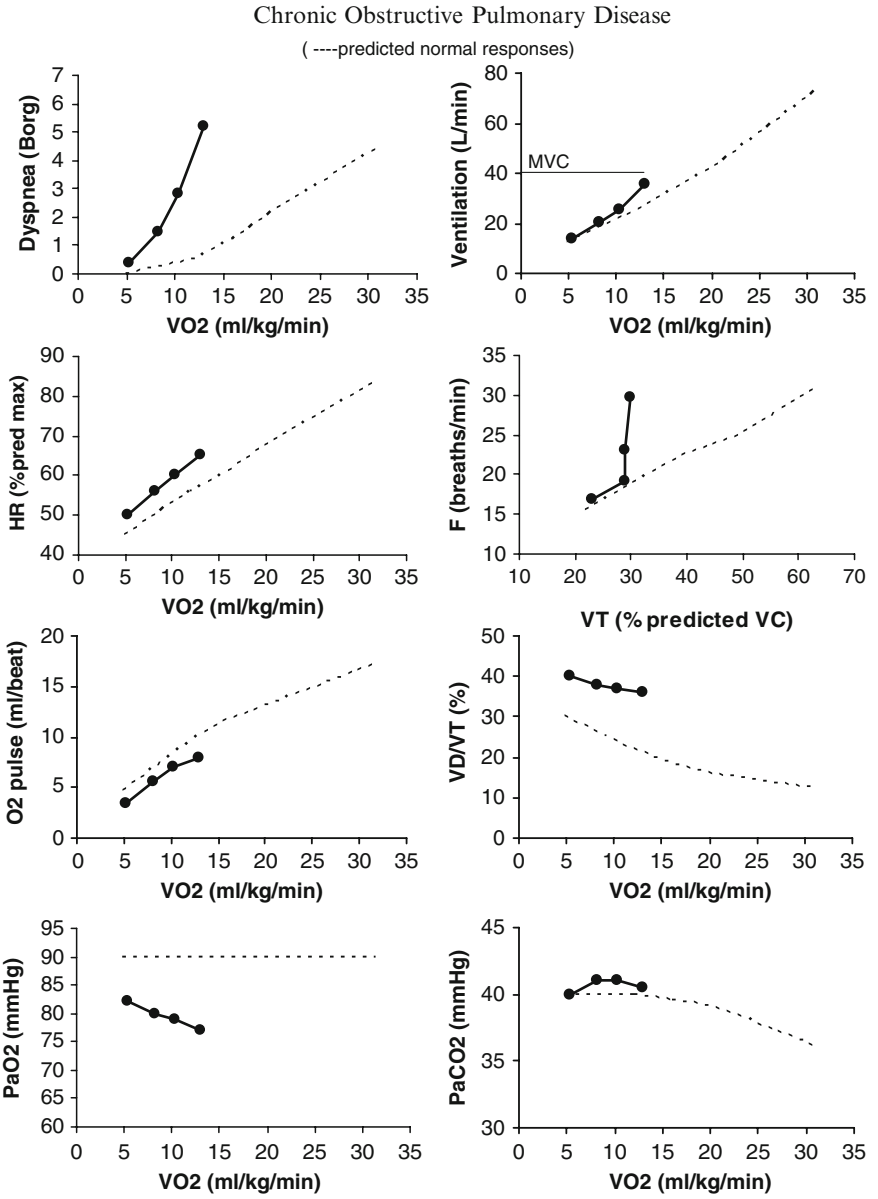


Fig. 3.3. Typical exercise responses in severe COPD (*dotted lines* indicate age-matched normal responses established in our laboratory). See text for discussion and abbreviations. *HR* heart rate, *F* respiratory frequency, *VD* dead space volume, PaO_2 arterial partial pressure of oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide (With permission from Reference [153])

symptoms during the test and the reason for stopping the test. Incremental and constant load endurance testing, using cycle ergometry or treadmill, are used extensively and these approaches have the potential to produce different, but complimentary, clinical information. A cycle ergometer is preferred to a treadmill as it allows an accurate measure of work and, in contrast to other forms of exercise testing is a low impact exercise with less ventilatory demand than walking tests [101]. Peak $V'O_2$ measured by a CPET shows a stronger correlation with mortality than FEV_1 [86].

It has been argued that testing by cycle ergometry poorly mimics the activities of daily living and, therefore, may not be relevant in assessing COPD patients. However, the CPET, regardless of protocol, is able to define the physiologic limits of exercise function for an individual. COPD patients will vary in the ways in which they adapt daily activities to fit within these physiologic limits; however, these limits are clearly relevant to daily life for symptomatic patients and for patients who avoid activities that may result in dyspnoea. Knowledge of the $V'O_2$ or MET (metabolic rates based on multiples of the resting $V'O_2$) equivalents of various activities of daily living permits a crude estimation of the patient's functional capacity. Generally speaking, a peak $V'O_2$ of <15 mL/kg/min in a patient with COPD represents severe functional disability.

An extension of the CPET is the measurement of DH during exercise. The amount of DH on exercise cannot be reliably predicted from measurement of resting DH yet is an important determinant of exercise dyspnoea and an important factor limiting exercise capacity in COPD [23, 46, 102–105]. While DH may be a beneficial adaptation early in exercise [105], at higher workloads, DH forces tidal breathing to occur at higher lung volumes close to TLC where the respiratory system is less compliant (Fig. 3.4). As tidal volume (V_T) expands to reach a minimal inspiratory reserve volume (IRV) of approximately

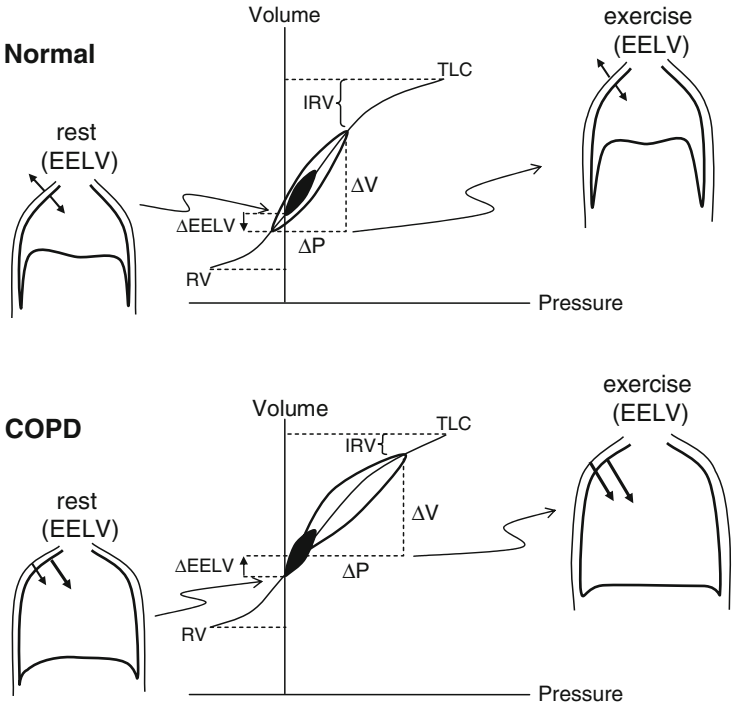


Fig. 3.4. Pressure–volume (*P–V*) relationships of the total respiratory system in health and in COPD. Tidal pressure–volume curves during rest (*filled area*) and exercise (*open area*) are shown. In COPD, because of resting and dynamic hyperinflation (a further increased EELV), exercise tidal volume (V_T) encroaches on the upper, alinear extreme of the respiratory system's *P–V* curve where there is increased elastic loading. In COPD, the ability to further expand V_T is reduced, i.e., inspiratory reserve volume (*IRV*) is diminished. In contrast to health, the combined recoil pressure of the lungs and chest wall in hyperinflated patients with COPD is inwardly directed during both rest and exercise; this results in an inspiratory threshold load on the inspiratory muscles. *EELV* end-expiratory lung volume, *EILV* end-inspiratory lung volume, *RV* residual volume, *TLC* total lung capacity (With permission from Reference [154])

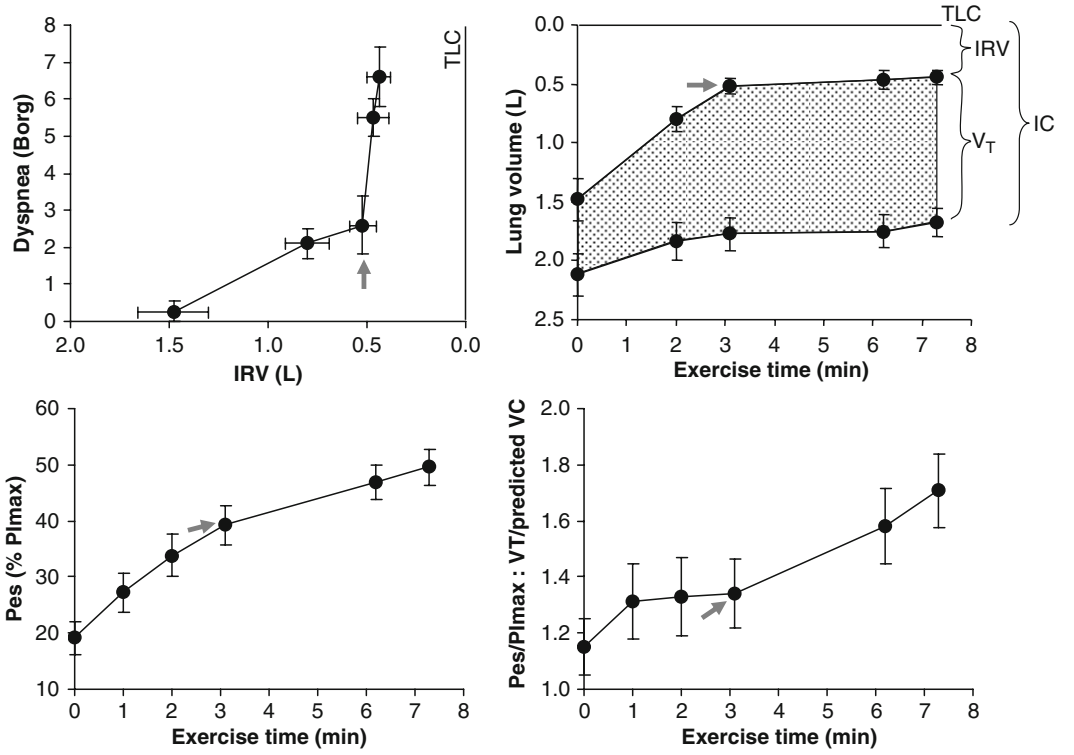


Fig. 3.5. The mechanical threshold of dyspnoea is indicated by the abrupt rise in dyspnoea after a critical "minimal" inspiratory reserve volume (*IRV*) is reached which prevents further expansion of tidal volume (V_T) during exercise. Beyond this dyspnoea/IRV inflection point during exercise, dyspnoea intensity, respiratory effort (Pes/PImax), and the ratio of Pes/PImax to tidal volume displacement (V_T standardized as a percentage of predicted vital capacity [*VC*]) all continued to rise. Arrows indicate the dyspnoea/IRV inflection point. Values are expressed as means ± SEM. *IC* inspiratory capacity (Modified from Reference [105]. With permission Reference [153])

0.5 L below TLC, the inspiratory muscles become burdened with significant increases in elastic and inspiratory threshold loading (Fig. 3.4). This leads to a dissociation between effort and V_T displacement and a sensation of unsatisfied inspiration or dyspnoea (Fig. 3.5) [102, 105]. The consequences of DH are summarized in Table 3.1.

A variety of methods have been used to track changes in EELV and hence DH during exercise in the context of a standardized exercise test, the simplest of which is intermittent IC measurement (Fig. 3.6). IC measurements have been shown to be highly reproducible during cycle exercise [55, 56]. EELV is calculated as TLC minus IC with the assumptions that TLC does not change during exercise and that the patient is capable of producing a maximal IC effort during exercise. There is good evidence that these assumptions are valid provided the patient is motivated to make maximal inspiratory efforts during the measurement and that they do not have critical inspiratory muscle weakness [102, 106–110]. Other techniques, while more complicated, are able to track absolute lung volumes during exercise and include volume dilution techniques, body plethysmography adapted for exercise, and optoelectronic plethysmography [109, 111].

DH with exercise in patients with moderate to severe COPD averages about 0.4 L, equivalent to a reduction in IC at peak exercise of 20% of the resting value [46, 55, 56]; however, there is a wide variation between individuals and patients with a more emphysematous phenotype showing greater DH [46].

Table 3.1 Negative effects of dynamic hyperinflation during exercise.

Increased elastic load of breathing/reduced dynamic compliance of respiratory system
Inspiratory threshold loading
Reduced tidal volume expansion leading to:
Tachypnea
Increased dead space to tidal volume ratio
Relative alveolar hypoventilation/elevated $PaCO_2$
Greater exertional dyspnoea
Early ventilatory limitation to exercise
Reduced cardiovascular function

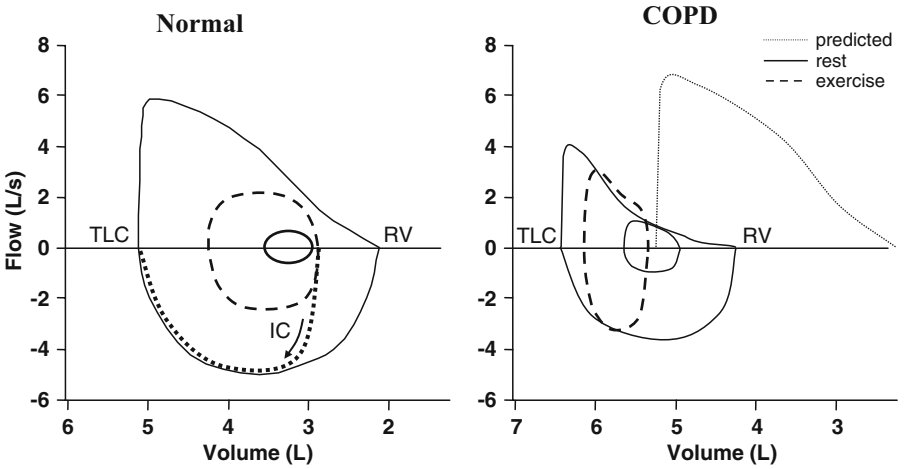


Fig. 3.6. Comparison of maximal and tidal resting and exercise flow-volume loops in a patient with COPD during exercise. Flow-volume loops showing the effects of exercise on tidal volume in COPD and in age-matched health. The *solid loops* represent the outer maximal limits of flow and volume and the inner resting tidal volumes. The larger *dashed loops* represent the increased tidal volumes and flows seen with exercise. The *dotted line* on the left panel represents the IC maneuver to TLC which is used to anchor tidal flow-volume loops within the respective maximal loops. Healthy subjects are able to increase both their tidal volumes and inspiratory and expiratory flows. In COPD, expiratory flow is already maximal during resting ventilation; the predicted normal maximal expiratory loop is shown as a *thin dotted line* in the right panel. In order to increase expiratory flow further, these patients must hyperinflate. See text for abbreviations (With permission from reference)

The pattern of breathing becomes more shallow and rapid as DH progresses. In moderate to severe COPD, there is a discernible "ceiling" during exercise when tidal volume and IRV reach a plateau value and further increases in ventilation can only be achieved by increasing respiratory rate (Figs. 3.3 and 3.5). The greater the resting and dynamic hyperinflation, the lower the ventilation (and work rate) at which the mechanical V_T plateau is discernible [46] (Fig. 3.7). In extreme cases, the lack of ability to increase V_T further in the setting of severe ventilation-perfusion abnormalities may lead to alveolar hypoventilation and arterial oxygen desaturation [112]. In the absence of EELV measurements during a CPET, the presence of exercise limiting DH can be inferred from a plateau in V_T expansion.

There is preliminary evidence that significant DH during exercise may be present in patients with mild COPD [113, 114]. The clinical relevance of DH in mild COPD is yet to be determined.

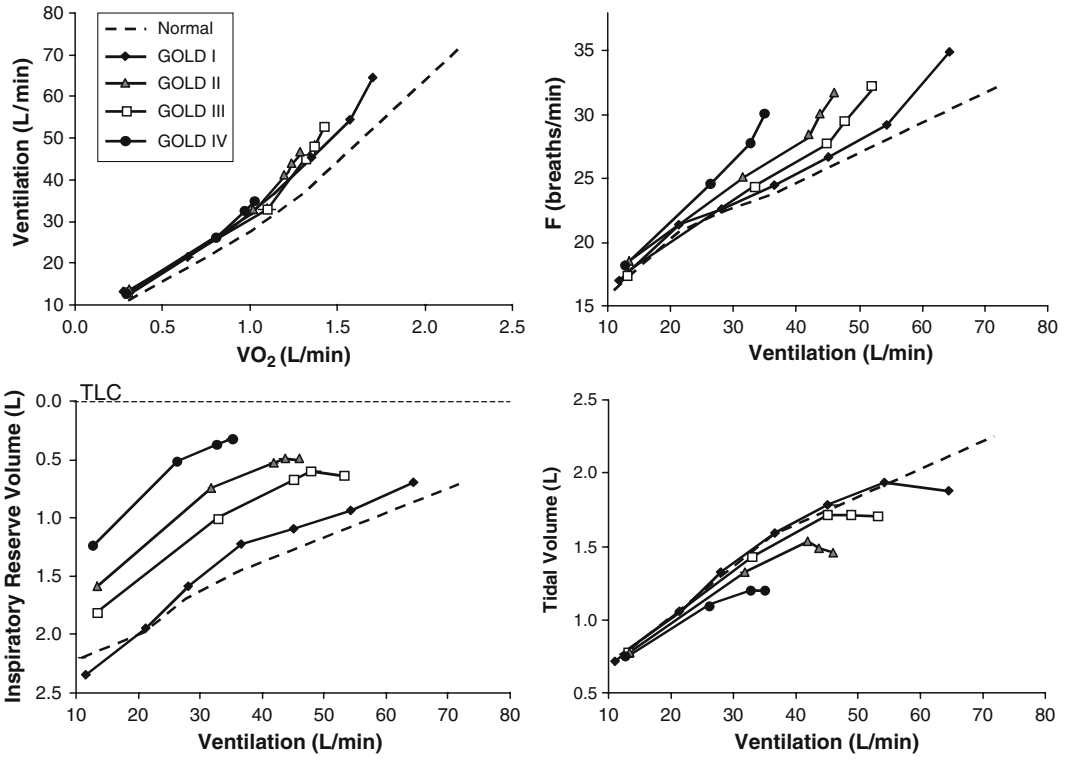


Fig. 3.7. Example of ventilatory response to exercise in a patient with mild, moderate, severe, and very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease 2006 (GOLD I, GOLD II, GOLD III, and GOLD IV, respectively). *Dashed lines* indicate age-matched normal response established in our laboratory. Changes in operating lung volumes and breathing pattern are shown as ventilation increases with exercise. Note that in COPD there is a discernible mechanical ceiling during exercise when inspiratory reserve volume and tidal volume reach a plateau value and further increases in ventilation can only be achieved by increasing tachypnea. Note also that the greater the resting and dynamic hyperinflation, the lower the ventilation at which the mechanical tidal volume plateau is discernible

A further extension of CPET is the ability to compare the exercise tidal flow-volume loop to the maximal resting loop (Fig. 3.6). This provides information about the presence and degree of EFL during exercise.

Testing for Complications of COPD

Evaluation of the complications of COPD forms an integral part of severity assessment. Systemic catabolism manifested as weight loss is associated with poorer survival. This can be approximated by measuring the body mass index (BMI). A value of <21 kg/m [2] is associated with reduced survival [115, 116]. Tissue loss or more accurately fat-free mass loss may be assessed by bioelectric impedance or by dual-energy X-ray absorptiometry. A low fat-free mass is associated with dyspnoea, impaired exercise performance, and health-related quality of life [117]. Peripheral muscle cross-sectional area or maximum voluntary contraction strength may be a better predictor of mortality than BMI or FEV_1 [118, 119].

Like the peripheral muscles, ventilatory muscles may be weak in COPD patients. Ventilatory muscle strength can be assessed by the maximal inspiratory and expiratory

mouth pressure tests or more accurately by esophageal pressure during a maximal sniff maneuver using an esophageal balloon catheter.

Mild pulmonary hypertension, as a result of destruction of the pulmonary vascular bed and chronic hypoxemia, is a common finding associated with advanced COPD. Several smaller studies have shown significant pulmonary hypertension during exercise in COPD. Elevated pulmonary artery pressures may be associated with reduced survival [120] and higher rates of hospitalization with a COPD exacerbation [121]. Mean pulmonary artery pressures <30 mmHg are unlikely to be clinically important unless respiratory failure is also present [1, 122].

Arterial blood gas analysis is useful as a measure of respiratory function in COPD. Testing is indicated in patients with a resting oxyhemoglobin saturation <92% [123] or with a FEV_1 <40% of predicted normal. The development of respiratory failure is indicated by arterial tensions of oxygen <60 mmHg (some suggest <50 mmHg) with or without carbon dioxide >50 mmHg (some suggest >45–50 mmHg) [1]. The presence of respiratory failure moves a patient from severe to very severe in the GOLD classification of severity [1]. Incipient respiratory failure may be detected by pulse oximetry with oxyhemoglobin desaturation during weight-bearing exercise [65, 124].

Composite Scoring Systems of Severity

Reliance on a single index of COPD severity will misclassify many patients with this heterogeneous disorder. Particularly in advanced disease, factors other than air flow such as physical deconditioning and psychosocial function become more important correlates of morbidity and mortality [125]. There has been great interest in developing a composite score to accurately reflect COPD severity incorporating several dimensions of the disease. A simple score is the BODE index which incorporates airway function, exercise, body mass, and symptom dimensions [115]. This index is a better predictor of subsequent survival than any individual component. The performance of this and other composite scoring systems are being evaluated as measurements of COPD severity and may in the future serve as a measure of therapeutic outcome in clinical practice and in clinical trials.

Monitoring Disease Progression

The various tests of COPD severity described above may also be used to monitor disease progression. The test most evaluated in the literature for this purpose is the FEV_1. The rate of decline in FEV_1 is normally about 25–30 mL/year after the age of 25–30 years although there is marked interindividual variation and it is likely that FEV_1 decline accelerates with advanced age [126, 127]. In COPD patients, this rate can be greater than 100 mL/year [128]. The rate of decline is greater in current smokers [129] and may be greater in patients with frequent COPD exacerbations [130]. It may take several years of monitoring an individual to estimate the rate of FEV_1 decline, distinct from the random effects of measurement error. There is unlikely to be a benefit in performing spirometry more frequently than annually for this purpose [1]. It may be difficult to decide if an observed rate of FEV_1 decline is normal or not as there is no definitive normal range due to the limitations of cross-sectional data and the incomplete follow up and cohort effects of longitudinal data [131]. Even if clearly abnormal, the prognostic value of the rate of FEV_1 decline is uncertain; however, high rates are associated with a slightly higher mortality [128].

Multiple dimensions of COPD should be evaluated to accurately monitor progress in COPD. In addition to spirometry, tissue loss assessed by weight or fat-free mass, lung volumes and the IC/TLC ratio, presence of pulmonary hypertension, and exercise capacity assessed by 6MWD or peak $V'O_2$ should be monitored. Also important are symptoms and quality of life measures and the number, frequency, and severity of COPD exacerbations [132].

Evaluation of Therapeutic Interventions

Many therapeutic interventions are available for COPD that may result in improved symptoms and quality of life. The functional correlates of these clinical improvements may be detected through physiologic testing and can provide objective evidence for the effectiveness of a therapeutic intervention. As discussed earlier, significant clinical benefit may be derived from a therapeutic intervention in COPD in the absence of a significant change in FEV_1. The poor correlation between FEV_1 and clinical response to intervention is largely due to the fact that interventions may modify DH and, to a lesser extent, EFL without greatly affecting FEV_1.

Volume responses have traditionally been assessed by the FVC. Measurement of the FEV_6 appears to be more sensitive than the FVC in detecting enhanced lung emptying after pharmacotherapy [133, 134].

The (reduced) IC, a measure of DH, shows a greater response to bronchodilator therapy than either the FEV_1 or FVC [76]. As previously discussed, resting IC has been shown to correlate well with exercise capacity in severe COPD [51]. The benefit of an increased resting IC is to delay the onset of the mechanical limitation of ventilation during exercise from DH by providing a greater IC reserve, pharmacologic lung volume reduction. The rate of DH during exercise does not appear to change much following bronchodilator therapy. Improvements in resting IC of approximately 10% predicted or 0.3–0.4 L generally translate into clinically important improvements in dyspnoea and exercise capacity [23–25]. Post-bronchodilator improvements in resting IC are seen more often in patients who are flow-limited at rest [50–52].

Another means of assessing the response of DH-related exercise limitation to therapy is through exercise testing. The 6MWT has been shown to be responsive to interventions such as exercise training, short-acting bronchodilator therapy, lung volume reduction surgery, and administration of supplemental oxygen [20, 135–138].

Endurance time during high-intensity exercise has been increasingly used to assess exercise tolerance before and after a therapeutic intervention. In COPD, there is an increasing evidence that high-intensity constant-load endurance protocols with measurement of endurance time, symptoms (e.g., dyspnoea and leg fatigue), and CPET variables of interest (e.g., IC, V'_E, $V'O_2$, $V'_E/V'CO_2$, breathing frequency, V_T expansion, heart rate) at a standardized time are superior to other protocols in demonstrating the underlying physiologic mechanisms responsible for increases in exercise tolerance induced by a particular intervention [139]. In recent years, these CPET protocols have been used to demonstrate the positive effects of interventions such as bronchodilator therapy [55, 56, 81], oxygen [140, 141], heliox administration [142–144], optimized low-level continuous positive airway pressure [145], lung volume reduction surgery [146], and pulmonary rehabilitation [147, 148] (Fig. 3.8). Physiologic variables may improve during exercise post-bronchodilator, even in the absence of any change at rest. Many classes of bronchodilators have been shown to increase IC during exercise and

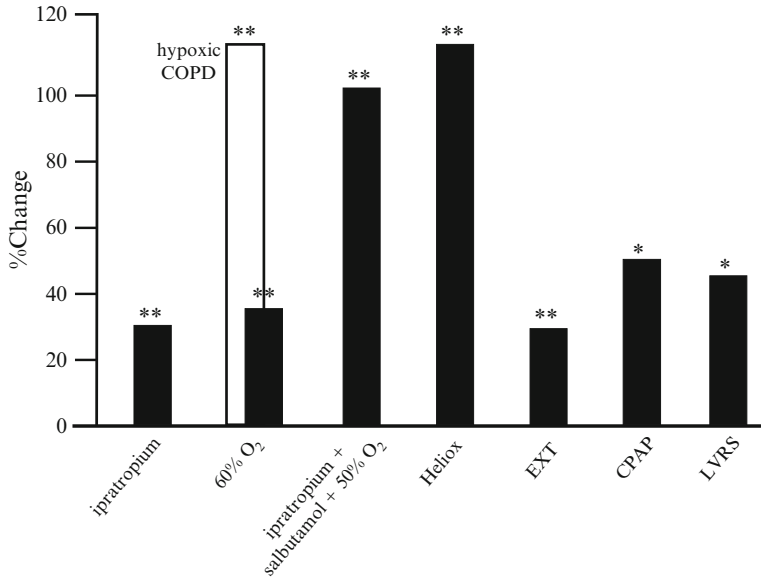


Fig. 3.8. Exercise endurance increases significantly (*$P<0.05$, **$P<0.01$) in response to various interventions in COPD: nebulized ipratropium bromide 500 µg, 60% O_2 (shown for both hypoxic (open bar) and nonhypoxic (solid bar) patients), nebulized ipratropium 0.5 mg + salbutamol 2.5 mg with 50% O_2, Heliox administration (21% oxygen, 79% helium), exercise training (*EXT*), optimized low-level continuous positive airway pressure (*CPAP*), and lung volume reduction surgery (*LVRS*) (Data from References [23, 140, 142, 145, 146, 150, 151])

improve exercise endurance, often in the absence of an improvement in FEV_1 or FVC at rest [25, 55, 77, 81].

Currently, the high-intensity exercise endurance protocol appears to be the most responsive exercise test for the evaluation of the efficacy of therapeutic interventions in COPD.

Composite scoring systems such as the BODE index have been shown to be responsive to therapeutic interventions [149]. Further research is required to determine whether the use of composite scoring systems which combine subjective and objective measures offers benefits beyond the current practice of making subjective and objective assessments separately.

Conclusions

Recent developments in the physiologic assessment of COPD have resulted in several new trends. Post-bronchodilator measurements are now increasingly used for the FEV_1/FVC ratio in diagnosis and the FEV_1 in severity assessment. The FEV_6 is emerging as a valid alternative to the FVC for diagnosis and evaluation of therapeutic response. There is a shift from the exclusive reliance on spirometry to evaluate severity, disease progression, and response to interventions to a wider assessment encompassing multiple dimensions of COPD. The emergence of sensitive endurance CPET has provided a new understanding of the mechanisms of dyspnoea and exercise limitation and how various interventions work to improve these outcomes.

References

1. Global Initiative for Chronic Obstructive Lung Disease (2006) Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease; Available at: www.goldcopd.com
2. Badgett RG, Tanaka DJ, Hunt DK et al (1993) Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? Am J Med 94(2):188–196
3. Thurlbeck WM, Simon G (1978) Radiographic appearance of the chest in emphysema. Am J Roentgenol 130(3):429–440
4. Pellegrino R, Viegi G, Brusasco V et al (2005) Interpretative strategies for lung function tests. Eur Respir J 26:948–968
5. Calverley PMA, Pearson MG (2003) Clinical and laboratory assessment. In: Calverley PMA, MacNee W, Rennard SI, Pride NB (eds) Chronic obstructive pulmonary disease, 2nd edn. Arnold, London, pp 282–309
6. Hardie JA, Buist AS, Vollmer WM et al (2002 November 1) Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J 20(5):1117–1122
7. Akpinar-Elci M, Fedan KB, Enright PL (2006 February 1) FEV6 as a surrogate for FVC in detecting airways obstruction and restriction in the workplace. Eur Respir J 27(2):374–377
8. Vandevoorde J, Verbanck S, Schuermans D, Kartounian J, Vincken W (2006 February 1) Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV1/FEV6 and FEV6. Eur Respir J 27(2):378–383
9. Vandevoorde J, Verbanck S, Schuermans D, Kartounian J, Vincken W (2005 May) FEV_1/FEV_6 and FEV_6 as an alternative for FEV1/FVC and FVC in the spirometric detection of airway obstruction and restriction. Chest 127(5):1560–1564
10. Hansen JE, Sun XG, Wasserman K (2006 June) Should forced expiratory volume in six seconds replace forced vital capacity to detect airway obstruction? Eur Respir J 27(6): 1244–1250
11. Zielinski J, Bednarek M, Gorecka D et al (2006 April 1) Increasing COPD awareness. Eur Respir J 27(4):833–852
12. Zielinski J, Bednarek M (2001 March 1) Early detection of COPD in a high-risk population using spirometric screening. Chest 119(3):731–736
13. Stratelis G, Jakobsson P, Molstad S, Zetterstrom O (2004) Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Br J Gen Pract 54(500):201–206
14. Gorecka D, Bednarek M, Nowinski A et al (2003 June 1) Diagnosis of airflow limitation combined with smoking cessation advice increases stop-smoking rate. Chest 123(6):1916–1923
15. Walker PP, Mitchell P, Diamantea F, Warburton CJ, Davies L (2006) Effect of primary-care spirometry on the diagnosis and management of COPD. Eur Respir J 28(5):945–952
16. Wolkove N, Dajczman E, Colacone A, Kreisman H (1989 December) The relationship between pulmonary function and dyspnea in obstructive lung disease. Chest 96(6):1247–1251
17. Jones PW, Baveystock CM, Littlejohns P (1989) Relationships between general health measured with the sickness impact profile and respiratory symptoms, physiological measures, and mood in patients with chronic airflow limitation. Am Rev Respir Dis 140(6):1538–1543
18. Sin DD, Jones RL, Mannino DM, Paul Man SF (2004 August 15) Forced expiratory volume in 1 second and physical activity in the general population. Am J Med 117(4):270–273
19. LoRusso TJ, Belman MJ, Elashoff JD, Koerner SK (1993 December 1) Prediction of maximal exercise capacity in obstructive and restrictive pulmonary disease. Chest 104(6):1748–1754
20. Hay JG, Stone P, Carter J et al (1992 June) Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. Eur Respir J 5(6): 659–664
21. Bauerle O, Chrusch CA, Younes M (1998 January) Mechanisms by which COPD affects exercise tolerance. Am J Respir Crit Care Med 157(1):57–68
22. Carlson DJ, Ries AL, Kaplan RM (1991 August) Prediction of maximum exercise tolerance in patients with COPD. Chest 100(2):307–311

23. O'Donnell DE, Lam M, Webb KA (1998 November 1) Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158(5):1557–1565
24. Chrystyn H, Mulley BA, Peake MD (1988 December 10) Dose response relation to oral theophylline in severe chronic obstructive airways disease. BMJ 297(6662):1506–1510
25. Belman MJ, Botnick WC, Shin JW (1996 March 1) Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153(3):967–975
26. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC (2003) Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax 58(5):388–393
27. Anthonisen NR, Wright EC, Hodgkin JE (1986) Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis 133(1):14–20
28. Stavem K, Aaser E, Sandvik L et al (2005 April 1) Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. Eur Respir J 25(4):618–625
29. Hyatt RE (1983 July 1) Expiratory flow limitation. J Appl Physiol 55(1):1–7
30. Dawson SV, Elliott EA (1977 September) Wave-speed limitation on expiratory flow-a unifying concept. J Appl Physiol 43(3):498–515
31. Eltayara L, Becklake MR, Volta CA, Milic-Emili J (1996 December 1) Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154(6):1726–1734
32. Johnson BD, Weisman IM, Zeballos RJ, Beck KC (1999 August) Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. Chest 116(2):488–503
33. Johnson BD, Reddan WG, Pegelow DF, Seow KC, Dempsey JA (1991 May) Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. Am Rev Respir Dis 143(5 Pt 1):960–967
34. Calverley PMA, Koulouris NG (2005 January 1) Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. Eur Respir J 25(1):186–199
35. Koulouris NG, Valta P, Lavoie A et al (1995 February 1) A simple method to detect expiratory flow limitation during spontaneous breathing. Eur Respir J 8(2):306–313
36. Ninane V, Leduc D, Kafi S et al (2001 May 1) Detection of expiratory flow limitation by manual compression of the abdominal wall. Am J Respir Crit Care Med 163(6):1326–1330
37. Mead J, Whittenberger JL (1953) Physical properties of human lungs measured during spontaneous respiration. J Appl Physiol 5(12):779–796
38. Dellaca RL, Santus P, Aliverti A et al (2004 February 1) Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J 23(2):232–240
39. Detels R, Tashkin DP, Simmons MS et al (1982 November 1) The UCLA population studies of chronic obstructive respiratory disease. 5. Agreement and disagreement of tests in identifying abnormal lung function. Chest 82(5):630–638
40. Hansen EF, Vestbo J, Phanareth K, Kok-Jensen A, Dirksen A (2001 March 1) Peak flow as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163(3):690–693
41. Vinegar A, Sinnett EE, Leith DE (1979 May) Dynamic mechanisms determine functional residual capacity in mice, Mus musculus. J Appl Physiol 46(5):867–871
42. Gelb AF, Gutierrez CA, Weisman IM et al (2004 December) Simplified detection of dynamic hyperinflation. Chest 126(6):1855–1860
43. Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE (2005 September 1) Physiological changes during symptom recovery from moderate exacerbations of COPD. Eur Respir J 26(3):420–428
44. Stevenson NJ, Walker PP, Costello RW, Calverley PM (2005 December 15) Lung mechanics and dyspnea during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 172(12):1510–1516
45. O'Donnell DE (2006 April) Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 3(2):180–184

46. O'Donnell DE, Revill SM, Webb KA (2001 September 1) Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164(5):770–777
47. Pare PD, Wiggs BJ, Coppin CA (1983) Errors in the measurement of total lung capacity in chronic obstructive lung disease. Thorax 38(6):468–471
48. Bohadana AB, Peslin R, Hannhart B, Teculescu D (1982 March) Influence of panting frequency on plethysmographic measurements of thoracic gas volume. J Appl Physiol 52(3):739–747
49. Brown R, Slutsky AS (1984 December) Frequency dependence of plethysmographic measurement of thoracic gas volume. J Appl Physiol 57(6):1865–1871
50. Tantucci C, Duguet A, Similowski T et al (1998 October 1) Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. Eur Respir J 12(4):799–804
51. Diaz O, Villafranca C, Ghezzo H et al (2000 August 1) Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J 16(2):269–275
52. Boni E, Corda L, Franchini D et al (2002 June 1) Volume effect and exertional dyspnoea after bronchodilator in patients with COPD with and without expiratory flow limitation at rest. Thorax 57(6):528–532
53. Casanova C, Cote C, de Torres JP et al (2005 March 15) Inspiratory-to-total lung capacity ratio predicts mortality in patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 171(6):591–597
54. O'Donnell DE, Travers J, Webb KA, He Z, Lam Y-M, Hamilton A, Kesten S, Maltais F, Magnussen H (2009) Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. Eur Respir J 34(4):866–874. doi:doi:10.1183/09031936.00168708 , published online 12 March 2009
55. O'Donnell DE, Fluge T, Gerken F et al (2004 June 1) Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 23(6):832–840
56. Maltais F, Hamilton A, Marciniuk D et al (2005 September) Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest 128(3):1168–1178
57. Simon G (1971) Principles of chest x-ray diagnosis, 3rd edn. Butterworth, London
58. Simon G, Pride NB, Jones NL, Raimondi AC (1973 January) Relation between abnormalities in the chest radiograph and changes in pulmonary function in chronic bronchitis and emphysema. Thorax 28(1):15–23
59. Burki NK, Krumpelman JL (1980 February) Correlation of pulmonary function with the chest roentgenogram in chronic airway obstruction. Am Rev Respir Dis 121(2):217–223
60. Nakano Y, Muro S, Sakai H et al (2000 September) Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med 162(3 Pt 1):1102–1108
61. de Jong PA, Muller NL, Pare PD, Coxson HO (2005 July) Computed tomographic imaging of the airways: relationship to structure and function. Eur Respir J 26(1):140–152
62. Park KJ, Bergin CJ, Clausen JL (1999 May 1) Quantitation of emphysema with three-dimensional CT densitometry: Comparison with two-dimensional analysis, visual emphysema scores, and pulmonary function test results. Radiology 211(2):541–547
63. Morrison NJ, Abboud RT, Ramadan F et al (1989 May) Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema. Am Rev Respir Dis 139(5):1179–1187
64. Leech JA, Martz L, Liben A, Becklake MR (1985) Diffusing capacity for carbon monoxide. The effects of different derivations of breathhold time and alveolar volume and of carbon monoxide back pressure on calculated results. Am Rev Respir Dis 132(5):1127–1129
65. Flynn E, O'Driscoll R (2002 July 1) Exercise testing in the consulting room. Chest 122(1):383
66. Hadeli KO, Siegel EM, Sherrill DL, Beck KC, Enright PL (2001 July) Predictors of oxygen desaturation during submaximal exercise in 8,000 patients. Chest 120(1):88–92

67. O'Donnell DE, Webb KA (1992 September) Breathlessness in patients with severe chronic airflow limitation. Physiologic correlations. Chest 102(3):824–831
68. Anthonisen NR, Lindgren PG, Tashkin DP et al (2005) Bronchodilator response in the lung health study over 11 yrs. Eur Respir J 26(1):45–51
69. Calverley PMA, Burge PS, Spencer S, Anderson JA, Jones PW (2003 August 1) Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 58(8):659–664
70. Kerstjens HA, Brand PL, Quanjer PH et al (1993) Variability of bronchodilator response and effects of inhaled corticosteroid treatment in obstructive airways disease. Dutch CNSLD Study Group. Thorax 48(7):722–729
71. Tobin MJ, Hughes JA, Hutchison DC (1984 August) Effects of ipratropium bromide and fenoterol aerosols on exercise tolerance. Eur J Respir Dis 65(6):441–446
72. Leitch AG, Hopkin JM, Ellis DA, Merchant S, McHardy GJ (1978 December 1) The effect of aerosol ipratropium bromide and salbutamol on exercise tolerance in chronic bronchitis. Thorax 33(6):711–713
73. Muir JF, Benhamou D, Cuvelier A et al (2004) FEV1 reversibility does not adequately predict effect of formoterol via AerolizerR in chronic obstructive pulmonary disease. Int J Clin Pract 58(5):457–464
74. Tashkin D, Kesten S (2003 May 1) Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. Chest 123(5):1441–1449
75. Newton MF, O'Donnell DE, Forkert L (2002 April) Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest 121(4):1042–1050
76. O'Donnell DE, Forkert L, Webb KA (2001 December) Evaluation of bronchodilator responses in patients with "irreversible" emphysema. Eur Respir J 18(6):914–920
77. O'Donnell DE, Lam M, Webb KA (1999 August 1) Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160(2):542–549
78. Celli B, ZuWallack R, Wang S, Kesten S (2003 November) Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 124(5):1743–1748
79. Olsen CR, Hale FC (1968 August) A method for interpreting acute response to bronchodilators from the spirogram. Am Rev Respir Dis 98(2):301–302
80. Boggs PB, Bhat KD, Vekovius WA, Debo MS (1982 March) The clinical significance of volume-adjusted maximal mid-expiratory flow (iso-volume FEF25–75%) in assessing airway responsiveness to inhaled bronchodilator in asthmatics. Ann Allergy 48(3):139–142
81. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA (2004 July 1) Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. Eur Respir J 24(1):86–94
82. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA (2003 August 1) Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. Thorax 58(8):654–658
83. Taube C, Lehnigk B, Paasch K et al (2000 July 1) Factor analysis of changes in dyspnea and lung function parameters after bronchodilation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 162(1):216–220
84. Hansen EF, Phanareth K, Laursen LC, Kok-Jensen A, Dirksen A (1999) Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159(4):1267–1271
85. Ortega F, Montemayor T, Sanchez A, Cabello F, Castillo J (1994 September 1) Role of cardiopulmonary exercise testing and the criteria used to determine disability in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 150(3):747–751
86. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T (2003 February 15) Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 167(4):544–549
87. Pollock M, Roa J, Benditt J, Celli B (1993 November) Estimation of ventilatory reserve by stair climbing. A study in patients with chronic airflow obstruction. Chest 104(5):1378–1383

88. McGavin CR, Artvinli M, Naoe H, McHardy GJ (1978 July 22) Dyspnoea, disability, and distance walked: comparison of estimates of exercise performance in respiratory disease. Br Med J 2(6132):241–243
89. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR (2004 January 1) The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 23(1):28–33
90. Wu G, Sanderson B, Bittner V (2003 July) The 6-minute walk test: How important is the learning effect? Am Heart J 146(1):129–133
91. Guyatt GH, Pugsley SO, Sullivan MJ et al (1984 November 1) Effect of encouragement on walking test performance. Thorax 39(11):818–822
92. Knox AJ, Morrison JF, Muers MF (1988 May 1) Reproducibility of walking test results in chronic obstructive airways disease. Thorax 43(5):388–392
93. Stevens D, Elpern E, Sharma K et al (1999 November) Comparison of hallway and treadmill six-minute walk tests. Am J Respir Crit Care Med 160(5 Pt 1):1540–1543
94. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE (1992 December) Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 47(12):1019–1024
95. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA (1994 November) Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. Eur Respir J 7(11):2016–2020
96. Eaton T, Young P, Nicol K, Kolbe J (2006) The endurance shuttle walking test: a responsive measure in pulmonary rehabilitation for COPD patients. Chron Respir Dis 3(1):3–9
97. Onorati P, Antonucci R, Valli G et al (2003 May) Non-invasive evaluation of gas exchange during a shuttle walking test vs. a 6-min walking test to assess exercise tolerance in COPD patients. Eur J Appl Physiol 89(3–4):331–336
98. Revill SM, Morgan MDL, Singh SJ, Williams J, Hardman AE (1999 March 1) The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. Thorax 54(3):213–222
99. Revill SM, Singh SJ, Morgan MD (2000 August) Randomized controlled trial of ambulatory oxygen and an ambulatory ventilator on endurance exercise in COPD. Respir Med 94(8):778–783
100. Turner SE, Eastwood PR, Cecins NM, Hillman DR, Jenkins SC (2004 September) Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests. Chest 126(3):766–773
101. Palange P, Forte S, Onorati P et al (2000 May 1) Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. J Appl Physiol 88(5):1715–1720
102. O'Donnell DE, Bertley JC, Chau LK, Webb KA (1997 January) Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. Am J Respir Crit Care Med 155(1):109–115
103. Marin JM, Carrizo SJ, Gascon M et al (2001 May) Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163(6):1395–1399
104. Puente-Maestu L, de Garcia PJ, Martinez-Abad Y et al (2005 August) Dyspnea, ventilatory pattern, and changes in dynamic hyperinflation related to the intensity of constant work rate exercise in COPD. Chest 128(2):651–656
105. O'Donnell DE, Hamilton AL, Webb KA (2006 October) Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J Appl Physiol 101(4):1025–1035
106. Sinderby C, Spahija J, Beck J et al (2001 June) Diaphragm activation during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163(7):1637–1641
107. Bellemare F, Grassino A (1983 July) Force reserve of the diaphragm in patients with chronic obstructive pulmonary disease. J Appl Physiol 55(1 Pt 1):8–15
108. Stubbing DG, Pengelly LD, Morse JL, Jones NL (1980 September) Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. J Appl Physiol 49(3):511–515

109. Vogiatzis I, Georgiadou O, Golemati S et al (2005 September) Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. Thorax 60(9):723–729
110. Yan S, Kaminski D, Sliwinski P (1997 July) Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 156(1):55–59
111. Aliverti A, Stevenson N, Dellaca RL et al (2004 March 1) Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. Thorax 59(3):210–216
112. O'Donnell DE, D'Arsigny C, Fitzpatrick M, Webb KA (2002 September 1) Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. Am J Respir Crit Care Med 166(5):663–668
113. Ofir D, Laveneziana P, Webb KA, Lam Y-M, O'Donnell DE (2008 Mar 15) Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. Am J Respir Crit Care Med 177(6):622–629
114. He Z, Lam M, Webb K, O'Donnell DE (2005) Ventilatory constraints during exercise in patients with mild COPD (abstract). Am J Respir Crit Care Med 171:A304
115. Celli BR, Cote CG, Marin JM et al (2004 March 4) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350(10):1005–1012
116. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP (1999 December 1) Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160(6):1856–1861
117. Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM (2000 September) Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 94(9):859–867
118. Marquis K, Debigare R, Lacasse Y et al (2002 September 15) Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166(6):809–813
119. Swallow EB, Reyes D, Hopkinson NS et al (2007 February 1) Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax 62(2):115–120
120. Weitzenblum E, Hirth C, Ducolone A et al (1981 October 1) Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. Thorax 36(10):752–758
121. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E (1999 January 1) Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159(1):158–164
122. Biernacki W, Flenley DC, Muir AL, Macnee W (1988 December 1) Pulmonary hypertension and right ventricular function in patients with COPD. Chest 94(6):1169–1175
123. Roberts CM, Bugler JR, Melchor R, Hetzel MR, Spiro SG (1993 April) Value of pulse oximetry in screening for long-term oxygen therapy requirement. Eur Respir J 6(4):559–562
124. Spence DP, Hay JG, Carter J, Pearson MG, Calverley PM (1993 November 1) Oxygen desaturation and breathlessness during corridor walking in chronic obstructive pulmonary disease: effect of oxitropium bromide. Thorax 48(11):1145–1150
125. Martinez FJ, Foster G, Curtis JL et al (2006 June 15) Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med 173(12):1326–1334
126. Ware JH, Dockery DW, Louis TA et al (1990) Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. Am J Epidemiol 132(4):685–700
127. van Pelt W, Borsboom GJ, Rijcken B et al (1994 May) Discrepancies between longitudinal and cross-sectional change in ventilatory function in 12 years of follow-up. Am J Respir Crit Care Med 149(5):1218–1226
128. Mannino DM, Davis KJ (2006 June 1) Lung function decline and outcomes in an elderly population. Thorax 61(6):472–477

129. Anthonisen NR, Connett JE, Kiley JP et al (1994 November 16) Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 272(19):1497–1505
130. Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA (2002 October 1) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57(10):847–852
131. Kerstjens HA, Rijcken B, Schouten JP, Postma DS (1997 September) Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax 52(9):820–827
132. Oga T, Nishimura K, Tsukino M et al (2007 January) Longitudinal deteriorations in patient reported outcomes in patients with COPD. Respir Med 101(1):146–153
133. Rabe KF, Bateman ED, O'Donnell D et al (2005 August 13) Roflumilast–an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 366(9485):563–571
134. Swanney MP, Jensen RL, Crichton DA et al (2000 September) FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med 162(3 Pt 1):917–919
135. Martinez FJ, de Oca MM, Whyte RI et al (1997 June) Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. Am J Respir Crit Care Med 155(6):1984–1990
136. O'Donnell DE, McGuire M, Samis L, Webb KA (1995 December) The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. Am J Respir Crit Care Med 152(6 Pt 1):2005–2013
137. Leach RM, Davidson AC, Chinn S et al (1992 October) Portable liquid oxygen and exercise ability in severe respiratory disability. Thorax 47(10):781–789
138. Davidson AC, Leach R, George RJ, Geddes DM (1988 December) Supplemental oxygen and exercise ability in chronic obstructive airways disease. Thorax 43(12):965–971
139. Oga T, Nishimura K, Tsukino M et al (2000 June) The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. A comparison of three different exercise tests. Am J Respir Crit Care Med 161(6):1897–1901
140. Peters MM, Webb KA, O'Donnell DE (2006 July) Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. Thorax 61(7):559–567
141. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R (2003 November 1) Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med 168(9):1034–1042
142. Palange P, Valli G, Onorati P et al (2004 November) Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. J Appl Physiol 97(5):1637–1642
143. Eves ND, Petersen SR, Haykowsky MJ, Wong EY, Jones RL (2006 October 1) Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 174(7):763–771
144. Laude EA, Duffy NC, Baveystock C et al (2006 April 15) The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease: a randomized crossover trial. Am J Respir Crit Care Med 173(8):865–870
145. O'Donnell DE, Sanii R, Giesbrecht G, Younes M (1988 November) Effect of continuous positive airway pressure on respiratory sensation in patients with chronic obstructive pulmonary disease during submaximal exercise. Am Rev Respir Dis 138(5):1185–1191
146. O'Donnell DE, Webb KA, Bertley JC, Chau LK, Conlan AA (1996 July) Mechanisms of relief of exertional breathlessness following unilateral bullectomy and lung volume reduction surgery in emphysema. Chest 110(1):18–27
147. Porszasz J, Emtner M, Goto S et al (2005 October) Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 128(4):2025–2034

148. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S (2005 March) Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 127(3):809–817
149. Cote CG, Celli BR (2005 October 1) Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J 26(4):630–636
150. O'Donnell DE, Bain DJ, Webb KA (1997 February 1) Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. Am J Respir Crit Care Med 155(2):530–535
151. O'Donnell DE, D'Arsigny C, Hollingworth EN, Webb KA (2000) Oxygen reduces dynamic hyperinflation and improves exercise performance in hypoxic patients with COPD. Am J Respir Crit Care Med 161:A753
152. Laveneziana P, O'Donnell DE (2007). The role of spirometry in evaluating therapeutic responses in advanced COPD. Dis Manage Health Outcomes 15(2): 91–100
153. O'Donnell DE, Ofir D, Laveneziana P (2007). Patterns of cardiopulmonary response to exercise in lung diseases. Eur Respir Mon 40:69–92
154. O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. COPD: J of COPD 3(4):219–232

4

Outcome Measures and Prognostic Markers for COPD

Mario Cazzola and Barry J. Make

Key Points:

- Lung function, most commonly measured by the FEV_1, does not provide a complete picture of the impact of COPD. Assessment of both physiologic and symptomatic outcomes is recommended to more fully assess response to therapeutic interventions.
- Indices of resting and dynamic hyperinflation are associated with exercise capacity and mortality.
- Assessment of response to therapy should include patient-centered outcomes such as health-related quality of life and respiratory symptoms measured with validated questionnaires.
- Cardiopulmonary exercise tests provide more information about the nature of exercise capacity that may be clinically important. Field tests of exercise performance, such as the 6-min walk test, are commonly used to assess response to therapy.
- The presence and severity of exacerbations of COPD as an outcome measure can be based on symptoms but can additionally be linked to such symptoms as require changes in therapy and the need for healthcare utilization.
- Mortality is an important outcome in patients with COPD. Several clinical features are known to correlate with mortality, and a multi-dimensional score (the BODE index) has recently been found to be more predictive of mortality than lung function alone.
- Assessment of the presence and the degree of emphysema and airway disease by chest CT scan can provide important phenotypic information.
- Body composition and other systemic manifestations of COPD may be important outcomes.

Keywords Biomarkers • dyspnoea • exercise • health status • lung function • outcomes

Introduction

The term COPD, a disease condition characterized by the presence of incompletely reversible airflow limitation, is commonly used to indicate different entities such as chronic bronchitis, emphysema, and variably also unremitting asthma, each of which has its own outcomes and prognostic markers. This is one reason why many researchers and clinicians have difficulty in understanding what constitutes a response to a therapeutic intervention in COPD. This difficulty is amplified by the fact that COPD

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_4,

Table 4.1 Important Outcomes in COPD [139].

Function
Physiology (e.g., FEV_1, lung volumes)
Functional capacity (e.g., exercise tests, walk tests)
Patient effects
Respiratory symptoms (e.g., dyspnoea, cough, sputum)
Health status (e.g., health-related quality of life)
Psychological (e.g., depression, anxiety)
Neuropsychological function (e.g., memory, cognition)
Course of the disease
Exacerbations
Mortality
Costs (e.g., hospitalizations, medications)
Disease
Pathophysiology
Pathology
Radiology
Other
Need for medications and therapies
Caregiver burden
Health-enhancing behaviors (e.g., smoking cessation, patient adherence to prescribed treatments)
Assistive technology (e.g., wheelchair, walker)
Satisfaction with care
Adverse effects of therapy (e.g., medication side effects)
Complications/co-morbidities (e.g., pulmonary hypertension, osteoporosis)

is a multi-component disease characterized by a range of pathological changes, which include mucus hypersecretion, airway narrowing and loss of alveoli in the lungs, and such systemic effects as loss of lean body mass and cardiovascular effects [1]. COPD patients are also heterogeneous in terms of their clinical presentation, disease severity, and rate of disease progression [1].

Consequently, the impact of COPD on an individual patient depends not just on the degree of airflow limitation (most commonly measured by the forced expiratory volume in 1 s, FEV_1). Rather, symptoms (especially breathlessness and decreased exercise capacity) and complications of the disease are additional key components of the evaluation of the disease progression and the potential effect of therapy [2], supporting the need to explore outcome measures in addition to lung function. There has been a surge of recent interest in patient-centered outcomes for evaluating new interventions that have the potential for modifying the clinical course of COPD. Table 4.1 outlines various clinical outcome measures that are used in COPD.

Lung Function

FEV_1 and the rate of FEV_1 decline are the most widely used outcome measures for clinical trials of COPD treatment and prevention of COPD progression. It remains a valuable primary endpoint that regulatory authorities regard as an acceptable measure of efficacy for COPD pharmacological trials in combination with instruments that encompass symptomatic endpoints. The use of this marker is supported by the concept that COPD is the consequence of accumulating loss of FEV_1 [3]. Extrapolation from cross-sectional pathologic and radiologic studies suggests that the decline in FEV_1 is

associated with progression of anatomic processes in patients with predominant airway disease as well as in those with predominant emphysema. However, this assumption has not been proved in long-term prospective studies using more sensitive methods to assess airway and parenchymal changes along with lung function measures. Nevertheless, FEV_1 is commonly used in assessing the progression of both disease phenotypes [3].

It is well known that the degree of airflow limitation, as measured by FEV_1, does not necessarily correlate strongly with patient-reported clinical outcomes such as health status, dyspnoea, or exercise performance [4–6]. This is likely the result of other pathophysiologic (i.e., dynamic hyperinflation) and psychological (i.e., coexisting anxiety and depression) factors, which also affect symptoms. Lung hyperinflation is present in patients with more advanced COPD at rest owing to the effects of increased lung compliance as a result of the permanently destructive changes of emphysema and expiratory flow limitation and worsens with activity [7]. Changes in FEV_1 should not be regarded as a surrogate for changes in clinical outcomes, and thus clinical outcomes should be measured separately to complement other markers of physiologic impairment when assessing a therapy for COPD.

In moderate-to-severe COPD, airflow limitation is usually associated with gas trapping and hyperinflation as assessed objectively by an increase in residual volume (RV) and thoracic gas volume (TGV) [8]. Ultimately, as hyperinflation increases, there is an associated decrease in inspiratory capacity (IC) and an inability to expand tidal volume to meet increased metabolic demands [9]. These physiologic abnormalities are associated with symptoms of dyspnoea, exercise intolerance, and patient impairment and disability [10, 11]. Hence, it might be expected that strategies that decrease hyperinflation should improve the aforementioned parameters. Several studies have demonstrated a reduction in dynamic hyperinflation and improvement in exercise capacity following bronchodilators [12, 13]. In patients with decreased IC at rest, there is an increase of IC and increased tidal volume and minute ventilation after administration of bronchodilators. This increase correlates closely with improvement in a sensation of dyspnoea and exercise capacity [14]. However, measuring IC after a pharmacological intervention without plethysmographic determination of the static lung volumes may not be an adequate reflection of the underlying changes in these volumes [15]. In hyperinflated patients, RV or forced vital capacity (FVC) may be useful measures for identifying a therapeutic response that may not be determined from measuring FEV_1 alone [8].

Hyperinflation has also recently been reported to be of prognostic significance. Casanova et al. have shown that the inspiratory capacity/total lung capacity ratio is a predictor of mortality [16].

Patient-Reported Outcomes

"Patient-reported outcomes" refers to characteristics of importance, which are obtained by eliciting direct responses from patients using validated questionnaires. Understanding the importance of patient-reported outcomes in COPD compared to physiological outcomes that may be considered more physician-centered is indispensable, because patients and physicians do not always share viewpoints on what is important in this disease. As both types of outcomes are complementary during the long-term follow-up of COPD, their assessment will enable clinicians to evaluate the overall effectiveness of the impact of the therapeutic interventions on patients.

Dyspnoea and health-related quality of life (health status) are generally considered the most important patient-centered outcomes for characterizing response to treatment in COPD.

Dyspnoea

Dyspnoea, a debilitating and disabling symptom of COPD, is now considered a fundamental outcome because of its direct relation with both the patient's health-related quality of life (HRQOL) and a likely predictor of survival [17]. Nonetheless, a discrepancy often exists between the patient's perception and the physician's clinical evaluation of the impact of symptoms that frequently accompany COPD, particularly as it relates to dyspnoea [18]. This likely occurs because dyspnoea arises "from interactions among multiple physiological, psychological, social, and environmental factors and may induce secondary psychological and behavioral responses" [19].

Instruments used to measure dyspnoea should rely on patient report, be multidimensional where possible, adhere to standardized methodology, and ideally be self-administered [17]. On the basis of various characteristics, dyspnoea assessment instruments may be grouped into three categories [18]: (1) standardized questionnaires, which require patients to recall dyspnoea symptoms that occurred during activities of daily living over a previous period; (2) instruments that evaluate the patient's current level of dyspnoea; (3) health-related quality of life (HRQOL) instruments, which include a dyspnoea domain and dyspnoea score. The Medical Research Council (MRC) scale [20] considers a single dimension (i.e., physical tasks, such as walking, that provoke breathlessness), the Baseline (BDI) and Transition (TDI) Dyspnoea Indices [21] consider three components (functional impairment, magnitude of task, and magnitude of effort), and the dyspnoea domain of the Chronic Respiratory Questionnaire (CRQ) [22] incorporates five physical activities that are specific for the individual patient; these are the three clinical instruments most widely used to quantify dyspnoea.

The MRC scale is not generally considered satisfactory as an evaluative instrument to measure changes in dyspnoea because its broad grades are generally unresponsive to interventions such as pharmacotherapy [17]. The responsiveness of the TDI and the dyspnoea component of the CRQ, which are multidimensional clinical instruments, has been demonstrated in numerous multicenter randomized clinical trials with pharmacotherapy and pulmonary rehabilitation, in patients with COPD [17]. Such measures to assess breathlessness cannot determine the etiology of the dyspnoea, and comorbid and associated conditions such as cardiac disease may confound the ability to relate changes in dyspnoea solely to the underlying lung disease.

Health Status

Standardized measures of health status provide a method of assessing the impact of the disease on patients' daily lives, activity, and well-being. The term "quality of life" (QOL) is often used loosely in this context, but this is inappropriate. Multiple factors determine an individual's quality of life. Even in very ill people, health usually forms only a minor determinant of an individual's quality of life – employment, finances, family, and social factors being collectively more important [23]. Health-related quality of life (HRQOL) is a more specific term, but since peoples' lives are so varied, the impact of disease will also be varied. It is appropriate to use HRQOL when referring to individuals, but to use "health status" when measuring groups of patients.

Health is an abstract concept, but it is possible to produce standardized health status measures that have true interval-scaling properties (i.e., the questionnaire behaves like a ruler). By contrast, QOL is personal to each individual. While there is a relationship between reduced lung function and impaired health [24], this is not sufficiently strong for spirometric measures to provide a reliable estimate of HRQOL [25]. For that reason, measurements of health status must be made using specifically designed questionnaires.

There are three broad types of health status questionnaires [26]. Each has its purpose. Disease-specific measures are targeted at patients with COPD directly, so they should be able to identify small differences between levels of disease severity (discriminative properties) and be sensitive to clinically worthwhile changes with therapy (evaluative properties). Generic questionnaires that can be used in a variety of diseases and are not limited to patients with respiratory disorders may have reasonably good discriminative properties in COPD, but may not be less sensitive to change [27]. Health utility instruments provide a different perspective. They are generic questionnaires, but their design is driven from a health economic perspective in which death is included as a health state. They may have discriminative properties in COPD, but may be less effective at evaluating changes. Despite these theoretical concerns, all three types of questionnaires have been successfully used in assessing outcomes of therapies in COPD, including bronchodilators, pulmonary rehabilitation, and lung volume reduction surgery.

The importance of the evaluation of health status in COPD is highlighted by studies that show correlations between health status and other clinical outcomes. For example, poor scores on the St George's Respiratory Questionnaire (SGRQ), an instrument that measures disease-specific health status, were associated with mortality, hospital readmission, and increased healthcare resource consumption [28, 29]. Nevertheless, it must be noted that the perception of QOL varies among individuals with otherwise similar objective physiologic abnormalities [30]. A meta-analysis of the published COPD clinical trials has documented that the SGRQ does not correlate with the severity of the disease based on the severity of airway obstruction [31].

Exercise Capacity

Exercise capacity has become an important outcome measure in COPD, as many patients complain of exercise intolerance and exertional dyspnoea, and because it is a major determinant of an impaired health status [24, 32]. Moreover, exercise intolerance is an important predictor of mortality [33].

In COPD patients, exercise tolerance cannot be predicted by resting lung function measurements (i.e., FEV_1) [34]. Exercise impairment in these patients does not depend only on ventilatory limitation or gas interchange abnormalities [35–37]. Factors such as skeletal muscle dysfunction can contribute to impaired exercise capacity. An American Thoracic Society/American College of Chest Physicians statement [38] emphasized the utility of clinical exercise testing in the assessment of impairment in patients with COPD, specifically noting its advantages in terms of standardizing the measurement of both exertional dyspnoea and exercise intolerance, two hallmarks of disability in patients with COPD. Several studies have shown that the measurement of operating lung volumes during clinical exercise testing complements the measurements of dyspnoea and endurance time and allows for a more complete characterization of the efficacy of COPD treatments at the impairment/disability interface [4, 39–43].

There are two types of clinically applicable exercise tests: laboratory-based tests and field tests. Laboratory exercise protocols require a treadmill and cycle ergometer (cardiopulmonary exercise testing, CPET) provide a global assessment of the integrative responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function. Simple exercise tests, such as the 6-min walking test (6MWT) and shuttle walk test, can be performed without elaborate equipment [34].

Currently, both the 6MWT and CPET are commonly used for functional assessment. Whether a 6MWT and/or CPET should be used depends on the questions being asked and the available resources; both provide complementary, albeit different, information [38]. CPET is clinically useful in the evaluation of patients with COPD when an objective determination of exercise capacity (oxygen uptake at peak exercise, and work at peak exercise) is necessary to establish exercise limitation, to assess other factors that may be contributing to exercise limitation (occult myocardial ischemia), to relate symptoms to exercise limitation, especially when exertional symptoms are disproportionate to resting pulmonary function tests, and to determine whether hypoxemia contributes to exercise limitation, and supplemental oxygen requirements may be directly quantified [38]. As such, CPET may be preferred in circumstances where important information is required for clinical decision making. Nonetheless, field tests have been used extensively in trials to evaluate possible benefits of therapeutic interventions. Because walking is one of the simplest and most common activities, it is an integrative useful test to assess the physical, psychological, and emotional capabilities of patients. The 6MWT test has established reliability and validity in predicting survival in a variety of settings, including following pulmonary rehabilitation [44] and after lung volume-reduction surgery (LVRS) [45]. It correlates well with VO_2 peak [46] and with HRQOL [47]. In addition, a threshold (54 m) for noticeable differences in patients' subjective comparison ratings of their walking has been determined [48]. Owing to these advantages and its relative standardization [49], the 6MWT test is increasingly used to complement the evaluation of patients with COPD. In addition to the distance covered, it is useful to record, at the beginning and end of exercise, the intensity of breathlessness (and sometimes leg fatigue), heart rate, and arterial O_2 saturation.

Exacerbations

Exacerbations of COPD cause morbidity, hospital admission, mortality, and strongly influence QOL [50] and increase healthcare costs. In addition, functional status and HRQOL can remain impaired for some time following an exacerbation [51] and, moreover, frequent exacerbations may accelerate the rate of decline of lung function over time in patients with COPD [52]. The incidence of exacerbations is an important outcome that should always be considered, but the incidence varies according to the definition used [53].

Unfortunately, there is no accepted agreed definition for an exacerbation of COPD, since exacerbations have a variety of causes and severities [54]. What, for empiric purposes, constitutes an exacerbation? Can an exacerbation be defined as two or more days of increased symptoms accompanied by reduced activity level? How are severity and duration defined? This important clinical phenomenon needs to be standardized to enhance its utility as a trial outcome and permit meta-analysis across trials to inform decision making.

Despite its importance, the definition and empiric measurement of exacerbation have been elusive. Considerable heterogeneity in the etiology and manifestation of COPD exacerbations makes their definition and quantification extremely difficult. The wealth of definitions employed to date can be categorized broadly on the basis of their description of patient symptoms (symptom-based definitions) or definitive events (event-based definitions) [55]. Symptoms are of fundamental importance and are the primary concern of the patient, and thus exacerbations can be generally considered as a change in symptoms that prompts contact with healthcare professionals [55]. The advantage of this definition is that it considers both patient report and healthcare utilization as key features. Assessment of patient symptoms and subsequent improvement with therapy is therefore a fundamental consideration for both patient and physician. Identification of a standardized symptom-based definition is likely to be complicated by the highly varied nature of COPD and its exacerbations. As patient symptomatology varies greatly, and an absolute level of dyspnoea or sputum volume cannot be described as diagnostic, a subjective assessment of "worsening" is required. This raises the question as to who is best placed to make this judgment: the patient or the doctor?

Event-based definitions have been increasingly used in an attempt to circumvent the problems associated with identifying and defining symptoms or groups of symptoms, and simply capture all patients whose condition has changed sufficiently to require an unscheduled visit to a healthcare provider, an emergency department visit, hospitalization, or a change of treatment (generally therapy with systemic steroids or antibiotics) [55]. Classification of exacerbations based on events offers a straightforward approach and is therefore widely used in clinical trials. Event-based criteria do, however, require a sequence of decision making, involving both the patient and the doctor. In any case, in the absence of definitive signs and symptoms on which to base a diagnosis, event-based definitions currently represent the most unambiguous and practical approach to clearly identifying episodes of exacerbation [55]. A general definition such as "an exacerbation of COPD is an increase in respiratory symptoms over baseline that usually requires medical intervention" is event-based and initiated by patient symptoms. Published clinical trials of bronchodilators and/or inhaled corticosteroids in COPD commonly report exacerbations as an outcome of therapy [56, 57]. It has been suggested that many exacerbations are unreported raising the question as to whether these symptoms should be collected.

The great variability in the course of exacerbations of COPD even in patients with similar degrees of pulmonary impairment renders the prediction of the outcome in a given patient very difficult. Consequently, the effect of any given therapeutic intervention may be not only to reduce the frequency of exacerbations, but also to reduce their severity. The classification in types I to III according to the Anthonisen's criteria [58] is not a severity scale, but a classification that indicates the likelihood of bacterial infection as cause of an exacerbation. The severity of exacerbations may be based on the degree of healthcare utilization, but this definition has the disadvantage of having different criteria for hospital admission or different patterns of use of antibiotics and/or oral steroids in different settings or countries. Each exacerbation should be classified according to severity scale (*mild*: increase in respiratory symptoms controlled by the patient with an increase in the usual medication; *moderate*: the one requiring treatment with systemic corticosteroids and/or antibiotics; *severe*: exacerbations requiring hospitalization or a visit to the emergency department) that is an integration of the severity scale proposed in the ATS/ERS COPD guidelines for COPD [1]. The severity of the exacerbations is closely related to the severity of the baseline disease; i.e., severe COPD

patients are more likely to be hospitalized because of an exacerbation. Therefore, distribution of severity of exacerbations generally parallels distribution of severity of COPD in a given population.

Mortality

Mortality remains to be the most important and robust clinical outcome in COPD research. The recognition and modification of likely surrogates for mortality in COPD may provide an opportunity to reduce morbidity and improve survival using smaller sample sizes.

The most widely used prognostic factor in stable COPD has been FEV_1 [59]. Recently, it has been documented that rapid lung function decline was independently associated only with a modest increased risk of COPD deaths [60]. Also the ratio of IC to total lung capacity (IC/TLC) is a predictor of respiratory and all-causes mortality in COPD [16]. Variables other than lung function and the degree of airflow obstruction are also predictors of mortality and these include hypoxemia or hypercapnia [61], higher dyspnoea score [62], a low body mass index (BMI) [63], reduced exercise capacity [32], frequent exacerbations/hospitalizations [64], cor pulmonale [65], and C-reactive protein (CRP) [66]. A multi-component score, the BODE index, has also been shown to be a predictor of mortality. BODE is a 10-point scale that combines measures of BMI (B), the degree of airflow obstruction (O) measured by FEV_1, dyspnoea (D), and exercise capacity (E) measured by the 6-min walk distance into a single metric, thus encompassing the pulmonary as well as the systemic effects of COPD [67]. The clinical phenotype of the patient with COPD may also impact prognosis [68], as earlier reports suggested that emphysema is associated with a worse prognosis than chronic bronchitis or asthma [69, 70].

A recent report from the National Emphysema Treatment Trial [71] has shown that mortality in patients with COPD with moderate to severe emphysema, as defined by high-resolution CT scan, plus severe, chronic airflow obstruction, is influenced by numerous clinical and physiologic factors. Increased mortality is observed in patients with greater age, lower BMI, O_2 utilization (in contrast to PaO_2), and greater hyperinflation. Exercise capacity, as quantified by cardiopulmonary exercise testing in contrast to 6MWT distance, proves a powerful independent predictor of survival. By contrast, a multidimensional index, the modified BODE index, proved a weak independent predictor in patients with severe emphysema. These data suggest that readily available clinical parameters may be useful in predicting outcome in severe emphysema.

Several factors have been reported as risk factors for mortality after exacerbations. They are $PaCO_2$, O_2 saturation and resting oxygen uptake [72], low BMI [73], older age [65], cardiac factors [65], other comorbidities [65], and severity of illness, serum albumin level, functional status, and PaO_2 [73].

One of the major limitations of accurately ascertaining causes of death in COPD cohorts is the difficulty in differentiating between various causes of deaths in clinical settings [74]. For example, there may be diagnostic problems separating sudden deaths related to cardiac arrhythmias from mortality related to acute massive pulmonary embolism, or separating deaths from heart failure secondary to cardiac ischemia from these related to cor pulmonale [74]. McGarvey et al. [75] recently reported on a method of assigning cause of death using algorithms applied to careful analysis of complete medical records as part of the TORCH trial.

The main causes of death in mild or moderate COPD are lung cancer and cardiovascular diseases, while in more advanced COPD (<60% FEV_1), respiratory failure becomes the predominant cause [74]. Addressing the potential link between COPD

and comorbidities, such as cancer and cardiovascular diseases, may be of paramount importance in modifying the morbidity and mortality associated with COPD across the full spectrum of COPD severity from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0 to 4 [74].

Imaging

It is conceivable that a better characterization of the underlying disease by sophisticated imaging techniques and a quantification of emphysema may help to reduce the variability of response to therapeutic interventions in COPD patients and tailor treatments to individual patients. Until now, clinical imaging of the lung parenchyma has been performed with techniques such as chest radiography and X-ray computed tomography. The diagnosis of emphysema on the plain radiograph depends upon the detection of the indirect signs of reduced and distorted pulmonary vascularity and hyperinflation [76]. Although the chest radiograph may detect moderate to severe emphysema and can detect extensive bullous disease, it does not allow for a reliable diagnosis of mild emphysema [76]. Another limitation of the chest radiograph is that it does not provide a reliable method to quantify the severity of emphysema and is not sensitive enough to detect subtle changes over time [76].

Computed tomography (CT) is superior to chest radiography in diagnosing emphysema and characterizing the extent and severity of disease [77]. With the latest technical advances in CT, in vivo measurements of human airway dimensions, such as lumen area and wall thickness, have now become feasible even for small bronchi. The CT scan, particularly high-resolution computed tomography (HRCT), defined as thin-section CT (sections 1–2 mm in thickness) optimized by using an edge-enhancing reconstruction algorithm, has, in fact, gained wide acceptance as a diagnostic and investigational radiological tool for the evaluation of airway and parenchymal anatomy, although lack of standardization of the procedures for HRCT acquisition and interpretation complicate the process of unraveling the relationship between HRCT data and lung function derangement in patients with COPD. However, several studies have provided information on how to standardize the acquisition and the interpretation of HRCT in COPD. First, a spirometrically gated HRCT technique has been developed to scan the chest at predefined lung volumes in order to avoid the influence of the level of lung inflation during scanning on HRCT attenuation measurements [78]. Second, the percentage of lung area with attenuation values $\leq$ 950 Hounsfield units (HU) during inspiration and $\leq$ 910 HU during expiration have been proposed, but not necessarily universally accepted as the HRCT attenuation thresholds that best quantify in vivo the morphometric extent of emphysema [79]. Third, quantitative HRCT data have been shown to provide a more consistent and less biased assessment of disease extent than subjective visual analysis and scoring [80]. HRCT attenuation parameters obtained during inspiration can be used to assess the extent of parenchymal destructive changes compatible with emphysema [81].

To obtain a more complete evaluation of the morphologic counterpart of the functional changes that interfere with the health status of COPD patients, it has been suggested that the inspiratory HRCT attenuation data should be complemented with attenuation measurements obtained at full expiration [81]. Differentiation of X-ray low attenuation resulting from emphysema from that resulting from air trapping cannot be obtained by any single physical measurement of lung density. Evaluation of only inspiratory measurements or only expiratory measurements cannot provide a complete analysis of the

dysfunction present in COPD [81]. Both provide valuable data regarding the complexity of the disease, and they should be utilized concomitantly. In any case, one investigation reported that emphysema volumes measured from expiratory multidetector CT scans (slice thickness, 1/0.8 mm) better reflect pulmonary function test abnormalities in patients with severe emphysema than those from inspiratory scans [82].

When combined with comprehensive lung function and lung inflammation, assessment of emphysema by HRCT chest scan may provide more accurate phenotyping of patients with COPD [83] Airway measurements derived from three spirometrically gated thin-section CT scans obtained at defined anatomic levels can enable the differentiation of patients who have COPD with chronic bronchitis from those who have COPD without chronic bronchitis, which is a distinction that correlates with pulmonary functional impairment. HRCT has been used to measure dynamic changes in airway caliber in vivo that are not detectable by conventional global lung measurements such as airway and lung resistance [84]. In addition, HRCT chest scan would allow the identification of bronchiectasis and bronchiolitis [85].

Recent analytical methods, moreover, offer the possibility of further defining subtypes of emphysema [86, 87]. Imaging methods using hyperpolarized gas magnetic resonance imaging techniques cannot only image alveolar structures, but have the possibility of providing very subtle quantitative measures of alveolar size [88, 89]. Magnetic resonance imaging, moreover, may be able to distinguish centrilobular emphysema by specifically quantifying small airway diameters [90].

It must be highlighted that the use of imaging for the assessment of emphysema has some limitations [83]. First, it may not be easy to obtain in a number of centers. Second, it exposes the patient to radiation. Third, it cannot be taken as an indisputable "gold standard" for the quantification of emphysema as it provides correlation coefficients with lung pathology ranging from 0.7 to 0.9.

Biomarkers

A widely used definition endorsed by the National Institutes of Health in the USA is that a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions [91]. In this context, biomarkers are generally not considered to be physiological measurements, such as FEV_1 or exercise capacity. In COPD, several types of biomarkers (in blood, bronchial biopsies, sputum, bronchoalveolar lavage (BAL), and exhaled breath) have been measured that are related to disease pathophysiology and the inflammatory and destructive process in the lung. To be used as outcome measures in COPD, such biomarkers would have to be sensitive to change with therapeutic intervention and would have to predict clinical outcome reliably. Unfortunately, to date, none of them is in routine use for the diagnosis of COPD, for predicting disease progression, or for predicting response to therapy although these biomarkers are reflective of the disease, and have potential use for regulatory purposes [92].

Franciosi et al. [31] reviewed over 600 published studies that covered almost 150,000 patients with COPD, and observed that only sputum neutrophils and IL-8, as well as serum tumor necrosis factor (TNF)-α and CRP, showed any trend toward separating different stages of COPD, although this assumes that our current staging system is the best method of assessing disease severity. However, the authors [31] highlighted that they were faced with a shortage of data in the later stages of the disease. Another aspect they had to consider was the specificity of these cytological and biochemical

variables. The few inflammatory cells and mediators that were affected across COPD stages may not bear a causal relationship with the severity of the disease itself. Rather, they may only reflect local and systemic inflammatory conditions and may not be specific to COPD. In addition, the dynamics of inflammatory cell migration was not considered in the sampled matrices (i.e., blood, tissue biopsy, BAL, and sputum). The correspondence between local and systemic measurements of inflammatory cells such as lymphocytes was often unclear. These measurements were usually obtained at different times from different individuals rather than concurrently within each individual. Hence, parallel sampling schemes for local and systemic matrices would be required for characterizing the inflammatory component of this disease.

Unfortunately, there is significant overlap of biomarkers in healthy smokers and patients suffering from other airway diseases (asthma, interstitial lung diseases, and chronic cough). The large heterogeneity of COPD patients may additionally obscure results. A biomarker, by definition, should possess sufficient discriminatory power (specificity and sensitivity) to accurately reflect disease state. Considering the low specificity of each of these inflammatory mediators, an alternative approach would be to use a combination of markers to facilitate identification of the smoker at high risk for the COPD phenotype [93].

In any case, although there is an association between increased plasma CRP level and impaired lung function in COPD [94], we still do not know if this systemic marker of inflammation is a "spill-over" from a site primarily in the lungs, a marker of a systemic inflammatory process that is causing damage in the lungs, or the result of a secondary process in other organs following primary disease in the lungs [91].

Markers reported to be higher in blood during exacerbation compared with the baseline state include CRP [95], IL-8 [96], TNF-α [97], leptin [97], endothelin-1 [98], eosinophil cationic protein [99], myeloperoxidase [99], fibrinogen [100], IL-6 [100], α_1-antitrypsin [101], and leukotriene B_4 [102]. Nevertheless, Franciosi et al. [103] reviewed the literature in an attempt to identify which biomarkers change in a consistent manner with the severity of the exacerbation event. All suggested biomarkers for exacerbations failed to show consistent trends or lacked sufficient data to permit any meta-analysis. Also Hurst et al. [104], who explored the use of measuring plasma biomarkers at exacerbation of COPD, documented that systemic biomarkers were not helpful in predicting exacerbation severity, although plasma CRP concentration, in the presence of a major exacerbation symptom, seems to be useful in the confirmation of COPD exacerbation. Interestingly, the acute-phase response at exacerbation is strongly related to indices of monocyte function. It must be highlighted, in any case, that a recent paper has suggested that procalcitonin could be a suitable biomarker of exacerbations of COPD, which may be used to target management for each patient and episode more specifically, allowing a sustained reduction in antibiotic use for the treatment of COPD both at short-term and long-term follow-up [105].

Non-pulmonary Markers

There is a growing realization that COPD is a multiorgan-system disease. In particular, there is evidence that the skeletal muscles lose mass and do not function normally, and that this contributes to exercise intolerance [106]. The fat-free mass is also a significant determinant of exercise capacity in patients with COPD, but loss of skeletal muscle mass is the main cause of weight loss in COPD, whereas loss of fat mass contributes to a lesser extent [107]. The observed relationships between weight loss, muscle wasting,

and muscle weakness [108, 109], which are independent of FEV_1, as well as the known close relationship between respiratory muscle weakness and dyspnoea, indicate the importance of adequately recording and reporting all patient characteristics in sufficient detail. Therefore, standardized markers of skeletal muscle function and lean body mass must be considered. This enables investigators to better understand the physical status of their patients, in particular, the state of their peripheral muscles in the context of COPD.

Body Weight and Fat-Free Mass

Body mass index (BMI) is a measure of body weight corrected for body height: body weight/height^2 in kg/m^2, whereas fat-free mass index (FFMI) is a measure of fat-free mass corrected for body height: fat-free mass/height^2 in kg/m^2 [108].

Several studies [110–112] have documented the association between low body mass, and poor prognosis and mortality in patients with established COPD. Threshold value of 25 kg/m^2 was identified below which the mortality risk was clearly increased [113]. Wilson et al. [110] found that in male patients with COPD, weight was a significant predictor of survival even after adjusting for FEV_1. It must be highlighted that the relationship between body mass and pulmonary function is complex and is influenced by several factors that include age, gender, and smoking status, among others. Nonetheless, Harik-Khan et al. [114] have documented that middle-aged and older men with low body weight, as measured by BMI, are at a substantially higher risk of COPD developing even after adjusting for other potential risk factors, including cigarette smoking, age, FEV_1 percent predicted, abdominal obesity, and educational status.

The body mass can be divided into two compartments: fat mass and fat-free mass (FFM). The first is, in principle, a metabolic inactive energy store, whereas the latter contains the metabolic active organs, skeletal muscle being the largest of these organs. Low FFM is a frequently occurring phenomenon in unselected patients with COPD [115]. Regarding BMI, a low FFMI is associated with mortality, and even in patients with normal BMI, a low FFMI is associated with an unfavorable prognosis [116]. Tissue depletion occurs commonly in COPD patients, its prevalence increasing from 20% in clinically stable outpatients up to 35% in patients who are eligible for pulmonary rehabilitation [117, 118]. Loss of FFM adversely affects respiratory and peripheral muscle function, exercise capacity, and health status [118–122]. Because FFMI is associated with prognosis, it seems that assessment of FFM provides important information in COPD and should be considered in the routine evaluation of patients with this condition [115].

Based on the observation that a BMI greater than 24 kg/m^2 is associated with better survival, it has been proposed that obesity could be protective in COPD [123]. However, it must be mentioned that the notion that fat accumulation is protective in COPD may be an oversimplification that neglects the potential consequences of obesity in this disease. It is worth noting that an increased BMI does not protect against fat-free mass depletion in COPD, since there is a preferential loss of muscle tissue in this disease [117]. In fact, muscle mass may be reduced despite a normal BMI [117]. Furthermore, a reduced muscle mass is associated with increased rates of death, irrespective of BMI [115, 124, 125]. These considerations do not reflect the general effects of obesity on mortality in the general population.

Measurement of Quadriceps Muscle Function

Assessment of body composition can be very helpful for better understanding the heterogeneity in clinical manifestations of COPD. FFM is a strong predictor of peripheral

skeletal muscle weakness of upper and lower extremities [120]. Quadriceps muscle weakness has been observed in patients with COPD [126, 127] and has been related to exercise intolerance [128], utilization of healthcare resources [129], and survival in patients with moderate to severe COPD [130]. Unfortunately, measurements of quadriceps muscle function are not yet standard, mainly due to their expense and need for a trained operator.

Besides the impact of loss of peripheral muscle mass on morbidity and prognosis in patients with COPD, there is also growing attention to the qualitative changes in the muscles of these patients. In particular, quadriceps muscle biopsies have demonstrated that fiber atrophy is mainly confined to the type IIA/IIX and IIX fibers, and also that activity of aerobic enzymes is decreased [131, 132]. It has been recently reported that these metabolic and muscle features can influence the susceptibility of patients with COPD to fatigue [133].

The Conclusions of the Report of the ATS/ERS Task Force on the COPD Outcomes

By the time patients with COPD seek medical attention, they usually have significant symptoms, especially dyspnoea, reduced exercise performance, and impaired health status. These aspects of COPD morbidity have been investigated for many years, and their association with the disease process has resulted in measurable outcomes used for the assessment of pharmacological treatment. The ATS/ERS Task Force has now critically assessed and summarized many of these outcomes [134]. Although some of these outcomes have been shown to change with therapy, their observed changes do not always reflect changes in traditional measures of disease severity such as FEV_1. This is because other pathophysiologic (e.g., dynamic hyperinflation of the lungs) and psychological (e.g., coexisting anxiety) influences also affect these outcomes. Therefore, changes in FEV_1 with therapy should not be regarded as a surrogate for changes in dyspnoea, exercise performance, or health status. These variables should be measured separately to complement other markers of physiologic impairment when assessing a therapy for COPD [135].

The ATS/ERS Task Force suggests that it is necessary that evaluation of COPD clinical outcomes include lung-function parameters other than FEV_1, for example, FVC and IC; and moreover, measures of dyspnoea; functional status and health status; exercise tolerance; and breathlessness after exercise. Depending upon the therapeutic mechanism of the intervention, a more practical approach may be the use of a multidimensional tool, such as the BODE index that combines body mass index, airflow obstruction, dyspnoea, and exercise capacity into one measure, thus encompassing the pulmonary as well as the systemic effects of COPD [67]. Another approach may be to consider various combinations of COPD outcomes and determine their associations using a principal components analysis (PCA) [136]. However, the applicability and reliability of the BODE index and PCA methods in pharmacological trials remains to be determined. BODE has been used as a predictor of the risk of death and several studies now suggest that it might a useful indicator of disease progression and treatment effect [137, 138]. In the case of PCA, it offers a more comprehensive means of evaluating COPD patients than relying simply on the degree of airflow limitation, but there is little evidence available at this time to recommend it as useful method in COPD research. Like any outcome or marker, BODE and PCA must be standardized, reproducible, sensitive to treatment effect, feasible for multi-center trials, and free

from safety or ethical problems. In other words, these measures must be scientifically validated and practical for the COPD research community and regulatory authorities to use in their decision making.

The frequency of exacerbations is another important outcome that should be considered in COPD pharmacological trials. The type of definition used for an exacerbation can significantly affect trial outcomes to the extent that any observed treatment benefit may vary. A general definition such as the one described earlier, "an exacerbation of COPD is an increase in respiratory symptoms over baseline that usually requires medical intervention" may be more applicable. However, each exacerbation should be classified according to a severity scale.

At this time, no surrogate marker of COPD or its exacerbations has been identified, or at least validated, other than FEV_1. Thus, consideration should be given about including potential surrogate markers as secondary endpoints in future clinical trials. This may lead to the identification of biomarkers that correlate with clinical outcome. Generation of such data may also help in the development of new hypotheses for future clinical trials.

Based on the rate of disease progression and the frequency of exacerbations, it is now recognized that pharmacological trials in stable COPD should be 6 months or longer in order to examine potential outcomes or support claims of treatment response, particularly for regulatory submissions. A minimum clinically important difference between a treated and an untreated group in either a cross-sectional or cohort study may not be observed with short-term treatment, bearing in mind the slow progression of COPD as measured by FEV_1. A longitudinal randomized controlled trial design may prove to be more useful for investigating clinical outcomes such as FEV_1 and determining the effect of treatment. Such a design would be applicable in pharmacological trials that use the change in frequency of COPD exacerbations as their principal outcome. In this case, the trial length would be at least 1 year to account for the observed seasonal variation of these exacerbations.

The use of a placebo-controlled trial would be also important to capture both the natural history of COPD and the effect of active treatment. However, certain investigators or countries may consider this type of trial unethical since they believe that all patients should have access to some existing treatment such as a bronchodilator. Since all known pharmacological treatments appear to provide symptomatic relief rather than an alteration in disease progression, a long-term placebo-controlled clinical trial would be scientifically and ethically justified for investigating outcomes and treatments in COPD.

References

1. Celli BR, MacNee W (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS paper. Eur Respir J 23:932–946
2. Tashkin DP (2006) Introduction. Am J Med 119(10 Suppl 1):1–3
3. Wise RA (2006) The value of forced expiratory volume in 1 second decline in the assessment of chronic obstructive pulmonary disease progression. Am J Med 119(10 Suppl 1):4–11
4. Diaz O, Villafranca C, Ghezzo H, Borzone G, Leiva A, Milic-Emil J, Lisboa C (2000) Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J 16:269–275
5. Eltayara L, Becklake MR, Volta CA, Milic-Emili J (1996) Relationship between chronic dyspnea and expiratory flow-limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154:1726–1734
6. Hay JG, Stone P, Carter J, Church S, Eyre-Brook A, Pearson MG, Woodcock AA, Calverley PM (1992) Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. Eur Respir J 5:659–664

7. O'Donnell DE (2006) Impatting patient-centred outcomes in COPD: breathlessness and exercise tolerance. Eur Respir Rev 15:37–41
8. Celli B, ZuWallack R, Wang S, Kesten S (2003) Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 124:1743–1748
9. Pellegrino R, Rodarte JR, Brusasco V (1998) Assessing the reversibility of airway obstruction. Chest 114:1607–1612
10. Cooper CB (2006) The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 119(10 Suppl 1): 21–31
11. O'Donnell DE, Laveneziana P (2006) The clinical importance of dynamic lung hyperinflation in COPD. COPD 3:219–932
12. O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K (2006) Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. Chest 130:647–656
13. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H (2004) Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 23:832–840
14. Di Marco F, Milic-Emili J, Boveri B, Carlucci P, Santus P, Casanova F, Cazzola M, Centanni S (2003) Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. Eur Respir J 21:86–94
15. Newton MF, O'Donnell DE, Forkert L (2002) Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest 121:1042–1050
16. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, Celli BR (2005) Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 171:591–597
17. Mahler DA (2006) Mechanisms and measurement of dyspnea in chronic obstructive pulmonary disease. Proc Am Thorac Soc 3:234–238
18. Ries A (2006) Impact of chronic obstructive pulmonary disease on quality of life: the role of dyspnea. Am J Med 119(10 Suppl 1):12–20
19. American Thoracic Society (1999) Dyspnea: mechanisms, assessment, and management: a consensus statement. Am J Respir Crit Care Med 159:321–340
20. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH (1959) The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 5147:257–266
21. Mahler DA, Weinberg DH, Wells CK, Feinstein AR (1984) The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 85:751–758
22. Williams JE, Singh SJ, Sewell L, Guyatt GH, Morgan MD (2001) Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). Thorax 56:954–959
23. Hickey AM, Bury G, O'Boyle CA, Bradley F, O'Kelly FD, Shannon W (1996) A new short form individual quality of life measure (SEIQoL-DW): application in a cohort of individuals with HIV/AIDS. Br Med J 313:29–33
24. Jones PW (2001) Health status measurement in chronic obstructive pulmonary disease. Thorax 56:880–887
25. Jones PW, Quirk FH, Baveystock CM (1994) Why quality of life measures should be used in the treatment of patients with respiratory illness. Monaldi Arch Chest Dis 49:79–82
26. Jones PW (2006) Health status: what does it mean for payers and patients? Proc Am Thorac Soc 3:222–226
27. Jones PW, Bosh TK (1997) Changes in quality of life in COPD patients treated with salmeterol. Am J Respir Crit Care Med 155:1283–1289
28. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Felez M, Khalaf A, Marrades RM, Monso E, Serra-Batlles J, Anto JM (2002) Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:680–685

29. Osman IM, Godden DJ, Friend JA, Legge JS, Douglas JG (1997) Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. Thorax 52:67–71
30. O'Boyle CA, McGee H, Hickey A, O'Malley K, Joyce CR (1992) Individual quality of life in patients undergoing hip replacement. Lancet 339:1088–1091
31. Franciosi LG, Page CP, Celli BR, Cazzola M, Walker MJ, Danhof M, Rabe KF, Della Pasqua OE (2006) Markers of disease severity in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 19:189–199
32. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T (2003) Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 167:544–549
33. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR (2004) The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 23:28–33
34. Rabinovich RA, Vilaró J, Roca J (2004) Evaluation exercise tolerance in COPD patients: the 6-minute walking test. Arch Bronconeumol 40:80–85
35. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ (1992) Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis 146:935–940
36. Montes de Oca M, Rassulo J, Celli B (1996) Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. Am J Respir Crit Care Med 154:1284–1289
37. Montes de Oca M, Celli BR (2000) Respiratory muscle recruitment and exercise performance in eucapnic and hypercapnic severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:880–885
38. ATS/ACCP statement on cardiopulmonary exercise testing (2003) Am J Respir Crit Care Med 167:211–277
39. Belman MJ, Botnick WC, Shin JW (1990) Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with COPD. Am J Respir Crit Care Med 153:967–975
40. O'Donnell DE, Webb KA (1993) Exertional breathlessness in patients with chronic airflow limitation: the role of hyperinflation. Am Rev Respir Dis 148:1351–1357
41. O'Donnell DE, Lam M, Webb KA (1998) Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:1557–1565
42. O'Donnell DE, Revill SM, Webb KA (2001) Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:770–777
43. Johnson BD, Weisman IM, Zeballos RJ, Beck KC (1999) Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. Chest 116:488–503
44. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL (1996) Variables related to increased mortality following outpatient pulmonary rehabilitation. Eur Respir J 9:431–435
45. Szekely LA, Oelberg DA, Wright C, Johnson DC, Wain J, Trotman-Dickenson B, Shepard JA, Kanarek DJ, Systrom D, Ginns LC (1997) Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. Chest 111:550–558
46. Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L (1995) The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. Chest 108:452–459
47. Guyatt GH, Townsend M, Keller J, Singer J, Nogradi S (1991) Measuring functional status in chronic lung disease: conclusions from a randomized control trial. Respir Med 85(Suppl B):17–21
48. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt H (1997) Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. Am J Respir Crit Care Med 155:1278–1282
49. American Thoracic Society Statement (2002) Guidelines for the six-minute walk test. Am J Respir Crit Care Med 166:111–117

50. Papi A, Luppi F, Franco F, Fabbri LM (2006) Pathophysiology of exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 3:245–251
51. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA (2000) Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:1608–1613
52. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57:847–852
53. O'Reilly JF, Williams AE, Holt K, Rice L (2006) Defining COPD exacerbations: impact on estimation of incidence and burden in primary care. Prim Care Respir J 15:346–353
54. Burge S, Wedzicha JA (2003) COPD exacerbations: definitions and classifications. Eur Respir J Suppl 41:46s–53s
55. Pauwels R, Calverley P, Buist AS, Rennard S, Fukuchi Y, Stahl E, Löfdahl CG (2004) COPD exacerbations: the importance of a standard definition. Respir Med 98:99–107
56. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK (2000) Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. Br Med J 320:1297–1303
57. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H (2003) Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 22:912–919
58. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA (1987) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 106:196–204
59. Sin DD, Wu L, Man SF (2005) The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. Chest 127:1952–1959
60. Mannino DM, Reichert MM, Davis KJ (2006) Lung function decline and outcomes in an adult population. Am J Respir Crit Care Med 173:985–990
61. Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease: a clinical trial. Ann Intern Med 93:391–398
62. Nishimura K, Izumi T, Tsukino M, Oga T (2002) Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 121:1434–1440
63. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP (1999) Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:1856–1861
64. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R (2005) Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 60:925–931
65. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R (1997) Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Respir J 10:2794–2800
66. Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD (2006) C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax 61:849–853
67. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012
68. Burrows B, Bloom JW, Traver GA, Cline MG (1987) The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. N Engl J Med 317:1309–1314
69. Burrows B, Earle RH (1969) Prediction of survival in patients with chronic airways obstruction. Am Rev Respir Dis 99:865–871
70. Boushy SF, Thompson HK Jr, North LB, Beale AR, Snow TR (1973) Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis 108:1373–1383

71. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, DeCamp MM, Benditt J, Sciurba F, Make B, Mohsenifar Z, Diaz P, Hoffman E, Wise R (2006) Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med 173:1326–1334
72. Sukumalchantra Y, Dinakara P, Williams MH Jr (1966) Prognosis of patients with chronic obstructive pulmonary disease after hospitalization for acute ventilatory failure: a three-year follow-up study. Am Rev Respir Dis 93:215–222
73. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA (1996) Outcomes following acute exacerbation of severe chronic obstructive lung disease: the SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 154:959–967
74. Sin DD, Anthonisen NR, Soriano JB, Agusti AG (2006) Mortality in COPD: Role of comorbidities. Eur Respir J 28:1245–1257
75. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA (2007) Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 62:411–415
76. Cleverley JR, Muller NL (2000) Advances in radiologic assessment of chronic obstructive pulmonary disease. Clin Chest Med 21:653–663
77. Zompatori M, Fasano L, Fabbri M, Maraldi F, Carvelli P, Laporta T, Pacilli A (1997) Assessment of the severity of pulmonary emphysema by computed tomography. Monaldi Arch Chest Dis 52:147–154
78. Kalender WA, Rienmuller R, Seissler W, Behr J, Welke M, Fichte H (1990) Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT. Radiology 175:265–268
79. Gevenois PA, De Vuyst P, Sy M, Scillia P, Chaminade L, de Maertelaer V, Zanen J, Yernault JC (1996) Pulmonary emphysema: quantitative CT during expiration. Radiology 199:825–829
80. Bankier AA, De Maertelaer V, Keyzer C, Gevenois PA (1999) Pulmonary emphysema: subjective visual grading versus objective quantification with macroscopic morphometry and thin-section CT densitometry. Radiology 211:851–858
81. Camiciottoli G, Bartolucci M, Maluccio NM, Moroni C, Mascalchi M, Giuntini C, Pistolesi M (2006) Spirometrically gated high-resolution CT findings in COPD: lung attenuation vs lung function and dyspnea severity. Chest 129:558–564
82. Zaporozhan J, Ley S, Eberhardt R, Weinheimer O, Iliyushenko S, Herth F, Kauczor HU (2005) Paired inspiratory/expiratory volumetric thin-slice CT scan for emphysema analysis: comparison of different quantitative evaluations and pulmonary function test. Chest 128:3212–3220
83. Cerveri I, Dore R, Corsico A, Zoia MC, Pellegrino R, Brusasco V, Pozzi E (2004) Assessment of emphysema in COPD: a functional and radiologic study. Chest 125:1714–1718
84. Brown RH, Croisille P, Mudge B, Diemer F, Permutt S, Togias A (2000) Airway narrowing in healthy humans inhaling methacholine without deep inspirations demonstrated by HRCT. Am J Respir Crit Care Med 161:1256–1263
85. Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, Reznek RH, Wedzicha JA (2004) Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170:400–407
86. Hoffman EA, Reinhardt JM, Sonka M, Simon BA, Guo J, Saba O, Chon D, Samrah S, Shikata H, Tschirren J, Palagyi K, Beck KC, McLennan G (2003) Characterization of the interstitial lung diseases via density-based and texture-based analysis of computed tomography images of lung structure and function. Acad Radiol 10:1104–1118
87. Chabat F, Yang GZ, Hansell DM (2003) Obstructive lung diseases: texture classification for differentiation at CT. Radiology 228:871–877
88. Salerno M, de Lange EE, Altes TA, Truwit JD, Brookeman JR, Mugler JP 3rd (2002) Emphysema: hyperpolarized helium 3 diffusion MR imaging of the lungs compared with spirometric indexes - initial experience. Radiology 222:252–260

89. Fain SB, Altes TA, Panth SR, Evans MD, Waters B, Mugler JP 3rd, Korosec FR, Grist TM, Silverman M, Salerno M, Owers-Bradley J (2005) Detection of age-dependent changes in healthy adult lungs with diffusion-weighted ^{3}He MRI. Acad Radiol 12: 1385–1393
90. Yablonskiy DA, Sukstanskii AL, Leawoods JC, Gierada DS, Bretthors GL, Lefrak SS, Cooper JD, Conradi MS (2002) Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized 3He diffusion MRI. Proc Natl Acad Sci USA 99:3111–3116
91. Jones PW, Agusti AG (2006) Outcomes and markers in the assessment of chronic obstructive pulmonary disease. Eur Respir J 27:822–832
92. Barnes PJ, Chowdhury B, Kharitonov SA, Magnussen H, Page CP, Postma D, Saetta M (2006) Pulmonary biomarkers in COPD. Am J Respir Crit Care Med 174:6–14
93. Tzortzaki EG, Tsoumakidou M, Makris D, Siafakas NM (2006) Laboratory markers for COPD in "susceptible" smokers. Clin Chim Acta 364:124–138
94. Gan WQ, Man SF, Senthilselvan A, Sin DD (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59:574–580
95. Hurst JR, Perera WR, Wilkinson TMA, Donaldson GC, Wedzicha JA (2006) Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 173:71–78
96. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, Bouillon R, Decramer M (2003) Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. Thorax 58:752–756
97. Calikoglu M, Sahin G, Unlu A, Ozturk C, Tamer L, Ercan B, Kanik A, Atik U (2004) Leptin and TNF-α levels in patients with chronic obstructive pulmonary disease and their relationship to nutritional parameters. Respiration 71:45–50
98. Roland M, Bhowmik A, Sapsford RJ, Seemungal TA, Jeffries DJ, Warner TD, Wedzicha JA (2001) Sputum and plasma endothelin-1 levels in exacerbations of chronic obstructive pulmonary disease. Thorax 56:30–35
99. Fiorini G, Crespi S, Rinaldi M, Oberti E, Vigorelli R, Palmieri G (2000) Serum ECP and MPO are increased during exacerbations of chronic bronchitis with airway obstruction. Biomed Pharmacother 54:274–278
100. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, Jeffries DJ, Meade TW (2000) Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. Thromb Haemost 84:210–215
101. Stockley RA, Burnett D (1979) α-Antitrypsin and leukocyte elastase in infected and non-infected sputum. Am Rev Respir Dis 120:1081–1086
102. Shindo K, Hirai Y, Fukumura M, Koide K (1997) Plasma levels of leukotriene E_4 during clinical course of chronic obstructive pulmonary disease. Prostaglandins Leukot Essent Fatty Acids 56:213–217
103. Franciosi LG, Page CP, Celli BR, Cazzola M, Walker MJ, Danhof M, Rabe KF, Della Pasqua OE (2006) Markers of exacerbation severity in chronic obstructive pulmonary disease. Respir Res 7:74
104. Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, Vessey RS, Wedzicha JA (2006) Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 174:867–874
105. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, Huber P, Muller B, Tamm M (2007) Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 131:9–19
106. Skeletal muscle dysfunction in chronic obstructive pulmonary disease (1999) A statement of the American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med 159:S1–S40
107. Schols AM (2000) Nutrition in chronic obstructive pulmonary disease. Curr Opin Pulm Med 6:110–115

108. Schols AM, Wouters EF, Soeters PB, Westerterp KR (1991) Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 53:421–424
109. Arora NS, Rochester DF (1982 Jul) Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 126(1):5–8
110. Wilson DO, Rogers RM, Wright EC, Anthonisen NR (1989) Body weight in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 139:1435–1414
111. Gray-Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG (1996) Nutritional status and mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153:961–966
112. Chailleux E, Fauroux B, Binet F, Dautzenberg B, Polu JM (1996) Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation: a 10-year analysis of ANTADIR Observatory. Chest 109:741–749
113. Schols AM, Slangen J, Volovics L, Wouters EF (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797
114. Harik-Khan RI, Fleg JL, Wise RA (2002) Body mass index and the risk of COPD. Chest 121:370–376
115. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, Sorensen TI, Lange P (2006) Body Mass, Fat Free Body Mass and prognosis in COPD patients from a random population sample. Am J Respir Crit Care Med 173:79–83
116. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF (1994) Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. Eur Respir J 7:1793–1797
117. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF (1993) Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 147:1151–1156
118. Baarends EM, Schols AM, Mostert R, Wouters EF (1997) Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. Eur Respir J 10:2807–2813
119. Palange P, Forte S, Felli A, Galassetti P, Serra P, Carlone S (1995) Nutritional state and exercise tolerance in patients with COPD. Chest 107:1206–1212
120. Engelen MP, Schols AM, Does JD, Wouters EF (2000) Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 71:733–738
121. Palange P, Forte S, Onorati P, Paravati V, Manfredi F, Serra P, Carlone S (1998) Effect of reduced body weight on muscle aerobic capacity in patients with COPD. Chest 114:12–18
122. Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM (2000) Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 94:859–867
123. Pitta F, Troosters T, Spruit MA et al (2005) Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 171:972–7
124. Marquis K, Debigaré R, LeBlanc P et al (2002) Mid-thigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with COPD. Am J Respir Crit Care Med 166:809–813
125. Schols AM, Broekhuizen R, Weling-Scheepers CA et al (2005) Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 82:53–59
126. Bernard S, LeBlanc P, Whittom F, Carrier G, Jobin J, Belleau R, Maltais F (1998) Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:629–634
127. Gosker HR, Lencer NH, Franssen FM, van der Vusse GJ, Wouters EF, Schols AM (2003) Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. Chest 123:1416–1424
128. Gosselink R, Troosters T, Decramer M (1996) Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 153:976–980

129. Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G (1997) Muscle weakness is related to utilization of health care resources in COPD patients. Eur Respir J 10:417–423
130. Decramer M, de Bock V, Dom R (1996) Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153:1958–1964
131. Gosker HR, Engelen MP, van Mameren H, van Dijk PJ, van der Vusse GJ, Wouters EF, Schols AM (2002) Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. Am J Clin Nutr 76:113–119
132. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, LeBlanc P (1996) Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. Am J Respir Crit Care Med 153:288–293
133. Wouters EF (2006) Muscle wasting in chronic obstructive pulmonary disease: to bother and to measure! Am J Respir Crit Care Med 173:4–5
134. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Brusasco V, Burge PS, Calverley PMA, Celli BR, Jones PW, Mahler DA, Make B, Miravitlles M, Page CP, Palange P, Parr D, Pistolesi M, Rutten-Van Molken M, Stockley R, Sullivan SA, Wedzicha JA, Wouters EF (2008) Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 31:416–468
135. ZuWallack RL, Haggerty MC, Jones P (2004) Clinically meaningful outcomes in patients with chronic obstructive pulmonary disease. Am J Med 117(Suppl 12A):49S–59S
136. Celli BR, Calverley PM, Rennard SI, Wouters EF, Agusti A, Anthonisen N et al (2005) Proposal for a multidimensional staging system for chronic obstructive pulmonary disease. Respir Med 99:1546–1554
137. Cote CG, Celli BR (2005) Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J 26:630–636
138. Imfeld S, Bloch KE, Weder W, Russi EW (2006) The BODE index after lung volume reduction surgery correlates with survival. Chest 129:873–878
139. Make B (2003) COPD: developing comprehensive management. Respir Care 48:1225–1237

5

Management Guidelines for Chronic Obstructive Pulmonary Disease

Bartolome R. Celli

Key Points:

- COPD is a highly prevalent, under-diagnosed, under-treated and under-perceived disease.
- COPD is a multicomponent disease.
- COPD is a treatable disease.
- Therapy is effective for the respiratory manifestations of COPD.

Keywords Bronchodilators • COPD • guidelines • management

Introduction

The development of guidelines as a tool to provide healthcare deliverers with reliable applicable information related to single diseases, or specific areas of those diseases, was initially based on expert opinion. More recently, the generation of guidelines has relied on the strength of the evidence used to back the statements presented. However, it is fair to say that most of the elements contained in many of the guidelines still depend on the opinion of leaders in the field as well as the distilling of information that may not entirely be amenable to the grading of the evidence. Guidelines for the diagnosis and treatment of Chronic Obstructive Pulmonary Disease (COPD) have not escaped that reality and the most recent ones produced by the American Thoracic and the European Respiratory Societies as well as the Global Initiative for Obstructive Lung Disease or GOLD guidelines have utilized a blend of evidence and expert opinion with the aim of providing practitioners and healthcare workers with information that is easy to access and use. As the field has evolved rapidly, so have the guidelines and many of the concepts presented here will change as new information is gathered and incorporated into every day practice.

In this chapter, I review the salient features of the guidelines that relate to the comprehensive management of patients with COPD allowing then the specific chapters devoted to individual therapies to more exhaustively present the specific material addressed in each one of them.

Perhaps the greatest change in COPD has occurred in its definition. COPD has been re-defined by recent guidelines as: "A preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_5,

lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences" [1, 2].

This definition changes the paradigm that characterized older ones from previous guidelines [3, 4] in two important aspects. First, it presents a positive attitude towards the disease, and secondly, it highlights a salient feature of COPD, its frequent expression of systemic manifestations. This chapter summarizes the recent advances in the comprehensive management of this disease as advised by the guidelines, provides the evidence that patients with COPD respond to treatment, and that the treatment is effective in more than one outcome of importance to patients.

COPD Is Highly Prevalent, Under-Diagnosed, Under-Treated and Under-Perceived

COPD affects millions of individuals, limits the functional capacity of many of them, and has become an important cause of death world-wide. Although preventable, COPD has a long sub-clinical phase. Once symptoms develop, COPD usually results in progressive dyspnoea, at even lower levels of exercise, gas exchange imbalance, and respiratory failure [1–4]. In the end, death can occur either from respiratory failure or from frequently associated co-morbidities such as heart disease and lung cancer [5–7]. The estimated prevalence of COPD varies from 7% to 19% in several well-conducted studies around the world [8–13]. It is a disease that is increasing in women and if we assume the lowest prevalence, the total number of cases of COPD in the world approximates 280 million persons. Unfortunately, COPD remains largely under-diagnosed [14, 15]. Finally, due to many possible reasons patients under-perceive the magnitude of their problem and accept the limitations associated with disease progression as natural for a person who has smoked [16].

COPD a Multicomponent Disease

The airflow obstruction of COPD, as expressed by the forced expiratory volume in 1 s (FEV_1) is, by definition, only partially reversible [1, 2]. In a paradoxical way, we have used this defining physiology as the outcome to determine the effectiveness of interventions. It is no surprise that the lack of large response in FEV_1 to different therapies [17–26] has resulted in an undeserved nihilism. There is increasing evidence that independent of the degree of airflow obstruction, lung volumes are important in the genesis of the symptoms and limitations of patients with more advanced disease. A series of elegant studies have demonstrated that dyspnoea perceived during exercise, including walking, more closely relates to the development of dynamic hyperinflation than to changes in FEV_1 [27–31]. Further, the improvement in exercise brought about by several therapies including bronchodilators, oxygen, lung reduction surgery, and even rehabilitation is more closely related to delaying dynamic hyperinflations than by changing the degree of airflow obstruction [27–30, 32]. Casanova et al. showed that hyperinflation, expressed as the ratio of inspiratory capacity to total lung capacity (IC/TLC) predicted survival better than FEV_1 [33]. This provides us not only with new insights into pathogenesis, but also opens the door for new, imaginative ways to alter lung volumes and perhaps impact on disease progression.

That COPD may be associated with important systemic expressions in patients with more advanced disease is now accepted [1, 5, 34]. Perhaps as a consequence of a persistent systemic inflammatory state or due to other yet unproven mechanisms

such as imbalanced oxidative stress or abnormal immunological response the fact is that many patients with COPD may have decreased free fat mass, impaired systemic muscle function, anemia, osteoporosis, depression, pulmonary hypertension, and cor-pulmonale, all of which are important determinants of outcome. Indeed, dyspnoea measured with a simple tool such as the modified medical research scale (MMRC) [35], the body mass index (BMI) obtained by dividing the weight in kilogram by the height in meters squared (kg/m^2) [36, 37], and the timed walked distance in 6 min or 6MWD [38, 39] are all better predictors of mortality than the FEV_1. The incorporation of these variables into the multidimensional BODE index predicts survival even better [5]. The index is also responsive to exacerbations [40] and more importantly act as a surrogate marker of future outcome after interventions [41] thus providing clinicians with a useful tool to help determine a comprehensive severity of disease. Several chapters in this book more amply detail each of these concepts.

Based on the multidimensional nature of the disease and the availability of multiple effective therapies, the approach shown in Fig. 5.1 may more accurately help clinicians evaluate patients and choose therapies than the current approach of using primarily the FEV_1% from reference values. This novel approach is not yet part of any guidelines but is presented as a proposal as all guidelines agree that the evaluation of the nonpulmonary expressions of the disease is an important component in the comprehensive management of patients.

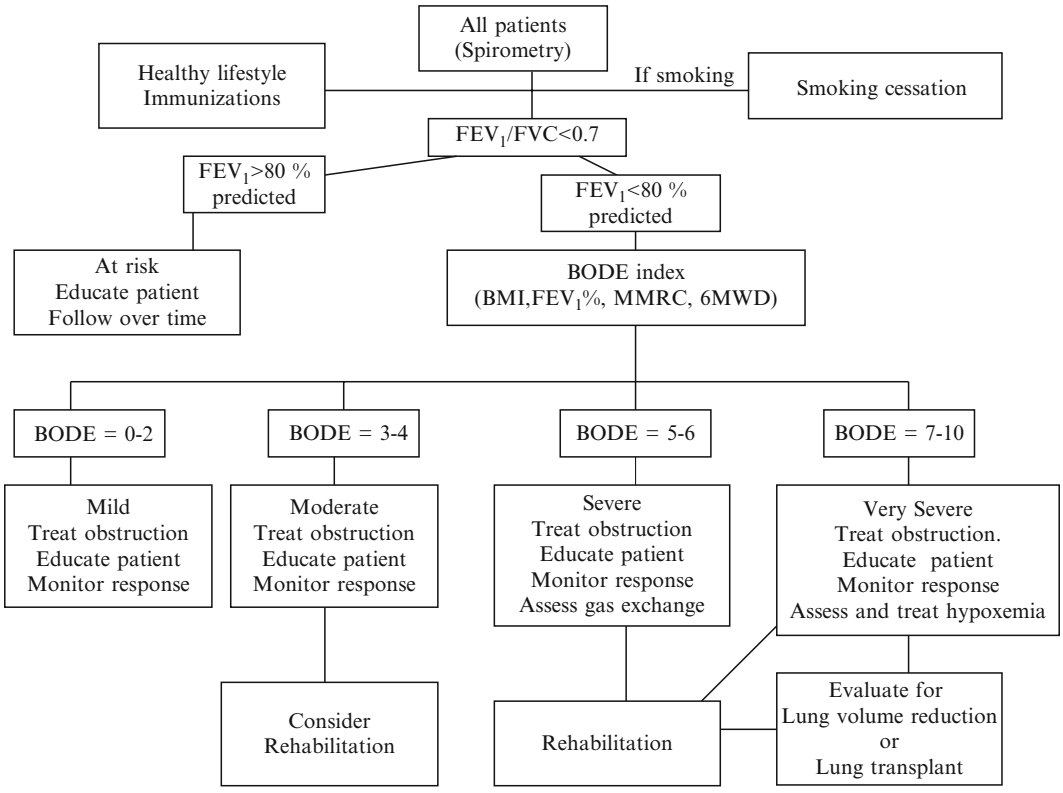


Fig. 5.1. Schematic algorithm to approach patients with chronic obstructive pulmonary disease (*COPD*). The evaluation of the multiple domains using simple validated tools can better help stage the global severity of the disease. This will help choose the best therapeutic options. *FVC* forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *BMI* body mass index, *MMRC* modified medical research council dyspnoea scale, *6MWD* 6 min walk distance

COPD, a Treatable Disease

Current evidence suggests that smoking cessation [6], long-term oxygen therapy in hypoxemic patients [42, 43], mechanical ventilation in acute respiratory failure [44–46], and lung volume reduction surgery for patients with upper lobe emphysema and poor exercise [47] capacity improve survival. The TORCH study in over 6,000 patients showed that the combination of salmeterol and fluticasone not only improved lung function and health status but that the relative risk of their dying over the 3 years of the study decreased by 17.5% [48]. Other therapies such as pulmonary rehabilitation and lung transplant improve symptoms and the quality of a patient's life, once the diagnosis has been established [1, 2, 49, 50]. All of these modalities of therapies and their effect are summarized in Table 5.1.

Therapy Is Effective for the Respiratory Manifestations of COPD

The overall goals of treatment of COPD are to prevent further deterioration in lung function, alleviate symptoms, treat complications, and prevent mortality [1, 3]. Once diagnosed, the patient should be encouraged to actively participate in disease management. This concept of *collaborative management* may improve self-reliance and esteem. All patients should be encouraged to lead a healthful lifestyle and exercise regularly. Preventive care is extremely important at this time and all patients should receive immunizations, including pneumococcal vaccine and yearly influenza vaccines [1, 3]. This comprehensive approach is summarized in Fig. 5.1.

Smoking Cessation and Decreased Exposure to Biomass Fuel

As smoking is the major cause of COPD, smoking cessation is the most important component of therapy for patients who still smoke [1, 3] and should be provided to all patient

Table 5.1 Effective therapies available for patients with stable chronic obstructive pulmonary disease.

Improve survival	May improve survival	Improve patient centered outcomes
Smoking cessation	Pharmacotherapy with salmeterol and fluticasone	Pharmacotherapy Short-acting bronchodilators Long-acting anti-muscarinics Long-acting beta-agonists Inhaled corticosteroids Theophylline Alpha-1-antitrypsin for selected patients Antibiotics for selected patients
Lung volume reduction surgery for selected patients	Pulmonary rehabilitation	Oxygen therapy
Noninvasive ventilation for acute chronic hypercapneic ventilatory failure		Surgery Lung volume reduction Lung transplant Pulmonary rehabilitation

who smoke. Because second hand smoking is known to damage lung function, limitation of exposure to involuntary smoke, particularly in children, should be encouraged. The factors that cause patients to smoke include: the addictive potential of nicotine, conditional responses to stimuli surrounding smoking, psychosocial problems such as depression, poor education and low income, and forceful advertising campaigns. As the causes that drive the patient to smoke are multifactorial, smoking cessation programs should also involve multiple interventions. The clinician should always participate in the treatment of smoking addiction because a physician's advice and intervention, and use of the appropriate medications including nicotine patch, gum, or inhalers, bupropion, and vernecicline help determine successful results [51–54]. The significant burden of COPD in patients exposed to biomass fuel in certain areas of the world should improve by changing the more efficient and less polluting sources of energy.

Pharmacological Therapy of Airflow Obstruction

Many patients with COPD require pharmacological therapy. This should be organized according to the severity of symptoms, the degree of lung dysfunction, and the tolerance of the patient to specific drugs [1, 3]. A step-wise approach similar in concept to that developed for systemic hypertension may be helpful since medications alleviate symptoms, improve exercise tolerance and quality of life and may decrease mortality. Tables 5.1–5.3 provide a summary of the evidence supporting the effect of individual and combined therapies on outcomes of importance to patients with COPD.

Bronchodilators

Several important concepts guide the use of bronchodilators. In some patients, the changes in the FEV_1 may be small and the symptomatic benefit may be due to other mechanisms such as a decrease in the hyperinflation of the lung [55, 56]. Some older COPD patients cannot effectively activate metered dose inhalers (MDI), and we should work with the patient to help him/her achieve mastery of the MDI. If this is not possible, use of a spacer or nebulizer to facilitate inhalation of the medication will help achieve the desired results. Mucosal deposition in the mouth will result in local side effects (i.e., thrush with inhaled steroids) or general absorption and its consequences (i.e., tremor after beta-agonists). Finally, the inhaled route is preferred

Table 5.2 Effect of individual pharmacological agents on important outcomes of patients with chronic obstructive pulmonary disease.

	FEV_1	Lung volume	Dyspnoea	QoL	AE	Exercise endurance	Disease modifier by FEV_1	Mortality	Side effects
Albuterol	Yes (A)	Yes (B)	Yes (B)	NA	NA	Yes (B)	NA	NA	Some
Ipratropium bromide	Yes (A)	Yes (B)	Yes (B)	No (B)	Yes (B)	Yes (B)	No	NA	Minimal
Long acting beta-agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	No	NA	Minimal
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	NA	NA	Minimal
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	No	No	Some
Theophylline	Some (A)	Yes (B)	Yes (A)	Yes (B)	NA	Yes (B)	NA	NA	Important

Level of evidence: *A* more than one randomized trial; *B* limited randomized trials, *NA* not available

Table 5.3 Effect of some combined pharmacological agents on important outcomes of patients with chronic obstructive pulmonary disease.

	FEV_1	Lung volume	Dyspnoea	QoL	AE	Exercise endurance	Disease Modifier by FEV_1	Mortality	Side Effects
Salmeterol + Theophylline	Yes (B)	NA	Yes (B)	Yes (B)	NA	NA	NA	NA	Some
Formoterol + Tiotropium	Yes (A)	NA	Yes (B)	Yes (B)	NA	NA	NA	NA	Minimal
Salmeterol + Fluticasone	Yes (A)	Yes (B)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	Yes	Some	Some
Formoterol + Budesonide	Yes (A)	NA	Yes (A)	Yes (A)	Yes (A)	NA	NA	NA	Minimal
Tiotropium + Salmeterol + Fluticasone	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	NA	NA	Some

Level of evidence: *A* more than one randomized trial; *B* limited randomized trials; *NA* not available

over the oral administration [1, 3], and long-acting bronchodilators are more effective than short-acting ones [1, 2].

The currently available bronchodilators include the following.

Beta-agonists: These drugs increase cyclic adenosine monophosphate (AMP) within many cells and promote airway smooth muscle relaxation. Other nonbronchodilator effects have been observed but their significance is uncertain. In patients with mild intermittent symptoms, it is reasonable to initiate drug therapy with an MDI of a short-acting beta-agonist as needed for relief of symptoms [1, 2]. In patients with persistent symptoms, the use of long-acting beta-agonists [1, 2, 57–60] twice daily is indicated. They prevent nocturnal bronchospasm, increase exercise endurance, and improve quality of life. The safety profile of Salmeterol in the TORCH trial [48] is reassuring to clinicians who frequently indicate selective long-acting beta-agonists to their patients with COPD.

Anticholinergics: These drugs act by blocking muscarinic receptors that are known to be functional in COPD. The appropriate dosage of the short-acting ipratropium bromide is 2–4 puffs 3 or 4 times a day, but some patients require and tolerate larger dosages [1, 3]. The therapeutic effect is a consequence of a decrease in exercise-induced increased lung inflation or dynamic hyperinflation [28]. The long-acting Tiotropium is very effective in inducing prolonged bronchodilation [18, 21] and decreased lung volume [55] in patients with COPD. In addition, it improves dyspnoea, decreases exacerbations [61], and improves health-related quality of life when compared to placebo and even to ipratroprium bromide. Furthermore, the effect of tiotropium on lung function is improved when added to another bronchodilator such as a long-acting beta2-agonist [62]. However, the results of the large UPLIFT trial evaluating the potential role of Tiotropium as a disease-modifying agent [63] did not demonstrate a long-term effect of tiotropium on the decline of lung function but demonstrated significant effects on reducing exacerbations and improving health status [63]. Currently, tiotropium represents a first-line agent for patients with persistent symptoms.

Phosphodiesterase Inhibitors: Theophylline is a nonspecific phosphodiesterase inhibitor that increases intra-cellular cyclic AMP within airway smooth muscle. The bronchodilator effects of these drugs are best seen at high doses where there is also a

higher risk of toxicity. Its potential for toxicity has led to a decline in its popularity. Theophylline is of particular value for less-compliant or less-capable patients who cannot use aerosol therapy optimally. The previously recommended therapeutic serum levels of 15–20 mg/dL are too close to the toxic range and are frequently associated with side effects. Therefore, a lower target range of 8–13 mg/dL is safer and still therapeutic in nature [1, 3]. The combination of two or more bronchodilators (theophylline, albuterol, and ipratropium) has some logical rationale as they seem to have additive effects and can result in maximum benefit in stable COPD [2, 64, 65]. A possible action of theophylline in the gene expression of events central to inflammation in COPD [66] deserves further investigation.

The specific phosphodiesterase E4 inhibitors such as roflumilast may have an anti-inflammatory effect but less gastrointestinal irritation and thus may prove extremely useful if their theoretical advantages are clinically confirmed. The first 6-month studies show modest bronchodilation effects and some effect on quality of life [67, 68]. More recently, two one-year studies confirmed the effects of roflumilast on reducing exacerbations and improving lung function in patients with severe COPD.

Anti-inflammatory Therapy

In contrast to their value in asthma management, anti-inflammatory drugs have not been documented to have a significant role in the routine treatment of patients with stable COPD [1, 2]. Cromolyn and nedocromil have not been established as useful agents although they could possibly be helpful if the patient has associated respiratory tract allergy. One study using monoclonal antibody against interleukin-8 [69] and another one against tumor necrosis factor alpha [70] failed to detect any response. However, patients were selected according to the degree of airflow obstruction and not based on the presence or level of the specific targeted molecule. The groups of leucotriene inhibitors that have proven useful in asthma have not been adequately tested in COPD, so a final conclusion about their potential use cannot be drawn.

Corticosteroids: Glucocorticoids act at multiple points within the inflammatory cascade although their effects in COPD appear more modest than in bronchial asthma. In outpatients, exacerbations necessitate a course of oral steroids as we will discuss later in the monograph but it is important to wean patients quickly as the older COPD population is susceptible to complications such as skin damage, cataracts, diabetes, osteoporosis, and secondary infection. These risks do not accompany standard doses of inhaled corticosteroid aerosols, which may cause thrush but pose a negligible risk for other outcomes such as cataract and osteoporosis. Several large multicenter trials evaluated the role of inhaled corticosteroids in preventing or slowing the progressive course of symptomatic COPD [23, 24, 71–73]. The results of these earlier studies showed minimal, if any, benefits in the rate of decline of lung function. On the other hand, in the one study where it was evaluated, inhaled fluticasone decreased the rate of loss of health-related quality of life and the exacerbations [23]. In addition, its regular use was also associated with a decreased rate of exacerbations. Recent retrospective analyses of large databases suggesting a possible effect of inhaled corticosteroids on improving survival [74, 75] was not confirmed in the TORCH trial where the inhaled corticosteroid only arm did not show improved survival compared with placebo whereas the combination arm was significantly more effective than ICS alone [48]. In that trial, the combination was superior in terms of all outcomes evaluated. This coupled with the more frequent development of investigator associated pneumonia in the patients receiving ICS suggests that ICS should not be prescribed alone but rather associated with a long-acting beta-agonist [48].

Combination Therapy

All the studies that have explored the value of combination of different agents have shown significant improvements over single agents alone and it may be time to think of it as first line therapy (Table 5.3). Initially, the inhaled combination of ipratroprium and albuterol proved effective in the management of COPD [26]. More recently, the combination of tiotropium and fromoterol, even when administered once daily, was almost as effective as the administration of tiotropium once daily and the recommended twice a day dose of formoterol [62]. Similarly, the combination of theophylline and salmeterol was significantly more effective than either agent alone [22]. The TORCH study showed an effect of the salmeterol/fluticasone combination on survival, FEV_1, exacerbation rate, and quality of life compared with placebo and either of the single components [48], confirming earlier studies that evaluated the combination of beta-agonists and corticosteroids [76–78]. A recent trial compared tiotropium plus placebo with tiotropium plus salmeterol and with tiotropium plus the combination of salmeterol and fluticasone in over 400 patients [79]. Although the primary outcome, the exacerbation rate, was similar among the groups, the number of hospitalizations, health-related quality of life, and lung function was significantly better in the group receiving tiotropium plus salmeterol and fluticasone.

Pending economic considerations, once symptoms become persistent, therapy should begin with a long-acting anti-muscarinic agent such as tiotropium or long-acting beta-agonists twice daily. Once a patient reaches an FEV_1 lower than 60% predicted, and continues to be symptomatic, the evidence from the TORCH trial supports the addition of the combination of ICS and LABA. Continuation of tiotropium is reasonable, given its effectiveness and safety record. I believe that all the trials support the concept that intense and aggressive therapy does modify the course of the disease, including rate of decline of FEV_1, as was shown in the TORCH study [48].

Mucokinetic

These drugs aim to decrease sputum viscosity and adhesiveness in order to facilitate expectoration. The only controlled study in the USA suggesting a value for these drugs in the chronic management of bronchitis was a multicenter evaluation of organic iodide [80]. This study demonstrated symptomatic benefits. Oral acetylcysteines are favored in Europe for their anti-oxidant effects. A large trial that was recently reported failed to document any substantial benefit [81]. Genetically engineered ribonuclease seems to be useful in cystic fibrosis, but is of no value in COPD [1, 2].

Antibiotics

In patients with evidence of respiratory tract infection, such as fever, leukocytosis, and a change in the chest radiograph, antibiotics have proven effective [82–85]. If recurrent infections occur, particularly in winter, continuous or intermittent prolonged courses of antibiotics may be useful [86]. The major bacteria to be considered are *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis*. The antibiotic choice will depend on local experience, supported by sputum culture, and sensitivities if the patient is moderately ill or needs to be admitted to hospital [1, 2].

Alpha 1-Antitrypsin

Although supplemental weekly or monthly administration of this enzyme may be indicated in nonsmoking, younger patients with genetically determined emphysema, in practice such therapy is difficult to initiate. There is evidence that the administration of alpha-1 antitrypsin is relatively safe [1, 3, 87, 88]. Although not entirely clear, the most likely candidates for replacement therapy would be patients with mild to moderate COPD.

Vaccination

Ideally, infectious complications of the respiratory tract should be prevented in patients with COPD by using effective vaccines. Thus, routine prophylaxis with pneumococcal and influenza vaccines is recommended [12, 89, 90].

Lung Volume Reduction

Multiple operations have been tried in patients with COPD [91]. Of these, bullectomy has proven useful in patients with large bullae and relatively preserved lung function. Lung transplantation results in normalization of pulmonary function, improvement in exercise capacity, and quality of life, but its effect on survival remains controversial [92–95]. Several issues must be considered when evaluating a candidate for lung transplantation including the patient's pulmonary disability, projected survival without transplantation, co-morbid conditions, and patient preferences. General guidelines include that the patient be younger than 65 years, without any other medical condition that could shorten predicted survival; not be addicted to substances such as alcohol, drugs, or cigarettes; not have persistent bacterial or fungal infections; not have thoracic malformations; or the need for high dose of corticosteroids. The presence of a high BODE index helps facilitate the selection of candidates for transplant since they have a very poor prognosis if left untreated [96].

The other surgical procedure that has received recent attention is pneumoplasty, or lung volume reduction surgery (LVRS) [47, 97–103]. It is an alternative for selected patients with severe inhomogeneous emphysema who remain symptomatic after optimal comprehensive medical therapy. LVRS improves FEV_1 by close to 10%, with larger improvements in exercise tolerance, dyspnoea, and health-related quality of life [47, 101–103]. The effect on survival is larger in patients with inhomogeneous upper lobe disease and limited exercise performance after rehabilitation [47, 104]. The recent reports evaluating techniques capable of achieving lung volume reduction without the surgical risk [104–106] open exciting new avenues. Indeed, the bronchoscopic placement of one-way valves [107] or biological substances [108–110] capable of inducing closure of emphysematous areas may add to an already exciting armamentarium to treat selected patients with advanced COPD.

Therapies That Are Effective for the Nonrespiratory Manifestations of COPD

The most exciting changes in the way we conceptualize COPD is the recognition of the extra-pulmonary manifestations of COPD [5, 111, 112]. Some of the most important advances in the therapy of COPD center around our capacity to impact on the disease without having to necessarily alter the lung function. Two of the most proven forms of therapy for COPD fall within this category; pulmonary rehabilitation and oxygen therapy. If we add mechanical ventilation during exacerbations, the field is wide open to explore even more exciting therapies.

Pulmonary Rehabilitation

Pulmonary rehabilitation is an essential component of the comprehensive management of patients with symptomatic COPD [1, 2, 113–120]. Patients with moderate to moderately severe disease are preferred targets for treatment to prevent the disabling effects of end-stage respiratory failure. The rehabilitation program should have resources

available to teach and supervise respiratory therapy techniques such as oxygen, use of inhalers and nebulizers, physical therapy (breathing techniques, chest physical therapy, postural drainage), exercise conditioning (upper and lower extremity), and activities of daily living (work simplification, energy conservation). Also desirable are services to evaluate and advise on nutritional needs, and psychological, and vocational counseling. Exercise training is the most important component of a pulmonary rehabilitation program. Maltais et al. [121] documented that the muscle biopsies of trained patients, but not controls, manifested significant increases in all enzymes responsible for oxidative muscle function. Pulmonary rehabilitation can change outcomes that predict survival [122]. Indeed, in a recently reported observational study Cote et al. [123] showed that rehabilitation improved the BODE score and the change in BODE reflected outcome prognosis.

Supplemental Oxygen Therapy

The results of the Nocturnal Oxygen Therapy Trial (NOTT) and Medical Research Council (MRC) studies showed that supplemental oxygen improves survival in hypoxemic COPD [42, 43]. Other beneficial effects of long-term oxygen include reduction in polycythemia, in pulmonary artery pressures, dyspnoea, hypoxemia during sleep, sleep, and may reduce nocturnal arrhythmias. Importantly, oxygen can also improve neuropsychiatric testing [124, 125] and exercise tolerance. [126–128]. The beneficial effects of oxygen without necessarily changing the degree of airflow obstruction provide evidence that the disease can be modified without changing the rate of decline of the FEV_1.

Exacerbations

An exacerbation of COPD is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management [1, 3, 129, 130]. Care must be taken to rule out heart failure, myocardial infarction, arrhythmias, and pulmonary embolism, all of which may present with clinical signs and symptoms similar to exacerbation of COPD. The pharmacological therapy of exacerbations is initiated with the same therapeutic agents available for the chronic management of COPD [1, 3]. The most important agents include anticholinergic and beta-agonist aerosols by nebulization. Several trials [131–133] have proven the usefulness of systemic corticosteroids. It is important to avoid prolonged (over 2 weeks) or high-dose therapy as older patients are susceptible to severe complications such as psychosis, fluid retention, and a vascular necrosis of bones. Antibiotics have been helpful in purulent exacerbations of COPD [134]. The antibiotics used in severe exacerbation have to be guided by knowledge of the prevalent pathogens in that area [1, 2]. Exacerbations are to be prevented and treated aggressively because they have a prolonged and intense effect on health-related quality of life and can result in accelerated loss of lung function [40, 135–137].

Ventilatory support should be considered if patients have persistent hypoxemia and/or hypercapnia with low pH (<7.35) despite maximal medical therapy [1]. Several randomized trials have shown that noninvasive positive pressure ventilation (NIPPV) is beneficial in selected patients with respiratory failure, decreasing the need for invasive mechanical ventilation and its complications, and possibly, improving survival [40–43].

Certain conditions would make patients less likely to respond to NIPPV. These conditions include respiratory arrest, medical instability (shock, cardiac ischemia), inability to protect the airway, excessive secretions, agitation or uncooperativeness, cranio-facial trauma, or deformity. However, the use of NIV in stable patients with COPD remains debatable and not routinely recommended [138, 139].

Conclusion

Over the years, our knowledge about COPD and the capacity to treat it has increased significantly. We now know that COPD is not just a disease affecting the lungs [140] but that it has important systemic consequences [141]. Smoking cessation campaigns have resulted in a decrease in smoking prevalence in the USA. Similar efforts in the rest of the world should have the same impact. The widespread application of long-term oxygen therapy for hypoxemic patients has resulted in increased survival. During this time, we have expanded our pharmacological armamentarium to effectively improve lung function and alter its rate of decline, exercise capacity, dyspnoea, quality of life, and even survival. Several studies have documented the benefits of pulmonary rehabilitation. Noninvasive ventilation has benefited patients with acute chronic failure. The revival of surgery for emphysema or, in the immediate future, endobronchial lung volume reduction should provide an alternative to lung transplant for those patients with severe COPD who are symptomatic even on maximal medical therapy. With all these options a nihilistic attitude toward the patient with COPD is not justified. The evidence presented by the guidelines supports a positive, aggressive, and constructive attitude.

References

1. Celli BR, MacNee W (2004) Standards for the diagnosis and treatment of COPD. Eur Respir J 23:932–946
2. Global Obstructive Lung Disease Initiative. www.GOLD.org (updated 2006)
3. American Thoracic Society (1995) Standards for the diagnosis and case of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:78–121
4. Pauwels RA et al (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 163(5):1256–1276
5. Celli BR, Cote CG, Marin JM, Casanova C, de Montes Oca M, Mendez RA, Pinto Plata V, Cabral HJ (2004) The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012
6. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE (2005) Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med 142:233–239
7. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA (May 2007) TORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 62(5):411–415
8. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC (2002) Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. MMWR 51:1–16
9. Celli BR, Halbert RJ, Isonaka S, Schau B (2003) Population impact of different definitions of airways obstruction. Eur Respir J 22:268–273
10. Menezes A, Perez-Padilla R, Jardim J, Muiño A, Lopez M, Valdivia G, Montes de Oca M, Talamo C, Hallal P, Victoria C (2005) Prevalence of chronic obstructive pulmonary disease in five Latin American cities: the PLATINO study. Lancet 366:1875–1881

11. Pena VS, Miravitlles M, Gabriel R, Jimenez-Ruiz CA, Villasante C, Masa JF, Viejo JL, Fernandez-Fau L (2000) Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest 118:981–989
12. Tzanakis N, Anagnostopoulou U, Filaditaki V, Christaki P, Siafakas N (2004) COPD group of the Hellenic Thoracic Society Prevalence of COPD in Greece. Chest 125:892–900
13. de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, Kunzli N, Leynaert B, Janson C, Gislason T, Vermeire P, Svanes C, Anto JM, Burney P (2004) European Community Respiratory Health Survey Study Group. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 59:120–125
14. Talamo C, de Oca MM, Halbert R, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, Pertuze J, Moreno D, Menezes AM; PLATINO team (2007) Diagnostic labeling of COPD in five Latin American cities. Chest 131:60–67
15. Damarla M, Celli B, Mullerova H, Pinto-Plata V (2006) Discrepancy in the use of confirmatory tests in patients hospitalized with the diagnosis of chronic obstructive pulmonary disease or congestive heart failure. Respir Care 51:1120–1124
16. Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA, Vestbo J (2002) Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J 20:799–805
17. Anthonisen NR, Connett JE, Kiley JP, Altose M, Bailey W, Sonia Buist A, Conway W, Enright P, Kanner R, O'Hara P, Owens G, Scanlon P, Tashkin D, Wise R (1994) Effect of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the lung health study. JAMA 272:1497–1505
18. Casaburi R, Mahler D, Jones P, Wanner A, SanPedro G, ZuWallack R, Menjoge S, Serby C, Witek T (2002) A long term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 19:217–224
19. Mahler D, Donohue J, Barbee R, Goldman M, Gross N, Wisnewiski M, Yancey S, Zakes B, Rickard K, Anderson W (1999) Efficacy of salmeterol xinoafate in the treatment of COPD. Chest 115:957–965
20. Jones P, Bosh T (1997) Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med 155:1283–1289
21. Vincken W, van Noord J, Greefhorst A, Bantje Th, Kesten S, Korducki L, Cornelissen P (2002) On behalf of the Dutch/Belgian tiotropium study group. Improved health outcome in patients with COPD during 1 year treatment with tiorpium. Eur Respir J 19:209–216
22. ZuWallack R, Mahler D, Reilly D et al (2001) Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 119:1628–1630
23. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK (2000) Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 320:1297–1303
24. The Lung Health Study Research Group (2000) Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 343:1902–1909
25. Hay JG, Stone P, Carter J, Church S, Eyre-Brook A, Pearson MG, Woodcock AA, Calverley PM (1992) Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. Eur Respir J 5:659–664
26. Friedman M, Serby C, Menjoge S, Wilson J, Hilleman D, Witek T (1999) Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest 115:635–641
27. Belman MJ, Botnick WC, Shin JW (1996) Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153:967–975
28. O'Donnell D, Lam M, Webb K (1999) Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:542–549
29. O'Donnell D, Voduc N, Fitzpatrick M, Webb K (2004) Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. Eur Respir J 24:86–94

30. O'Donnell D, Flugre T, Gerken F, Hamilton A, Webb K, Aguilaniu B et al (2004) Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. Eur Respir J 23:832–840
31. Marin J, Carrizo S, Gascon M, Sanchez A, Gallego B, Celli B (2001) Inspiratory capacity, dynamic hyperinflation, breathlessness and exercise performance during the 6 minute walk test in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:1395–1400
32. Martinez F, Montes de Oca M, Whyte R, Stetz J, Gay S, Celli B (1997) Lung-volume reduction surgery improves dyspnea, dynamic hyperinflation and respiratory muscle function. Am J Respir Crit Care Med 155:2018–2023
33. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, Celli BR (2005) Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 171:591–597, 15 Mar 2005
34. Agustí AG, Noguera A, Sauleda J et al (2003) Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 21:347–360
35. Nishimura K, Izumi T, Tsukino M, Oga T (2002) Dyspnea is a better predictor of 5-Year survival than airway obstruction in patients with COPD. Chest 121:1434–1440
36. Schols AM, Slangen J, Volovics L, Wouters EF (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797
37. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP (1999) Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160: 1856–1861
38. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL (1996) Variables related to increased mortality following out-patient pulmonary rehabilitation. Eur Respir J 9:431–435
39. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR (2004) The 6-minute walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 1:28–33
40. Cote CG, Dordelly LJ, Celli BR (2007) Impact of chronic obstructive pulmonary disease exacerbations on patient centered outcomes. Chest 131(3):696–704
41. Imsfeld S, Bloch KE, Weder W, Russi EW (2006) The BODE index after lung volume reduction surgery correlates with survival. Chest 129:835–836
42. Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 93:391–398
43. Report of the Medical Research Council Working Party (1981) Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1:681–685
44. Brochard L, Mancebo J, Wysocki M et al (1995) Noninvasive ventilation for acute exacerbation of chronic obstructive pulmonary disease. N Engl J Med 333:817–822
45. Kramer N, Meyer T, Meharg J, Cece R, Hill NS (1995) Randomized prospective trial of non-invasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 151:1799–1806
46. Bott J, Caroll P, Conway J et al (1993) Randomized controlled trial of nasal ventilation in acute ventilatory failure due to obstructive lung disease. Lancet 341:1555–1559
47. National Emphysema Treatment Trial Research Group (2003) A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073
48. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J (2007) TORCH investigators. Salmetrol abd fluticasone propionate and survival in chronic obstructive pulmonary disease. N Eng J Med 356:775–789, 22 Feb
49. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltais F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T (2006) ATS/ERS Pulmonary Rehabilitation Writing Committee. American

Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173:1390–1413
50. Ries AL, Kaplan RM, Limberg TM, Prewitt LM (1995) The effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 122:823–832
51. Kottke TE, Battista RN, DeFriese GH (1988) Attributes of successful smoking cessation interventions in medical practice: a meta-analysis of 39 controlled trials. JAMA 259:2882–2889
52. Fiore M, Bailey W, Cohen S, Dorfman S, Goldstein M, Gritz E, Heyman R, Jaen C, Kottke T, Lando H, Mecklenburg R, Mullen P, Nett L, Robinson L, Sistzer M, Tommasello A, Villejo L, Wewers M (June 2000) Treating Tobacco use and dependence. U.S. Department Of Health and Human Services, Rockville
53. Jorenby DE, Leischow SG, Nides MA et al (1999) A controlled trial of sustained release buproprion, a nicotine patch or both for smoking cessation. N Engl J Med 340:685–691
54. Keating GM, Siddiqui MA (2006) Varnicline: a review of its use as an aid to smoking cessation therapy. CNS Drugs 20:945–980
55. Celli B, ZuWallack R, Wang S, Kesten S (Nov 2003) Improvement of inspiratory capacity and hyperinflation with tiotropium in COPD patients with severe hyperinflation. Chest 124(5):1743–1748
56. O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K (2006) Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. Chest 130:647–656
57. Dahl R, Greefhorst LA, Nowak D, Nonikov V, Byrne AM, Thomson MH, Till D, Della CG (2001) Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:778–784
58. Tantucci C, Duguet A, Similowski T, Zelter M, Derenne J-P, Milic-Emili J (1998) Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. Eur Respir J 12:799–804
59. Rennard SI, Anderson W, ZuWallack R, Broughton J, Bailey W, Friedman M, Wisniewski M, Rickard K (2001) Use of a long-acting inhaled beta2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med Apr 163(5):1087–1092, 163:1087–1092
60. Ramirez-Venegas A, Ward J, Lentine T, Mahler D (1997) Salmeterol reduces dyspnea and improves lung function in patients with COPD. Chest 112:336–340
61. Niwehowener D, Rice K, Cote C, Paulson D, Cooper JA, Korducki L et al (2005) Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once daily anticholinergic: a randomized trial. Ann Intern Med 143:317–326
62. Van Noord J, Aumann J, Jasnseens E, Smeets J, Verhaert J, Disse B et al (2005) omparison of tiotropium q.d, formoterol bid and both combined qd in patients with COPD. Respir J 26:214–222
63. Decramer M, Celli B, Tashkin D, Pawels R, Burkhart D, Cassino C, Kesten S (2004) Clinical trial design considerations in assessing long-term functional impacts of Tiotropium. J COPD 1:303–312
64. COMBIVENT Inhalation Aerosol Study Group (1994) In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 105:1411–1419
65. Karpel JP, Kotch A, Zinny M, Pesin J, Alleyne W (1994) A comparison of inhaled ipratropium, oral theophylline plus inhaled β-agonist, and the combination of all three in patients with COPD. Chest 105:1089–1094
66. Barnes PJ, Ito K, Adcock IM (2004) Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase. Lancet 363:731–733
67. Rabe K, Bateman E, O'Donnell D, Witte S, Bredenbroker D, Bethke T (2005) Roflumilast-an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomized controlled trial. Lancet 366:563–571
68. Rennard S, Schachter N, Strek M, Rickard K, Amit O (2006) Cilomilast for COPD: results of a 6-month, placebo controlled study of a potent, selective inhibitor of posphodiesterase 4. Chest 129:56–66

69. Mahler D, Huang S, Tabrizzi M, Bell G (2004) Efficacy and safety of a monoclonal antibody recognizing interleukin – 8 in COPD: a pilot study. Chest 126:926–934
70. Rennard S, Fogarty C, Kelsen S, Long W, Ramsdell J, Allison J et al (2007) The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175:926–934
71. Vestbo J, TORCH Study Group (2004) The TORCH (towards a revolution in COPD health) survival study protocol. Eur Respir J 24:206–210
72. Pauwels R, Lofdahl C, Laitinen L, Schouten J, Postma D, Pride N, Ohlson S (1999) Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med 340:1948–1953
73. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K (1999) Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised trial. Lancet 353:1819–1823
74. Sin DD (2001) Tu JV Inhaled corticosteroids and the risk for mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:580–584
75. Soriano JB, Vestbo J, Pride N, Kin V, Maden C, Maier WC (2002) Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. Eur Respir J 20:819–824
76. Calverley PM, Boonsawat W, Cseke Z et al (2003) Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 22:912–919
77. Szafranski W, Cukier A, Ramirez A et al (2003) Efficacy and safety of budesonide/formoterol in the management of COPD. Eur Respir J 21:74–81
78. Cazzola M, Dahl R (2004) Inhaled combination therapy with inhaled long-acting beta-2-agonist and corticosteroids in stable COPD. Chest 126:220–237
79. Aaron S, Vandemheen KL, Fergusson D, Maltais F, Borbeau J, Goldstein R et al (2007) Tiotropium in combination with placebo, salmeterol or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 146(8):545–555
80. Petty TL (1990) The National Mucolytic Study: results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest 97:75–83
81. Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, van Schayck CP, Olivieri D, Del Donno M, De Backer W, Lankhorst I, Ardia A (2005) Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 365(9470):1552–1560, 30 Apr–6 May
82. Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA (1987) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Int Med 106:196–204
83. Saint S, Bent S, Vittinghoff F, Grady D (1995) Antibiotics in chronic obstructive pulmonary disease exacerbation. A metanalysis. JAMA 273:957–960
84. Stockley R, O'Bryan C, Pie A, Hill S (2000) Relationship of sputum color to nature and outpatient management of acute exacerbation of COPD. Chest 117:1638–1645
85. Miravitlles M (2002) Epidemiology of chronic obstructive pulmonary disease exacerbations. Clin Pulm Med 9(4):191–197
86. Adams SG, Melo J, Luther M, Anzueto A (2000) Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 117:1345–1352
87. Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, Skovgaard LT, Kok-Jensen A, Rudolphus A, Seersholm N, Vrooman HA, Reiber JH, Hansen NC, Heckscher T, Viskum K, Stolk J (1999) A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med 160:1468–1472
88. Sandhaus R (2004) Alpha-1-antitrypsin deficiency: new and emerging therapies for alpha-1antytripsin deficiency. Thorax 59:904–909
89. Nichol KL, Baken L, Nelson A (1999) Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. Ann Intern Med 130:397–403

90. Nichol KL, Mendelman PM, Mallon KP, Jackson LA, Gorse GJ, Belshe RB, Glezen WP, Wittes J (1999) Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. JAMA 282:137–144
91. Snider G (1996) Reduction pneumoplasty for giant bullous emphysema Implications for surgical treatment of nonbullous emphysema. Chest 109:540–548
92. Patterson G, Maurer J, Williams T, Cardoso P, Scavuzzo M, Todd T (1999) Comparison of outcomes of double and single lung transplantation for obstructive lung disease. J Thorac Cardiovasc Surg 110:623–632
93. Bando K, Paradis I, Keenan R et al (1995) Comparison of outcomes after single and bilateral lung transplantation for obstructive lung disease. J Heart Lung Transplant 14:692–698
94. Orens J, Becker F, Lynch J III, Christensen P, Deeb G, Martinez F (1995) Cardiopulmonary exercise testing following allogeneic lung transplantation for different underlying disease states. Chest 107:144–149
95. Hosenpud J, Bennett L, Keck B, Boucek M, Novick R (2001) The registry of the International Society for Heart and Lung Transplantation: eighteenth official report-2001. J Heart Lung Transplant 20:805–815
96. Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R, Martinez FJ, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachiery JL, Glanville AR (2006) Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 25:745–575
97. Cooper J, Patterson G, Sundaresan R, Trulock E, Yusen R, Pohl M, Lefrak S (1996) Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 112:1319–1330
98. Leyenson V, Furukawa S, Kuzma AM, Cordova F, Travaline J, Criner GJ (2000) Correlation of changes in quality of life after lung volume reduction surgery with changes in lung function, exercise, and gas exchange. Chest 118(3):728–735
99. Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, Pepper J, Agent P, Cullinan P, MacNeill S, Goldstraw P (2000) Effect of lung-volume-reduction surgery in patients with severe emphysema. N Eng J Med 343:239–245
100. Criner G, Cordova G, Furukawa S, Kuzma A, Travaline J, Leyenson V, O'Brien G (1999) Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:2018–2027
101. Flaherty KR, Kazerooni EA, Curtis JL et al (2000) Short-term and long-term outcomes after bilateral lung volume reduction surgery: prediction by quantitative CT. Chest 119:1337–1346
102. Celli BR, Montes de Oca M, Mendez R et al (1997) Lung reduction surgery in severe COPD decreases central drive and ventilatory response to CO_2. Chest 112:902–906
103. Flaherty KR, Kazerooni EA, Curtis JL, Iannettoni M, Lange L, Schork MA, Martinez FJ (2001) Short-term and long-term outcomes after bilateral lung volume reduction surgery: prediction by quantitative CT. Chest 119(5):1337–1346
104. National Emphysema Treatment Trial Research Group (NETT Research Group) (2001) Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 345:1075–1083
105. Szekely LA, Oelberg DA, Wright C et al (1997) Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. Chest 111:550–558
106. Glaspole IN, Gabbay E, Smith JA, Rabinov M, Snell GI (2000) Predictors of perioperative morbidity and mortality in lung volume reduction surgery. Ann Thorac Surg 69: 1711–1716
107. Hopkinson NS, Toma TP, Hansell DM, Goldstraw P, Moxham J, Geddes DM, Polkey MI (2005) Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med 17:453–460

108. Ingenito EP, Loring SG, Moy ML et al (2001) Comparison of physiological and radiological screening for lung volume reduction surgery. Am J Respir Crit Care Med 163:1068–1073
109. Ingenito EP, Reilly JJ, Mentzer SJ, Swanson SJ, Vin R, Keuhn H, Berger RL, Hoffman A (2001) Bronchoscopic volume reduction: a safe and effective alternative to surgical therapy for emphysema. Am J Respir Crit Care Med 164(2):295–301
110. Reilley J, Chest Reilly J, Washko G, Pinto-Plata V, Velez E, Kenney L, Berger R, Celli B (2007) Biological lung volume reduction: a new bronchoscopic therapy for advanced emphysema. Chest 131:1108–1113
111. Agusti A, Sauleda J, Miralles C et al (2002) Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:485–489
112. Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G (1997) Muscle weakness is related to utilization of health care resources in COPD patients. Eur Respir J 10:417–423
113. Reardon J, Awad E, Normandin E et al (1994) The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. Chest 105:1046–1052
114. Goldstein RS, Gork EH, Stubbing D et al (1994) Randomized controlled trial of respiratory rehabilitation. Lancet 344:1394–1397
115. Wykstra PJ, Van Altens R, Kraan J et al (1994) Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. Eur Respir J 7:269–273
116. Bendstrup KE, Ingenman Jensen J, Holm S, Bengtsson B (1997) Out-patient rehabilitation improves activities of daily living, quality of life, and exercise tolerance in chronic obstructive pulmonary disease. Eur Respir J 10:2801–2806
117. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shields K, Turner-Lawlor PJ, Pyne N, Newcombe RG, Lonescu AA, Thomas J, Turnbridge J (2000) Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomized controlled trial. Lancet 355:362–368
118. Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt G, Sanchis J (2000) Long-term effects of outpatient rehabilitation of COPD: a randomized trial. Chest 117:976–983
119. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW (1998) Randomised controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur Respir J 12:363–369
120. Trooster T, Gosselink R (2000) Decramer M Short and long term effects of outpatients pulmonary rehabilitation in chronic obstructive pulmonary disease: a randomized trial. Am J Med 109:207–212
121. Maltais F, LeBlanc P, Simard C et al (1996) Skeletal muscle adaptation to endurance training in patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 154:436–444
122. Ries A, Kaplan R, Myers R, Prewett L (2003) Maintenance after ehabilitation in lung disease. A randomized trial. Am J Respir Crit Care Med 167:880–888
123. Cote CG, Celli BR (2005) Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J 26:630–636
124. Prigatano GP, Parsons OA, Wright E, Levin DC, Hawryluk G (1983) Neuropsychologic test performance in mildly hypoxemic patients with chronic obstructive pulmonary disease. J Consult Clin Psychol 51:108–116
125. Grant I, Prigatano GP, Heaton RK, McSweeny AJ, Wright EC, Adams KM (1987) Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease. Arch Gen Psychiatry 44:999–1006
126. Criner GJ, Celli BR (1987) Ventilatory muscle recruitment in exercise with O_2 in obstructed patients with mild hypoxemia. J Appl Physiol 63:195–200
127. Vyas MN, Banister EW, Morton JW, Grzybowski S (1971) Response to exercise in patients with chronic airway obstruction. II. Effects of breathing 40 percent oxygen. Am Rev Respir Dis 103:401–412
128. Dean NC, Brown JK, Himelman RB, Doherty JJ, Gold WM, Stulbarg MS (1992) Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. Am Rev Respir Dis 146:941–945

129. Rodriguez-Roisin R (2000) Toward a consensus definition for COPD exacerbations. Chest 117:398s–401s
130. Celli B, Barnes P (2007) Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 29:1224–1238
131. Angus DL, RM CPM (1999) Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. Lancet 345:456–460
132. Thompson WH, Nielson CP, Carvalho P et al (1996) Controlled trial of oral prednisone in outpatients with cute COPD exacerbation. Am J Respir Crit Care Med 154:407–412
133. Nieweohner DE, Erbland ML, Deupree RH et al (1999) Effect of glucocorticoids on exacerbations of chronic obstructive pulmonary disease. N Engl J Med 340:1941–1947
134. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F (2001) Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomized placebo-controlled trial. Lancet 358:2020–2035
135. Seemungal TAR, Donaldson GC, Paul EA et al (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1418–1422
136. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57:847–852
137. Pinto-Plata V, Livnat G, Girish M, Cabral H, Masdin P, Linacre P, Drew R, Kenney L, Celli B (2007) Systemic cytokine, clinical and physiological changes in patients admitted with exacerbations of COPD. Chest 131:37–43
138. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, Santolaria F (2000) Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 118:1582–1590
139. Clinic E, Sturani C, Rossi A et al (2002) The Italian multicenter study on non-invasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 20:529–538
140. Barnes PJ, Shapiro S, Pawels R (2003) Chronic obstructive pulmonary disease; molecular and cellular mechanisms. Eur Respir J 22:672–688
141. Wouters E, Creutzberg E, Schols A (2002) Systemic effects of COPD. Chest 121:127S–130S

6

Pharmacological Therapy: Bronchodilators

Nicola A. Hanania and Mario Cazzola

Key Points:

- Bronchodilators play a pivotal role in the treatment of symptomatic patients with chronic obstructive pulmonary disease (COPD).
- Inhaled short-acting bronchodilators are currently recommended for rescue of symptoms in patients with mild disease, while inhaled long-acting bronchodilators are recommended as first-line agents for maintenance therapy in patients with moderate and severe disease and those with daily symptoms.
- Long-acting bronchodilators which include long-acting β_2-agonists and long-acting anticholinergic agents improve symptoms, exercise tolerance, health status and reduce exacerbations in patients COPD. However, they have no significant effects on long-term decline in lung function or mortality.
- The use of theophylline has declined in recent years because of its narrow therapeutic index and should be reserved as a third-line option in patients with very severe disease.
- When symptoms are not sufficiently controlled by the use of one bronchodilator, combining bronchodilators of different classes may be a more effective approach.
- Evidence supports the regular use of a combination of a long-acting β_2-agonist (LABA) and a long-acting anti-cholinergic agent (LAAC) in patients with severe COPD.
- Combining a long-acting β_2-agonist (LABA) with an inhaled corticosteroid has also been shown to be more effective than the use of either agent alone.
- Several novel bronchodilators are now in different stages of development for use alone or in combination with other agents.

Keywords Albuterol • anti-cholinergics • beta-agonists • bronchodilators • chronic obstructive pulmonary disease • formoterol • ipratropium bromide • salmeterol • theophylline • tiotropium

Introduction

Chronic obstructive pulmonary disease (COPD) is a multi-component disease characterized by progressive airflow limitation and an inflammatory response of the lung, principally caused by cigarette smoking. Progressive airflow limitation in COPD has significant consequences which lead to deterioration of health status (Fig. 6.1). As airflow obstruction is the mechanical hallmark of COPD, it would be expected

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_6,

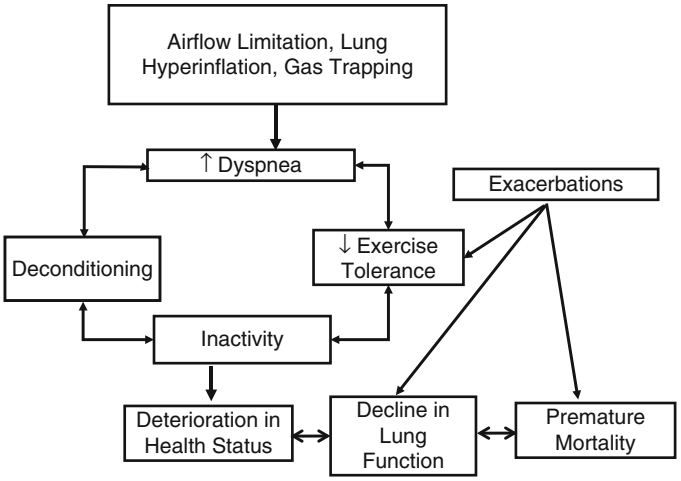


Fig. 6.1. Consequences of airflow limitation in chronic obstructive pulmonary disease (*COPD*)

Table 6.1 Stepwise approach to the pharmacologic management of COPD and the position of bronchodilators.

Severity	Spirometric Findings	Pharmacologic Intervention
Stage I: Mild	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$	Add a *short-acting bronchodilator* to be used when needed; anticholinergic or β_2-agonist
Stage II: Moderate	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$	Add *one or more long-acting bronchodilators* on a scheduled basis Consider pulmonary rehabilitation
Stage III: Severe	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$	Add inhaled steroids if repeated exacerbations
Stage IV: Very Severe	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$	Evaluate for adding oxygen Consider surgical options

that as the level of airflow limitation increases, so too would the severity of symptoms. By far, the most distressing symptoms for patients with COPD are dyspnoea and the progressive inability to engage in activities of daily living. Furthermore, the risk of acute exacerbation of COPD increases with the severity of airflow limitation causing further increase in morbidity from this disease. The main goals of management of COPD are focused on relieving symptoms, improving health status, preserving lung function decline, improving exercise performance, preventing exacerbations, and decreasing mortality. The National Heart, Lung and Blood institute (NHLBI), the Global Initiative for Obstructive Lund Disease (GOLD), the American Thoracic Society (ATS), the British Thoracic Society (BTS) and the European Respiratory Society (ERS) have published guidelines for the management of COPD (1–4). These guidelines emphasize the comprehensive and stepwise approach to the management of COPD and stipulate that all patients who are symptomatic merit a trial of pharmacologic intervention (Table 6.1). Bronchodilators are the mainstay of pharmacological therapy for COPD and are recommended by current national, and international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation. Bronchodilators are given on as-needed basis or on a regular basis to prevent or reduce symptoms. Short-acting agents are usually used for immediate relief

of symptoms while long-acting inhaled agents are generally preferred and are more convenient. Combinations of bronchodilators may improve efficacy and reduce risk of adverse effects than increasing the dose of a single agent. This review will provide the rationale for use and safety of bronchodilators in COPD.

Rationale for the Use of Bronchodilators in COPD

Bronchodilators work through their direct relaxation effect on airway smooth muscle cells (Table 6.2). However, several issues need to be considered when assessing the response to bronchodilator therapy. First, the lack of acute response to one class of bronchodilator does not necessarily imply non-responsiveness to another. Donohue and colleagues (5) reported that 73% of 813 COPD patients increased their forced expiratory volume in 1 s (FEV_1) by >12% or 200 mL following long-term salmeterol treatment. However, 11% of patients showed a similar increase in FEV_1 following acute administration of ipratropium, 27% following albuterol and 35% with both drugs combined. One further consideration is that a patient's FEV_1 response to acute bronchodilator therapy does not predict long-term response to bronchodilator therapy and may vary from day to day. Calverley et al. (6) performed acute bronchodilator testing using albuterol, ipratropium bromide, or a combination of the two on 660 COPD patients who had been classified according to both European Respiratory Society (ERS) and American Thoracic Society (ATS) spirometric criteria. Over the 2-month study period, 55% of patients classified as irreversible under ATS criteria changed to reversible status on at least one of the visits. In summary, the acute response to short-acting bronchodilators is of limited value in deciding future response to long-acting agents. In addition, studies that stratified patients as "responders" vs. "non-responders" consistently demonstrate a similar trend in the response to the therapeutic agent being investigated in both groups. In addition, to direct bronchodilator properties through their effects on airway smooth muscles, bronchodilators such as beta-agonists and theophylline may have several non-bronchodilator activities which may contribute to their beneficial effects in COPD (7–11, 11–13).

The clinical efficacy of bronchodilators has traditionally been assessed by the degree of improvement in forced expiratory volume in 1 s (FEV_1). This, however, is seemingly at odds with the poor correlations recognized between change of FEV_1 and both dyspnoea and exercise performance. The change in lung volumes, such as inspiratory capacity (IC), correlates better than the change in FEV1 with change in symptoms, such as dyspnoea and exercise tolerance (14). This suggests that assessment of bronchodilator treatment using indices of hyperinflation or air trapping may provide a better indicator of efficacy (15). Although changes in lung volumes are independent

Table 6.2 Rationale for the Use of Bronchodilators in COPD.

(1) Physiologic Effects
- (a) Airway smooth muscle relaxation
  - – Bronchodilation: Improve FEV1, lung volumes
  - – Decreased air trapping and dynamic hyperinflation
- (b) Non-bronchodilator effects

(2) Clinical Effects
- – ↓ Breathlessness (↓ airway resistance, ↓ hyperinflation)
- – ↑ Exercise tolerance (↓ dynamic hyperinflation)
- – ↑ Sleep quality (↓ nocturnal bronchospasm)
- – ↑ Health-related quality of life
- – ↓ Frequency of acute exacerbations

of changes in FEV_1, several studies have demonstrated that the more sustained airway patency offered by long-acting bronchodilators reduces air trapping (16, 17). Several other outcome measures are now used to assess response to bronchodilator therapy. The effects of commonly used bronchodilators on clinical outcomes in COPD are listed in Table 6.3. COPD exacerbation is another important but occasionally overlooked parameter (18). COPD exacerbations are very common, affecting about 20% of patients with moderate-to-severe COPD (1.3 events/year in patients with 40–45% predicted FEV1) and contribute to the deterioration in health status. The use of long-acting beta-agonists and long-acting anticholinergic agents reduce the frequency of exacerbation and severity of individual exacerbations (19–21). The effects of long-acting bronchodilators on health status have been well documented in several clinical trials (19, 21–24). Recent long-term studies including the Towards a Revolution in COPD Health trial (TORCH) and the Understanding of Potential Long-term Impact on Function with Tiotropium trial (UPLIFT) failed to demonstrate any significant long-term effect of long-acting bronchodilators on decline in lung function or mortality (25, 26)

Current Bronchodilators in COPD

Three classes of bronchodilators – β_2-agonists, anticholinergics, and methylxanthines – are currently available and can be used individually or in combination (Table 6.4). The use of short-acting bronchodilators is currently advocated for rescue of symptoms while inhaled long-acting bronchodilators is recommended as the treatment of choice for maintenance therapy.

Table 6.3 Summary of the effects of commonly-used bronchodilators on clinical outcomes in COPD.

Bronchodilator	FEV_1	Lung volume	Dyspnoea	HRQoL	Exercise endurance	Decline in Lung Function	Decrease Mortality
Short acting β_2-agonist	Yes[a]	Yes[b]	Yes[a]	–	Yes[b]	No	No
Ipratropium bromide	Yes[a]	Yes[b]	Yes[a]	No[b]	Yes[b]	No	No
Long acting β_2-agonist	Yes[a]	Yes[a]	Yes[a]	Yes[a]	Yes[b]	No	No
Tiotropium	Yes[a]	Yes[a]	Yes[a]	Yes[a]	Yes[b]	No	No
Theophylline	Yes[a]	Yes[b]	Yes[a]	Yes[b]	Yes[b]	No	No

Bronchodilators

[a]Randomized clinical trial, substantial numbers of studies with large study populations

[b]Randomized clinical trial, few studies or studies with small study populations

Table 6.4 Available bronchodilators in chronic obstructive pulmonary disease (COPD).

Short-acting	Long-acting	Fixed Combination
B_2-Agonists	**B_2-Agonists (LABA)**	**Brochodilator Combination**
Albuterol (Salbutamol)	Salmeterol	Albuterol (Salbutamol) + Ipratropium
Pirbuterol	Formoterol	
Levalbuterol	Arformoterol	**LABA + Inhaled Corticosteroid**
Procaterol		Fluticasone + Salmeterol
Terbutaline		Budesonide + Formoterol
		Beclomethasone + Formoterol
		Mometasone + Formoterol
Anticholinergics	**Anticholinergic (LAMA)**	
Ipratropium	Tiotropium	
Oxitropium	**Methylxanthines**	
	Theophylline	

β_2-Adrenoceptor Agonists

Pharmacology

β_2-agonists relax airway smooth muscles by binding to β_2-receptors and inducing structural changes that lead to the activation of G proteins and increase synthesis of cyclic adenosine monophosphate (cAMP) (27). This results in bronchial smooth muscle dilation. β_2-agonists are delivered through the inhaled or oral route although the latter is limited because of the increased risk of adverse effects. There are several important pharmacological differences among the existing beta-agonists (27, 28). First, is the onset of action which is similar with albuterol and formoterol (1–3 min) while it is more prolonged in the case of salmeterol. This difference in onset of action is related to the lipophilicity of each of these agents and their ability to activate the beta-receptor in the aqueous phase (albuterol and formoterol). Albuterol has a short duration of action lasting less than 6 h while the duration of action of salmeterol and formoterol is approximately 12 h. These agents also differ significantly in their ability to activate the β_2-receptor (intrinsic efficacy) which is dependent on their affinity and potency (27). While formoterol has a high intrinsic efficacy (strong agonist), albuterol and salmeterol have a very low intrinsic efficacy (weak agonists). The clinical relevance of this difference needs to be further explored in future trials.

Clinical Benefits

Short-acting β_2-agonists have a rapid onset of action and are very effective for rescue of symptoms in COPD. Albuterol is the most commonly used agent. In addition to their bronchodilatory properties, these agents are effective in increasing mucociliary clearance. A systematic review showed that regular use of short-acting beta-agonists in COPD was associated with improvement in lung function and dyspnoea (29). The two currently available LABAs – salmeterol and formoterol – have been shown significantly to improve lung function, health status, and symptom reduction, compared with both placebo (16, 30–32) and ipratropium (21, 33). In addition, because of formoterol's fast onset of action, it has a potential role as stand-alone medication or in combination with another bronchodilator in the management of acute COPD exacerbation (34, 35) and for use as a rescue and maintenance medication (36). A recent study demonstrated a superior effect of formoterol compared to tiotropium bromide in improving FEV_1 in the first 2 h after administration, however the area under the curve (AUC) FEV_1 over 12 h was similar between these two agents (37).

Several systematic reviews of LABAs reveal that these agents can reduce the rate of COPD exacerbations(19, 38). In a study of 634 patients with COPD, the administration of salmeterol for 12 months improved health outcomes including exacerbations, especially in patients who complied with therapy (39).

Role of Stereoisomers

The majority of currently used β_2- agonists are racemic compounds which contain a 50–50 mixture of the R and S-isomers of the agonist. However, recently the R-isomer for albuterol (levalbuterol) (40, 41) and the R,R-formoterol (arformoterol) are now available for use in COPD (42). Many of the pharmacological activity of the agonist usually resides in the (R)-enantiomer, whereas the anomalous actions of racemic β_2-agonists are now attributed to unsuspected properties of the (*S*)-enantiomer. In fact, recent data from an in vitro study indicate that S,S-formoterol is not biologically inert, such as that in racemic mixtures; it inhibited the beneficial effects of R,R,-formoterol on proliferation, anti-inflammatory cellular surface marker expression, and cytokine secretion (43). A recent trial investigating the efficacy and safety of several dose formulations of

arformoterol nebulization solution demonstrated a significant and sustained improvement in FEV_1 compared to placebo over 12 weeks (44).

Non-bronchodilator Effects of β_2-Agonists

β_2-agonists exert several non-bronchodilatory effects that may be of clinical relevance (8, 9). These include inhibition of airway smooth muscle cell proliferation and inflammatory mediator release, as well as non-smooth muscle effects, such as stimulation of mucociliary transport (45), cytoprotection of the respiratory mucosa, and attenuation of neutrophil recruitment and activation (9). However, many of these effects have been described in vitro studies and in vivo studies are still needed to fully explore these effects. More recently, the physiologic and clinical benefits of long-acting β_2-agonists (LABA) have been shown to be enhanced when administered in conjunction with inhaled corticosteroids (ICS) (46–49) which translate to clinical benefits. ICS and LABA combination products have been shown to improve lung function, symptoms, health status, and reduce exacerbations in patients with moderate to severe COPD (50–53).

Anticholinergics

Pharmacology

Parasympathetic activity in the large and medium-size airways is mediated through the M1 and M3 receptors and results in airways smooth muscle contraction, mucus secretion, and possibly increased ciliary activity. Interestingly, M_2 receptors are located on the postganglionic parasympathetic nerves and inhibit acetylcholine release from the nerve terminals. Increased cholinergic tone is important in the pathogenesis of COPD, contributing both to increased bronchial smooth muscle tone and to mucus hypersecretion (54, 55). Thus, anticholinergics reduce airway tone and improve expiratory flow limitation, hyperinflation, and exercise capacity in patients with COPD. Two anti-cholinergic bronchodilators are currently available in the United States for clinical use. The short-acting anticholinergic agent, ipratropium bromide, acts on all three muscarinic receptors. Its short duration of action requires dosing every 6 h.

Tiotropium is a relatively new anticholinergic agent which also binds to all three receptor subtypes; however, it dissociates rapidly from M_2 receptors. In contrast, its dissociation half-life from M_3 receptors is close to 35 h that results in a prolonged bronchodilatory effect. Its peak bronchodilatory effect is in 1–3 h, and continues for up to 32 h with a dip between 16 and 24 h related to circadian change. However, its bronchoprotective effect against a bronchospastic agent continues up to 48 h (56).

Clinical Benefits

The short-acting ipratropium has for a long time been used as monotherapy or in combination with albuterol in the maintenance therapy of COPD (15, 57, 58). However, several studies have now shown that the use of long-acting bronchodilators is superior in improving health outcomes. The use of tiotropium in patients with COPD results in improved health status, dyspnoea, and exercise capacity, and reduced hyperinflation and COPD-exacerbation rate in patients with moderate to severe COPD relative to placebo (23, 59, 60) and ipratropium (24). Data from large long-term trials showed that trough FEV_1 increased by 100–150 mL, and the peak FEV_1 increased by 150–200 mL above trough level after inhalation of 18 μg of tiotropium. No loss of efficacy was seen over the course of 1 year of regular treatment with tiotropium. Furthermore, in a

multicenter Veterans Administration trial involving 1,829 patients with severe COPD, the addition of tiotropium to other COPD therapies significantly reduced acute COPD exacerbations and reduced COPD hospitalizations when compared to placebo (20). Data from three more recent studies, specifically designed to explore the potential differences between tiotropium and salmeterol, seem to indicate a greater efficacy of tiotropium (61–63). More recently, data from the UPLIFT study (a large clinical trial which evaluated the effect of tiotropium on the decline of lung function and other outcomes over a 4-year period) demonstrated a significant effect of treatment with tiotropium on improving lung function, reduction in exacerbations, and improvement in health status compared to placebo treated patients(25). However, there was no effect of tiotropium on decline lung function compared to placebo.

Non-bronchodilator Effects of Anticholinergics

Some non-bronchodilator effects for the existing anticholinergics have been reported (64). Furthermore, results from a recent study performed on sputum cells obtained from COPD patients demonstrate that muscarinic receptors may be involved in airway inflammation in subjects with COPD through acetylcholine-induced, ERK1/2-dependent leukotriene B4 release (65). These results suggest that anticholinergic therapy may contribute to reduced neutrophilic inflammation in COPD, however these findings need to be further evaluated in human.

Methylxanthines

Pharmacology

Theophylline is a non-selective phosphodiesterase inhibitor that acts both as a weak bronchodilator and a respiratory stimulant. It has been shown to improve diaphragmatic contractility and has some anti-inflammatory properties (10). Because of its potential ability to activate the histone deacetylase (HDAC) system, theophylline may have the ability of enhancing the effects of inhaled corticosteroids in patients with COPD. However, because of its potential adverse effects and narrow therapeutic index, it should only be used when symptoms persist despite optimal bronchodilator therapy. Several studies have demonstrated the beneficial effects for theophylline when added to other treatments in patients with COPD (66, 67).

Combination Therapies

Bronchodilator Combination Therapy

Current guidelines highlight the fact that for patients whose conditions are not controlled with bronchodilator monotherapy, the use of a combination of more than one class of bronchodilators may be more effective than the use of single agents with respect to improvements in lung function, symptoms, and reducing the risk of adverse events. In particular, the use of an inhaled anticholinergic with a β_2-agonist seems to be a convenient way of delivering treatment and obtaining better results. Large studies have demonstrated that the combination of the short-acting β_2-agonist albuterol with the short-acting anticholinergic ipratropium is superior to either single agent alone (68). Some trials have highlighted that the addition of LABAs to ipratropium is more effective than either agent used alone (69, 70). In a 12-week trial, ZuWallack and colleagues showed that salmeterol plus theophylline caused significantly greater improvements in pulmonary functions and symptoms, compared with either single agent (71).

Considering that formoterol provides a greater degree of early bronchodilation (in the first 2 h) than tiotropium and comparable bronchodilation over 12 h (37), the

bronchodilator effect of single doses of formoterol 12 μg and tiotropium 18 μg, and formoterol 12 μg + tiotropium 18 μg given together was examined in stable COPD (72). Formoterol and tiotropium appeared complementary. Van Noord et al. (73) explored these effects elicited by 6 weeks of treatment with tiotropium 18 μg once daily in the morning, formoterol 12 μg twice a day, and tiotropium 18 μg + formoterol 12 μg once daily in the morning in patients suffering from moderate-to-severe COPD. Patients receiving combination treatment had a greater improvement in FEV_1 and FVC compared to those receiving the individual agents over 24 h. Tiotropium was superior to formoterol for FEV_1 response over 0–12 h (owing to significant differences from 8 to 12 h), but the two treatments were not significantly different for FEV_1 over 12–24 h or 0–24 h. Similar observation was documented from a more recently published 2-week study with tiotropium alone or tiotropium plus formoterol once- or twice-daily following a 2-week pretreatment period with tiotropium. In this study, the use of an additional evening dose of formoterol had clear added benefit compared to once a day formoterol (74).

LABA + Inhaled Corticosteroid Combination Therapy

The physiologic and clinical benefits of LABAs have been shown to be enhanced when administered in conjunction with inhaled corticosteroids (ICS) (26, 75). A study of fluticasone propionate 250 mcg and salmeterol 50 mcg showed improvement in lung function in patients with COPD, compared with monotherapy (50). Other studies have shown a reduction in exacerbation rate with combination therapy compared with single drug therapy or placebo (26, 52, 53). In two studies comparing ipratropium/albuterol given four times daily with fluticasone 250 mcg/salmeterol 50 mcg given twice daily, a significant difference in improvement in dyspnoea scores was seen among the two treatment groups (76, 77). The TORCH study investigated the role of fluticasone propionate/salmeterol combination therapy on all-cause mortality in a large cohort of patients with COPD over 3 years. While all-cause mortality was not significantly reduced with this combination therapy compared to placebo, there were significant reduction in moderate and severe exacerbations and improvement in health status compared to placebo. Furthermore, the exacerbation reduction in the combination group was significantly higher than that seen with monotherapy with inhaled fluticasone or salmeterol(26).

Anticholinergic + Inhaled Corticosteroid Combination Therapy

Emerging evidence from in vitro studies suggests an interaction between corticosteroid and muscarinic receptors which may provide a rationale for use of anticholinergic/corticosteroid combination therapies(48). Short-term trials suggest an additive effect for the administration of such medications in more severe patients with COPD (78) (79). However, the long-term clinical effects of such interaction need to be investigated in future clinical trials.

Delivering Bronchodilators to the Lung

To achieve maximal benefit, a bronchodilator must be correctly delivered to the airway using a proper technique. Inhaled bronchodilators have traditionally been delivered to the lung using a metered dose inhaler (MDI). However, a significant number of patients with COPD cannot effectively coordinate their breathing using an MDI. This problem may be remedied by the use of dry-powder devices (DPIs), an MDI with a spacer device, or a nebulizer. The chlorofluorocarbon propellants used in MDIs are currently being phased out and will eventually be replaced by hydrofluoroalkane propellants.

However, the reformulation of some bronchodilators using this propellant may be difficult, and thus DPIs are likely to become more popular in the years to come. DPIs are either single-dose, multi-dose, or reservoir devices that are breath-activated. It is important to mention that even the use of DPIs may not be very simple for some patients and may also be misused especially in the elderly (80). Therefore, when prescribed an MDI or DPI, elderly patients with COPD require more training and reinforcement than younger individuals (81).

Nebulizers require little patient cooperation, and can be used at any age for any disease severity or acuity (82). In addition, the use of nebulizer allows the delivery of larger doses of bronchodilator to the airway, especially during acute episodes of bronchospasm, and the combination of more than one bronchodilator for simultaneous administration. In fact, many patients prefer using a nebulizer over other devices. This was clearly shown in one questionnaire study of patients receiving home nebulizer treatment, which found that the majority of patients using a nebulizer reported increased feeling of personal well-being, better symptom control, increased confidence, and a greater perception of independence (83). Small-volume nebulizers are powered by a jet of compressed air to aerosolize the drug, whereas ultrasonic nebulizers utilize a vibrating crystal. A new generation of low-volume nebulizers which utilize a mesh or a multiple-aperture plate will potentially be more efficient in delivering bronchodilators because they have better deposition characteristics and waste little drug with minimal residual (84).

The results of a systematic review of 59 randomized controlled trials in which the same drug (bronchodilator or inhaled corticosteroid) was delivered using different delivery devices (MDI with or without a spacer, DPI, or a nebulizer) in patients with asthma or COPD were recently published. There were no differences in the efficacy outcomes (lung function or symptoms) in any patient groups between these devices (85). This review concludes that "for the treatment of COPD in the outpatient setting, the MDI, with or without spacer/holding chamber, the nebulizer, and the DPI were all appropriate for the delivery of inhaled β_2-agonists and anticholinergic agents."

Safety of Bronchodilator Therapy in COPD

While the safety of long-acting β_2-agonists as monotherapy in asthma has recently been questioned (86), the use of these medications in COPD has generally been described as safe. In general, short-acting β_2-agonists are well tolerated, except for occasional episodes of tachycardia and tremor. It has been reported that the continued use of β_2-agonists may be associated with an increase in cardiovascular risks compared to placebo (87). However, a meta-analysis ($N=2,853$) of data from seven clinical trials examining the effects of salmeterol in patients with COPD showed no clinically significant difference in the incidence of cardiovascular events between salmeterol and placebo (88). A more recent systematic review which included other long-acting β_2- agonists revealed similar results (89). It has also been suggested that tolerance to the bronchodilator effects of long-acting β_2- agonists (LABAs) may occur with their prolonged use in COPD (61, 90). However a study examining the bronchodilator effect of long-term use of salmeterol demonstrated a sustained bronchodilator effect for salmeterol administered for 6 months (32). Data from the TORCH study also suggest that 3-year chronic use of salmeterol as monotherapy in patients with COPD produced no increase in mortality as was suggested by the SMART trial in patients with asthma(26). Nevertheless, β_2-agonists should be used with caution in patients with underlying cardiac disorders including ischemic heart disease (87, 91).

While the use of anticholinergics may be associated with class side effects, such as dry mouth, an increased risk of glaucoma, and urinary retention. However, when used in recommended doses, currently used agents are generally safe as the quaternary nitrogen atom prevents them from being systemically absorbed. These agents should also be used with caution in patients with bladder neck obstruction due to prostatism, and patients with glaucoma. The long-term safety of tiotropium over 4 years was investigated in the UPLIFT study (25). This study showed no cardiovascular risks from the use of tiotropium over 4 years. Furthermore, a recent meta-analysis which included more than 19,000 subjects with COPD revealed that tiotropium was associated with a reduction in the risk of all-cause mortality, CV mortality, and CV events (92).

Theophylline is associated with tremors and nausea, and less frequently with cardiac arrhythmias and seizures (93). The risk of such adverse events can be reduced by monitoring the drug's plasma levels and reducing the dose accordingly.

Novel Bronchodilators

Several new bronchodilators are currently being studied in ongoing clinical trials that may improve the future treatment of COPD(94) (Table 6.5). The current opinion is that it will be advantageous to develop inhalers containing combination of several classes of long-acting bronchodilator drugs in an attempt to simplify treatment regimes as much as possible. Other agents include β_2-agonists, which can be administered once a day or through nebulization, PDE_4 inhibitors, and other combination agents.

Novel β_2-Agonists

A variety of beta-agonists with longer half lives are currently under development with the hopes of achieving once daily dosing (95). These isomeric preparations are hypothesized to have fewer side effects than the existing LABAs.

Once-daily β_2-adrenoceptor agonists (ultra LABAs), such as carmoterol, indacaterol, milveterol, vilanterol, olodaterol, LAS-100977, PF-00610355, are under

Table 6.5 Novel bronchodilators under development.

Novel β_2-agonists	Novel Anticholinergics	PDE4 inhibitors	Novel β_2-agonists + Novel Anticholinergics
Indacaterol	Glycopyrronium (NVA-237)	Roflumilast	Indacaterol + NVA-237 (QVA-149)
Carmoterol	Aclidinium	Cilomilast	Carmoterol + tiotropium
Milveterol	Darotropium bromide	AWD12–281 (GSK842470)	Olodaterol + tiotropium
Vilanterol	GSK-573719	NVP-ABE171	Formoterol + aclidinium
Olodaterol	TD-4208	GRC-3886	Formoterol + glycopyrrolate
LAS-100977	CHF 5407	V11294	Vilanterol + GSK-573719
PF-00610355	QAT370 BEA-2180BR Trospium Dexpirronium PF-3715455 or PF-3635659	HT0712 Tetomilast Tofimilast GSK256066	

development for the treatment of COPD. Indacaterol recently received approval for once daily use by the European Union. It is likely that once-daily dosing of a LABA will lead to enhancement of compliance with therapy and may have advantages leading to improved overall clinical outcomes in patients with COPD.

Novel Anticholinergics

Several new long-acting anticholinergic agents are under development and these include glycopyrronium (NVA-237), aclidinium, darotropium bromide, GSK-573719, TD-4208, CHF 5407, QAT370, BEA-2180BR, trospium, dexpirronium, and PF-3715455 or PF-3635659. Although clinical details are still not available, potential advantages of such agents over tiotropium may include a quicker onset of action and a better safety profile.

Phosphodiesterase-4 Inhibitors

PDE-4 metabolizes cAMP in airway smooth muscle cells and many inflammatory cells which play a major role in the inflammatory cascade of COPD. A number of PDE-4 inhibitors, some to be used by inhalation, are currently in various stages of development (roflumilast, cilomilast, AWD12–281 (GSK842470), NVP-ABE171, GRC-3886, V11294, HT0712, tetomilast, tofimilast, GSK256066). Selective inhibition of this enzyme has been shown to cause smooth muscle relaxation and anti-inflammatory effects. Although the bronchodilator effects of these agents are very modest, their combined anti-inflammatory and bronchodilator effects make them very appealing. Recently, the results of two large 1-year trials of roflumilast compared to placebo in patients with severe COPD were published (96). These studies demonstrated significant reduction in exacerbations requiring systemic steroids and improvement in trough FEV1 with roflumilast compared to placebo. In two other studies in patients with moderate COPD on treatment with either salmeterol or tiotropium, the addition of roflumilast demonstrated significant improvement in lung function and reduction in exacerbations (97).

Conclusions

The use of bronchodilators is central in the symptomatic management of COPD and currently available agents have been shown to have significant effects on the long-term outcome and management of COPD. The use of the inhaled route is currently preferred to minimize systemic effects. Quick-acting and short-acting agents are best used for rescue of symptoms while long-acting agents are best used for maintenance therapy. The choice of agents may be based primarily on individual response, cost, side effect profile, and availability.

References

1. Celli BR, Macnee W (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23:932–46
2. Fabbri L, Pauwels RA, Hurd SS (2004) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary updated 2003. COPD 1:105–41
3. Bellamy D (2004) The NICE COPD guidelines 2004-what are the messages for primary care? Prim Care Respir J 13:84–88

4. O'Donnell DE, Hernandez P, Aaron S, Bourbeau J, Marciniuk D, Hodder R et al (2003) Canadian thoracic society COPD guidelines: summary of highlights for family doctors. Can Respir J 10:183–85
5. Donohue JF (2004) Therapeutic responses in asthma and COPD. Bronchodilators. Chest 126:125S–37S
6. Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW (2003) Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 58:659–64
7. Hanania NA, Ambrosino N, Calverley P, Cazzola M, Donner CF, Make B (2005) Treatments for COPD. Respir Med 99(Suppl B):S28–S40
8. Johnson M, Rennard S (2001) Alternative mechanisms for long-acting beta(2)-adrenergic agonists in COPD. Chest 120:258–70
9. Hanania NA, Moore RH (2004) Anti-inflammatory activities of β_2-agonists. Curr Drug Targets Inflamm Allergy 3:271–77
10. Barnes PJ (2006) Theophylline for COPD. Thorax 61:742–44
11. Barnes PJ (2005) Targeting histone deacetylase 2 in chronic obstructive pulmonary disease treatment. Expert Opin Ther Targets 9:1111–21
12. Barnes PJ (2005) Theophylline in chronic obstructive pulmonary disease: new horizons. Proc Am Thorac Soc 2:334–39
13. Barnes PJ (2003) Theophylline: new perspectives for an old drug. Am J Respir Crit Care Med 167:813–18
14. O'Donnell DE, Webb KA (1993) Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. Am Rev Respir Dis 148:1351–57
15. O'Donnell DE, Lam M, Webb KA (1999) Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:542–49
16. Ramirez-Venegas A, Ward J, Lentine T, Mahler DA (1997) Salmeterol reduces dyspnea and improves lung function in patients with COPD. Chest 112:336–40
17. Celli B, ZuWallack R, Wang S, Kesten S (2003) Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 124:1743–48
18. Niewoehner DE (2006) The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. Am J Med 119:38–45
19. Sin DD, McAlister FA, Man SF, Anthonisen NR (2003) Contemporary management of chronic obstructive pulmonary disease: scientific review. J Am Med Assoc 290:2301–12
20. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L et al (2005) Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 143:317–26
21. Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME et al (1999) Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 115:957–65
22. Barr RG, Bourbeau J, Camargo CA, Ram FS (2006) Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. Thorax 61:854–62
23. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL et al (2002) A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 19:217–24
24. Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L et al (2002) Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Eur Respir J 19:209–16
25. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S et al (2008) A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 359:1543–54
26. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW et al (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356:775–89
27. Hanania NA, Sharafkhaneh A, Barber R, Dickey BF (2002) Beta-agonist intrinsic efficacy: measurement and clinical significance. Am J Respir Crit Care Med 165:1353–58

28. Lotvall J (2000) Pharmacology of bronchodilators used in the treatment of COPD. Respir Med 94(Suppl E):S6–10
29. Sestini P, Renzoni E, Robinson S, Poole P, Ram FS (2002) Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev CD001495
30. Boyd G, Morice AH, Pounsford JC, Siebert M, Peslis N, Crawford C (1997) An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J 10:815–21
31. Cazzola M, Matera MG, Santangelo G, Vinciguerra A, Rossi F, D'Amato G (1995) Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose-response study. Respir Med 89:357–62
32. Hanania NA, Kalberg C, Yates J, Emmett A, Horstman D, Knobil K (2005) The bronchodilator response to salmeterol is maintained with regular, long-term use in patients with COPD. Pulm Pharmacol Ther 18:19–22
33. Dahl R, Greefhorst LA, Nowak D, Nonikov V, Byrne AM, Thomson MH et al (2001) Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:778–84
34. Cazzola M, Santus P, Matera MG, Carlucci P, Belloli E, Di MF et al (2003) A single high dose of formoterol is as effective as the same dose administered in a cumulative manner in patients with acute exacerbation of COPD. Respir Med 97:458–62
35. Di MF, Verga M, Santus P, Morelli N, Cazzola M, Centanni S (2006) Effect of formoterol, tiotropium, and their combination in patients with acute exacerbation of chronic obstructive pulmonary disease: a pilot study. Respir Med 100:1925–32
36. Campbell M, Eliraz A, Johansson G, Tornling G, Nihlen U, Bengtsson T et al (2005) Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med 99:1511–20
37. Richter K, Stenglein S, Mucke M, Sieder C, Schmidtmann S, Harnest U et al (2006) Onset and duration of action of formoterol and tiotropium in patients with moderate to severe COPD. Respiration 73:414–19
38. Stockley RA, Whitehead PJ, Williams MK (2006) Improved outcomes in patients with chronic obstructive pulmonary disease treated with salmeterol compared with placebo/usual therapy: results of a meta-analysis. Respir Res 7:147
39. Stockley RA, Chopra N, Rice L (2006) Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. Thorax 61:122–28
40. Costello J (1999) Prospects for improved therapy in chronic obstructive pulmonary disease by the use of levalbuterol. J Allergy Clin Immunol 104:S61–S68
41. Truitt T, Witko J, Halpern M (2003) Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. Chest 123:128–35
42. Arformoterol (2004) (R, R)-eformoterol, (R, R)-formoterol, arformoterol tartrate, eformoterol-sepracor, formoterol-sepracor, R, R-eformoterol, R, R-formoterol. Drugs R D 5:25–27
43. Steinke JW, Baramki D, Borish L (2006) Opposing actions of (R, R)-isomers and (S, S)-isomers of formoterol on T-cell function. J Allergy Clin Immunol 118:963–65
44. Hanania NA, Donohue JF, Nelson H, Sciarappa K, Goodwin E, Baumgartner RA, Hanrahan JP (2010). The safety and efficacy of arformoterol and formoterol in COPD. COPD.;7:17–31.
45. Bennett WD, Almond MA, Zeman KL, Johnson JG, Donohue JF (2006) Effect of salmeterol on mucociliary and cough clearance in chronic bronchitis. Pulm Pharmacol Ther 19:96–100
46. Barnes NC, Qiu YS, Pavord ID, Parker D, Davis PA, Zhu J et al (2006) Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. Am J Respir Crit Care Med 173:736–43
47. Johnson M (2004) Interactions between corticosteroids and β_2-agonists in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc 1:200–206
48. Johnson M (2005) Corticosteroids: potential β_2-agonist and anticholinergic interactions in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2:320–325

49. Sin DD, Johnson M, Gan WQ, Man SF (2004) Combination therapy of inhaled corticosteroids and long-acting β_2-adrenergics in management of patients with chronic obstructive pulmonary disease. Curr Pharm Des 10:3547–60
50. Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S et al (2003) The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 124:834–43
51. Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T et al (2002) Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:1084–91
52. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A et al (2003) Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 361:449–56
53. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H (2003) Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 22:912–19
54. Gross NJ, Co E, Skorodin MS (1989) Cholinergic bronchomotor tone in COPD. Estimates of its amount in comparison with that in normal subjects. Chest 96:984–87
55. Gross NJ, Skorodin MS (1984) Role of the parasympathetic system in airway obstruction due to emphysema. N Engl J Med 311:421–25
56. O'Connor BJ, Towse LJ, Barnes PJ (1996) Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med 154:876–80
57. Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ et al (2006) Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 3:CD006101
58. Ayers ML, Mejia R, Ward J, Lentine T, Mahler DA (2001) Effectiveness of salmeterol versus ipratropium bromide on exertional dyspnoea in COPD. Eur Respir J 17:1132–37
59. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B et al (2004) Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 23:832–40
60. Anzueto A, Tashkin D, Menjoge S, Kesten S (2005) One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. Pulm Pharmacol Ther 18:75–81
61. Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr et al (2002) A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 122:47–55
62. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S (2003) Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 58:399–404
63. Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C (2005) Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther 18:397–404
64. Belmonte KE (2005) Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Proc Am Thorac Soc 2:297–304
65. Profita M, Giorgi RD, Sala A, Bonanno A, Riccobono L, Mirabella F et al (2005) Muscarinic receptors, leukotriene B4 production and neutrophilic inflammation in COPD patients. Allergy 60:1361–69
66. Cazzola M, Gabriella MM (2006) The additive effect of theophylline on a combination of formoterol and tiotropium in stable COPD: a pilot study. Respir Med 101:957–962
67. Man GC, Champman KR, Ali SH, Darke AC (1996) Sleep quality and nocturnal respiratory function with once-daily theophylline (Uniphyl) and inhaled salbutamol in patients with COPD. Chest 110:648–53
68. COMBIVENT Inhalation Aerosol Study Group (1994) In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 105:1411–1419
69. D'Urzo AD, De Salvo MC, Ramirez-Rivera A, Almeida J, Sichletidis L, Rapatz G et al (2001) In patients with COPD, treatment with a combination of formoterol and ipratropium

is more effective than a combination of salbutamol and ipratropium: a 3-week, randomized, double-blind, within-patient, multicenter study. Chest 119:1347–56
70. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM (2000) Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J 15:878–85
71. ZuWallack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K et al (2001) Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 119: 1661–70
72. Cazzola M, Di MF, Santus P, Boveri B, Verga M, Matera MG et al (2004) The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. Pulm Pharmacol Ther 17:35–39
73. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B et al (2005) Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 26:214–22
74. van Noord JA, Aumann JL, Janssens E, Verhaert J, Smeets JJ, Mueller A et al (2006) Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. Chest 129:509–17
75. Cazzola M, Dahl R (2004) Inhaled combination therapy with long-acting beta 2-agonists and corticosteroids in stable COPD. Chest 126:220–237
76. Donohue JF, Kalberg C, Emmett A, Merchant K, Knobil K (2004) A short-term comparison of fluticasone propionate/salmeterol with ipratropium bromide/albuterol for the treatment of COPD. Treat Respir Med 3:173–81
77. Make B, Hanania NA, ZuWallack R, Kalberg C, Emmett A, Brown CP et al (2005) The efficacy and safety of inhaled fluticasone propionate/salmeterol and ipratropium/albuterol for the treatment of chronic obstructive pulmonary disease: an eight-week, multicenter, randomized, double-blind, double-dummy, parallel-group study. Clin Ther 27:531–42
78. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R et al (2007) Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 146:545–55
79. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T et al (2009) Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 180:741–50
80. Melani AS, Zanchetta D, Barbato N, Sestini P, Cinti C, Canessa PA et al (2004) Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. Ann Allergy Asthma Immunol 93:439–46
81. Goodman DE, Israel E, Rosenberg M, Johnston R, Weiss ST, Drazen JM (1994) The influence of age, diagnosis, and gender on proper use of metered-dose inhalers. Am J Respir Crit Care Med 150:1256–61
82. Geller DE (2005) Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. Respir Care 50:1313–21
83. Barta SK, Crawford A, Roberts CM (2002) Survey of patients' views of domiciliary nebuliser treatment for chronic lung disease. Respir Med 96:375–81
84. Dhand R (2002) Nebulizers that use a vibrating mesh or plate with multiple apertures to generate aerosol. Respir Care 47:1406–16
85. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL et al (2005) Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 127:335–71
86. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM (2006) The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 129:15–26
87. Salpeter SR (2004) Cardiovascular safety of beta(2)-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review. Drugs Aging 21:405–14

88. Ferguson GT, Funck-Brentano C, Fischer T, Darken P, Reisner C (2003) Cardiovascular safety of salmeterol in COPD. Chest 123:1817–24
89. Rodrigo GJ, Nannini LJ, Rodriguez-Roisin R (2008) Safety of long-acting beta-agonists in stable COPD: a systematic review. Chest 133:1079–87
90. Donohue JF, Menjoge S, Kesten S (2003) Tolerance to bronchodilating effects of salmeterol in COPD. Respir Med 97:1014–20
91. Cazzola M, Matera MG, Donner CF (2005) Inhaled β_2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. Drugs 65:1595–610
92. Celli B, Decramer M, Leimer I, Vogel U, Kesten S, Tashkin DP (2010) Cardiovascular safety of tiotropium in patients with COPD. Chest 137:20–30
93. Barnes PJ (1997) Current therapies for asthma. Promise and limitations. Chest 111:17S–26S
94. Cazzola M, Matera MG (2009) Emerging inhaled bronchodilators: an update. Eur Respir J 34:757–69
95. Cazzola M, Matera MG, Lotvall J (2005) Ultra long-acting beta 2-agonists in development for asthma and chronic obstructive pulmonary disease. Expert Opin Investig Drugs 14:775–83
96. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ (2009) Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 374:685–94
97. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ et al (2009) Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 374:695–703

7

Pharmacological Therapy: Inhaled Corticosteroids

Paul Albert and Peter M.A. Calverley

Key Points:

- Inhaled corticosteroids have a more favourable safety profile than oral corticosteroids.
- Inhaled corticosteroids do not consistently modify inflammatory cell numbers in sputum or the airway wall of COPD patients.
- Inhaled corticosteroids produce small improvements in lung function with significantly better health status and exacerbation frequency than patients not so treated. The change in the number of exacerbations largely drives the improvement in exacerbation frequency. The effects of inhaled corticosteroids on the rate of decline of lung function remain controversial.
- Despite their symptomatic benefits inhaled corticosteroids alone do not modify the risk of dying from COPD.
- Bone and eye side effects are not increased in frequency in inhaled corticosteroid users but clinically diagnosed pneumonia is.
- Inhaled corticosteroids are not recommended for use as monotherapy in COPD but significantly increase clinical benefits when used together with long-acting beta-agonists and this includes a reduction in the risk of dying.

Keywords Anti-inflammatory • health status • pneumonia • inhaled corticosteroid

Introduction

Inflammation is now recognised as playing a key role in the development of COPD, its progression and the systemic or extra-pulmonary effects of this disorder. Given this central role, it is no surprise that clinicians have used corticosteroid treatment extensively in the management of COPD, especially given the dramatic responses seen in patients with asthma who were treated with these drugs. In contrast, and rather disappointingly, the changes seen in the clinical outcomes of COPD patients have been much more modest. This has led some physicians to state that inhaled corticosteroids are completely ineffective in COPD [1], a view for which the evidence from cellular science is more convincing than that observed when the clinical outcomes

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_7,

are viewed objectively. The resulting interplay of scientific disappointment weighed against modest clinical gains has generated many publications but little clarity and most clinicians remain bemused by the strongly held positions of the "pro" and "anti" inhaled corticosteroid camps.

The intention of this chapter is to set this debate in some context to focus on the things we know which seem likely to be true while acknowledging some of the methodological limitations which make at least some of the data about inhaled corticosteroids less reliable than others. Several important practical questions are considered:

1. Do inhaled corticosteroids have any anti-inflammatory effect on COPD?
2. Do inhaled corticosteroids change important clinical endpoints in COPD?
3. What side effects are associated with inhaled corticosteroid use?
4. How should we use inhaled corticosteroids in our clinical practice?

Fortunately, we now have a large body of evidence from different sources, some of the best of which has only become available in recent months, which helps clarify what was previously a rather confused picture.

Do Inhaled Corticosteroids Have Any Anti-inflammatory Effect in COPD?

Glucocorticosteroids are synthetic compounds based on the naturally occurring cortisone molecule. Not all are suitable for use by the inhaled route but the currently available compounds are summarised in Table 7.1. The mechanisms by which corticosteroids work within the cell are complex, involving several different pathways, the relative importance of which is debated. Corticosteroid molecules combine with a soluble receptor within the cytoplasm and the subsequent complex binds to the nucleus leading to an increase in the number of beta-2 receptors and the modulation of the transcription of pro-inflammatory proteins. Particular attention is being paid to the ability of these drugs to inhibit the unwinding of nuclear chromatin and hence the ease of access of the corticosteroid receptor complex to the nucleus. The process is mediated by the enzyme histone deacetylase. Failure of these drugs to interact with histone deacetylase 2 appears

Table 7.1 Inhaled corticosteroid preparations.

Drug	Available preparations	Daily dose	Regimen
Beclomethasone dipropionate	MDI, DPI	400–2,000 mcg	12 hourly
Budesonide	MDI, DPI, Neb	400–1,600 mcg 2,000–4,000 mcg in exacerbation	12 hourly
Fluticasone Propionate	MDI, DPI, Neb	200–2,000 mcg	12 hourly
Triamcinolone Acetonide	MDI, DPI	400–1,200 mcg	12 hourly
Mometasone Furoate	DPI	200–800 mcg	12–24 hourly
Ciclesonide	MDI	80–160 mcg	24 hourly

MDI metered dose inhaler, *DPI* dry powder inhaler, *Neb* nebuliser

to be a relatively specific feature of patients with COPD [2] and this may relate to continuing oxidative stress in these patients [3, 4]. How such changes relate to the proposed markers of continuing inflammation in COPD remains controversial as is the relevance of these processes to inflammation in other disorders which are characterised by inflammation with CD4+ T lymphocytes like rheumatoid arthritis. COPD markers of respiratory inflammation in induced sputum such as interleukin-8 and TNF-alpha are unaffected by treatment with either inhaled or oral corticosteroids [5]. However, some groups have suggested that inhaled corticosteroids can change the chemotactic activity in the sputum [6] and even circulating levels of inflammatory markers like C-reactive protein or IL-6 [7].

More direct evidence of any effect on the cells within the bronchial wall is lacking. Hattotuwa and colleagues gave 0.5 mg of fluticasone propionate twice daily to patients with moderately severe COPD for 3 months and found no difference in the cell content of the airway wall with the exception of a modest reduction in mast cell numbers at the end of this randomised blinded control study [8]. Some indirect evidence to suggest that inhaled corticosteroids produce histological changes comes from the observation that the number of lymphoid follicles associated with the airways is less in patients who received corticosteroid treatment before undergoing lung volume reduction surgery [9], although this is hardly a conclusive evidence of an anti-inflammatory effect for these agents. Although the data are meagre, most well-conducted studies point to little or no direct anti-inflammatory effects of inhaled corticosteroids in COPD. However, the potential for other benefits unrelated to inflammatory cell numbers does exist and changes in the degree of vascular leakage and hence oedema in the airway wall remains an attractive but unproven possibility which could account for at least some of the benefit seen.

Do Inhaled Corticosteroids Change Important Clinical Endpoints in COPD?

Although nebulised corticosteroids have been shown to be better than placebo in improving lung function in COPD patients who are exacerbating [10], they are somewhat less effective than oral prednisolone and given the cost differential between these treatments it seems unlikely that this therapy will become popular in routine care. Moreover, the lack of immediate symptomatic benefits with inhaled corticosteroids makes their use more suitable for maintenance rather than rescue treatment.

Much more evidence is available about the effects of inhaled corticosteroids in stable disease, and a range of studies of differing size and duration give basically similar results. Several different outcomes have been studied.

Decline in Lung Function

Throughout the 1990s, a series of randomised control trials addressed the question of whether inhaled corticosteroids modify the rate of decline of FEV_1 which is typically seen in populations of COPD patients. These studies gave conflicting results reflecting differences in patient selection and variations in the duration of follow-up [11, 12]. One Dutch study suggested that lung function monitored for 2 years after instituting inhaled corticosteroids was better than in the preceding 2 years of follow-up although this change was more evident in the pre-bronchodilator FEV_1 and the study was not a true randomised design.[13]

Subsequently, four large prospective randomised control trials, each of 3 years duration, studied whether or not the change in post-bronchodilator FEV_1, the reliable guide to disease progression [14–17], is modified by inhaled corticosteroids (Table 7.2). These studies encompassed a wide range of COPD severity ranging from individuals identified with mild disease in a prospective community sample to others with symptomatic COPD attending regular hospital follow-up. Their bias was towards current smokers, as this was an entry requirement for Euroscop and the original lung health study, although rather surprisingly, smoking status did not appear to modify the outcome, at least as related to the effect of inhaled corticosteroids. In no trial was the rate of FEV_1 decline different over 3 years when placebo and active treatments were compared. The effect of inhaled corticosteroids in the most severely affected patients may have been harder to detect given the asymmetrical pattern of drop-out in this study, i.e., patients on placebo were significantly more likely to be lost from follow-up and were also those who showed the most rapid loss of lung function [18]. This could not explain the data in the other three studies where equal numbers from each group were available for analysis by the end of the trial. Inevitably, meta-analyses of these data have followed and have drawn opposing conclusions [19–21]. The group who initially found no effect on decline in lung function in the pooled analysis have now repeated this analysis using data from other patient studies in addition to that they originally reported and their conclusion is unchanged [22]. However, other work taking virtually the same data and correcting an error made by the first group in assigning the rate of change of lung function now found a significant effect, particularly in those who had received more potent inhaled corticosteroids, budesonide and fluticasone propionate; this amounted to around 10 mL/year reduction in the rate of decline and the original studies were certainly not powered to detect this difference hence the meta-analysis including these data may be more relevant [21]. Post hoc analysis of the TORCH study (which entailed 26,000 spirometric assessments over 3 years) found that inhaled fluticasone propionate, alone (FP) or in combination with salmeterol (SFC), was associated with reduction in the rate of FEV_1 decline in patients with moderate to severe COPD (decline of 42 mL/year with FP, 39 mL/year with SFC and 55 mL/year with placebo) [23, 24].

Clinic Lung Function

A more consistent picture emerges when data a lung function of patients attending the clinic and specifically the post-bronchodilator FEV_1 is considered. Such changes take time to emerge but do begin to be evident within the first 2 weeks of randomisation to inhaled corticosteroid treatments [25]. No convincing effects on post-bronchodilator FEV_1 were seen when placebo and inhaled corticosteroid data were compared with the Danish and US long-term studies [14, 16]. In subsequent studies, FP at 1,000 mcg/day [26] and even at 500 mcg/day [26, 27] shows small but significant improvements in post-bronchodilator spirometry weeks to months after the onset of treatment. These changes could not be identified in studies using budesonide where only post-dose lung function data were available [28]. In general, these changes have been smaller in patients with more severe disease who were the ones recruited into the trials involving budesonide. However, post hoc analysis of data from a 1-year study in which FP was used as one of the comparison arms [29] shows that the increase in FEV_1 with fluticasone proprionate was lower in patients with a lower baseline value [30]. How important these changes in spirometry are clinically remains debatable but they do suggest that some biological effect is occurring with inhaled corticosteroid treatment which may be more relevant when other non-spirometric effects are considered.

Table 7.2 Randomised trials of 1 or more years comparing inhaled corticosteroids to placebo in stable COPD.

Study	Duration	Number relevant to this comparison	Drug/Dose	Mean (sd) FEV_1 post bronchodilator (% predicted)	FEV_1 change relative to placebo	Comment
CCLS	3 years	290	Budesonide 400 mcg bd	76 (18)	No change	No effect on FEV1 decline
Euroscop	3 years	1,277	Budesonide 400 mcg bd	73 (13)	Approx +40 mL	No effect on FEV1 decline; increased bruising; no loss of bone density
LHS II	3 years	1,116	Triamcinolone 600 mcg bd	67 (13)	No change	No effect on FEV1 decline; fewer unplanned visits; accelerated loss of bone density
ISOLDE	3 years	751	Fluticasone Propionate 500 mcg bd	49 (14)	+100 mL	No change in rate of decline in FEV1; 25% reduction in exacerbation rate to 0.99/year; reduced decline in health status
TRISTAN	1 year[a]	735	Fluticasone Propionate 500 mcg bd	46 (13)	+95 mL	19% reduction in exacerbation rate to 1.05/year; no bruising
Szafranski	1 year[a]	403	Budesonide 400 mcg bd	36 (12)	+52 mL	No clinical effect
Calverley	1 year[a]	513	Budesonide 400 mcg bd	42 (15)	No change	Delayed time to first course of oral corticosteroid
TORCH	3 years	3,058	Fluticasone Propionate 500 mcg bd	44 (12)	+47 mL	Reduced exacerbation rate (0.93 vs 1.13/ year); significant improvement in SGRQ[b] vs placebo (-2.0 units). No significant difference in mortality (16.0% vs 15.2 placebo)

[a]Decline in lung function not studied

[b]St George's Respiratory Questionnaire

Health Status or Quality of Life

A number of research questionnaires have been developed which have good measurement properties and which reliably capture the integrated effects of COPD on patient well-being [31, 32]. Studies using these health status questionnaires have shown that significant improvements in patient well-being can occur even when the change in spirometry is quite small [33]. Health status data have been collected almost exclusively in more severe disease (GOLD stages 3 and below), in patients rather than smokers with minimal symptomatology associated with their airflow obstruction and mostly, but not exclusively, using the St George's Respiratory Questionnaire (SGRQ). Treatment with inhaled corticosteroids in addition to short-acting bronchodilator therapy in the ISOLDE study did not change health status over the first 6 months of observation [34] although the use of an initial course of oral corticosteroids may have inadvertently served to standardise health status measurements before this trial began and hence prevent some of the spontaneous improvement in health status which is almost universally seen in patients randomised to placebo who enter a clinical trial. In the ISOLDE study, which lasted for 3 years, the rate of change of health status was modified in patients receiving inhaled corticosteroids by a mean of almost three units per year compared with placebo [17]. These changes were cumulative and suggest that the use of inhaled corticosteroids delays the time taken to reach a particular level of ill health rather than abolishing the progression of physical deterioration altogether. Similar data were seen in more severe patients when budesonide was used after an initial period of treatment with oral corticosteroids although again the magnitude of change differed depending upon the run-in period adopted in these 1-year studies [35]. Withdrawing inhaled corticosteroids was accompanied by a worsening of health status in Dutch trial using fluticasone [36], a finding confirmed when patients were randomised to either salmeterol, a long-acting beta-agonist (LABA), or salmeterol plus fluticasone [37]. Measurements related specifically to breathlessness are less often reported but in a 6-month study of stable patients where the transitional dyspnoea index was used to measure change, those individuals randomised to inhaled corticosteroids performed as well as those receiving the long-acting beta-agonists [26].

The large dataset available from the TORCH study has confirmed these observations over shorter periods [24]. In this trial, which was conducted without prior corticosteroid treatment, placebo-treated patients improved over the first 6 months of study but their health status deteriorated steadily thereafter. The improvement in those randomised to inhaled corticosteroids was greater and lasted longer but also declined with time, the total SGRQ score falling below the baseline value by the 3-year follow-up point. However, as in other studies the patients with the worst health status withdrew soonest and there were more of these in the placebo treated groups, suggesting that any comparison between the treatments is likely to be a conservative one.

Exacerbations

Defining COPD exacerbations remains contentious [38] but the recently proposed definition by GOLD has considerable merit ("An event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.") Most clinical trials to have studied inhaled corticosteroids have used this definition of a healthcare related event, although the Lung Health study of triamcinolone reported the number of new symptoms and the frequency of unplanned clinic visits which is likely to be only indirectly

related to the true number of exacerbations [16]. Exacerbations are more frequent in those with the worst lung function [39] and unsurprisingly it is this group where inhaled corticosteroids have been shown to be most effective. Table 7.3 summarises the key findings from recent trials in which the effect of inhaled corticosteroids on exacerbation rate has been reported. All of these studies have at least 12 months of data, which afforded a reasonable period for an event to occur and avoided issues of seasonality which might confound smaller briefer studies. Both the ISOLDE and TRISTAN studies involved similar patient groups (mean pre-bronchodilator FEV_1 44% predicted in each). Exacerbation frequency was reported in rather different ways and was similar in the groups who had received placebo with 1.3 events per year occurring [17, 29]. Using FP in the same dose in each study reduced exacerbations by 20–25% suggesting that the routine use of inhaled corticosteroids can be effective in patients like this. All the TRISTAN patients had a prior history of exacerbations and the same was true for patients receiving budesonide in two other trials where the baseline lung function was significantly lower (mean FEV_1 36% predicted)[28, 35]. Here the impact of the drug was much less impressive with no statistically significant reduction in exacerbation rate although the time to the first course of oral corticosteroids was delayed in one study [35]. The larger and longer TORCH study has confirmed that patients randomly assigned to inhaled corticosteroids are significantly less likely to exacerbate although the event rate in this trial was somewhat lower than the others reflecting both a different method of analysis and the lack of any requirement to prior exacerbation before study entry [24].

Attempts to generalise the findings from clinical trials to less selected patients included in large patient databases have met with only limited success. The initial suggestion that inhaled corticosteroids had a significant impact on exacerbation frequency and hospitalisations [40] being challenged on methodological grounds as this study exhibited immortal time bias [41], i.e., there was a difference in the exposure time and hence the risk of an exacerbation occurring between the groups simply because of the way the groups themselves were defined. Similar complex statistical issues affect how exacerbation rates are expressed [42]. These events are not normally distributed and each individual has their own inherent rate of exacerbation. Thus, the trials are able to detect whether or not there is a difference and in which direction it occurs but it becomes harder to develop a reliable parametric statistical measurement to say how big an effect is present. More sophisticated statistical methods, such as the recently proposed negative binomial distribution, appear to have overcome these problems although this area is likely to remain contentious. However, the data are expressed; those derived from randomised control trials remain substantially better than those in database studies because at least the patients were drawn randomly from the same initial population and hence the probability of an event occurring should be the same with only the treatment having an impact. This is particularly important given the uncertain nature of the diagnosis of COPD of some patients in the database sets and the lack of any information about disease severity.

Mortality

Despite the limitations noted above, until recently the only data available about the relationship of treatment to COPD mortality came from database studies where, in addition to the other limitations, there was a real risk of allocation bias where sicker patients received treatment and may thus do worse than those were not so intensively treated. The TORCH trial was primarily designed to remedy this defect [24] but even

Table 7.3 Studies of 1 or more years of the effect of inhaled corticosteroids on COPD exacerbations.

Study	Number relevant to this comparison	Duration (years)	Mean (sd) FEV_1 post bronchodilator (% pred)	Comparison	Outcome	Side effects
CCLS	290	3	76 (18)	Budesonide 400 mcg bd vs placebo	36 patients had temporary worsening in Budesonide group, 34 in placebo group	None reported
LHS II	1,116	3	67 (13)	Triamcinolone 600 mcg bd vs placebo	Fewer physician visits on active drug (1.2 vs 2.1 per 100-person years)	Significant reduction in lumbar spine and femoral density
ISOLDE	751	3	49 (14)	Fluticasone 500 mcg bd vs placebo	Exacerbations reduced significantly (1.32 vs 0.99 per year)	Bruising in 27 ICS patients, 15 on placebo; reduction in serum cortisol level with ICS but still in normal range
TRISTAN	735	1	46 (13)	Fluticasone 500 mcg bd vs placebo	Significantly fewer exacerbations with ICS (1.3 vs 1.06 per year)	No difference in occurrence of observed bruising; local class-related side effects
Szafransky	403	1	36 (12)	Budesonide 400 mcg bd vs placebo	No significant change in exacerbation rate (budesonide 1.84 vs placebo 1.87 per year)	No reported bruising (details limited)
Calverley	513	1	42 (15)	Budesonide 400 mcg bd vs placebo	Non-significant difference in exacerbation rate (1.8 vs 1.6 per year with ICS)	No excess of reported adverse events
TORCH	3,058	3	44 (12)	Fluticasone Propionate 500 mcg bd	Significant reduction in exacerbation rate (0.93 vs 1.13 per year) and requirement for systemic steroids (0.52 vs 0.80 per year). No significant difference in severe exacerbation requiring hospitalisation (0.17 vs placebo 0.19 per year)	Significantly higher rates of pneumonia in ICS group (18.3% vs 12.3%). Increased rates of dysphonia and candidiasis

this large and complex study has run into problems about interim analysis and differential dropout which were not envisaged when it began. One conclusion appears certain from the TORCH data, namely, no mortality benefit was observed between placebo and those patients who received inhaled corticosteroids alone. In the last 6 months of this study, the mortality rate in inhaled corticosteroid treated patients appeared to rise although it levelled off by the end of the trial and it is hard to know if this is random variation or not. However, the projected difference in mortality proposed by several database analyses [43–45] was not seen.

What Side Effects Are Associated with Inhaled Corticosteroid Use?

Corticosteroid treatment is associated with a formidable range of adverse events which are particularly concerning in older frail patients which might become more evident in older and frailer subjects with COPD. In practice it has been very difficult to establish whether treatment by the inhaled route is associated with significant problems and this must be an encouraging finding given that such differences were evident where oral corticosteroid use was more widespread. The local side effects of hoarseness, dryness of the mouth and candidiasis are more frequent in patients receiving inhaled corticosteroids. These will settle spontaneously or with the use of some form of volume spacer device or stop when treatment is discontinued although relatively few patients have to give up treatment because of these complaints. Larger randomised trials have shown that there is a reduction in morning cortisol levels although these generally stay within the normal range in almost all individuals. Even those who fall below the normal range are likely to spontaneously revert to normal values reflecting both the difficulty of this as an outcome for adrenal function and the small signal-size associated with systemic exposure to corticosteroids when given by the inhaled route [29]. Spontaneous skin bruising has been reported more frequently with inhaled corticosteroids, although in both the TRISTAN and the TORCH studies where this was specifically looked for, it was no more frequent in those on inhaled corticosteroids than those who received placebo [24]. The TORCH trial included specific sub-studies in US patients where bone mineral density measurements and slit-lamp assessments were made at randomisation, and over the subsequent 3 years, two findings became clear from these studies: first, the incidence of osteopaenia/ osteoporosis and of undetected cataracts is high in patients with COPD irrespective of their prior corticosteroid use; second, there were no obvious differences in bone mineral density or in the occurrence of cataracts in patients who were randomised to corticosteroid-containing treatments over the subsequent 3 years. These data do not exclude the potential for future risk but are generally encouraging and in keeping with the lack of significant differences in the occurrence of fractures in the larger TORCH population.

However, one unanticipated side effect was identified by TORCH. Patients who remained on the inhaled corticosteroids, either as monotherapy or in combination with the LABA, were significantly more likely to experience a physician-diagnosed pneumonia during the trial. There was no a priori definition of pneumonia but the same treatment difference was seen when episodes where a chest X-ray had been performed were examined. Surprisingly, the rate of hospitalisation did not differ between the groups between placebo and inhaled corticosteroid treatments or between patients on their LABA with or without inhaled corticosteroids. Similarly, mortality from pneumonia as a proportion of total mortality did not differ between the groups. As health status

was generally better in those receiving inhaled corticosteroids, the clinical significance of these events remains puzzling but more detailed and specific research is clearly required if we are to understand what has previously been an unrecognised problem.

How Should We Use Inhaled Corticosteroids in Our Clinical Practice?

The bulk of the reported clinical trial data suggests that inhaled corticosteroids have small but significant beneficial effects in the management of COPD. Although xno direct comparison has been made the known risks profile of using oral corticosteroids and especially their effects on skeletal muscle on bone means that inhaled corticosteroids remain the preferred way to deliver this form of anti-inflammatory treatment and even low doses of oral therapy are no longer advised. Currently available corticosteroids are given twice daily and there is a move towards dry powder formulations rather than metered dose inhalers, which is sensible as there is no need for additional or "rescue" treatment when these drugs are used for COPD patients. At present our data are based on studies with twice daily regimes but the advent of inhaled corticosteroids that appear to be as effective and have less potential for systemic availability may lead to more patients being treated with once-daily therapy.

Current clinical guidance suggests introducing inhaled corticosteroids in patients with an FEV_1 below 50% predicted who have a history of exacerbations – approximately three events in a 2-year period. These are a fair reflection of the previous evidence available when the guidelines were compiled. However, data from the TORCH study are likely to impact on this guidance which has already been modified in the UK after the National Institute for Clinical Excellence conducted a systematic review of the literature available in 2002 [46].

It is now clear that all the clinical benefits attributable to inhaled corticosteroids, including improvements in lung function, health status and exacerbation frequency, are greater in those patients where they are co-administered with a LABA. Moreover, the likelihood of dying was less in the TORCH trial in those patients who received this combination of treatments when compared with inhaled corticosteroids alone. Existing guidance from GOLD and the ATS/ERS suggests that long-acting inhaled bronchodilators should be given to most symptomatic COPD patients with an FEV_1 below 80% predicted and hence patients receiving inhaled corticosteroids should normally do so as part of combination treatment. We do not yet know if these treatments have to be delivered from the same inhaler or whether the combination of an inhaled corticosteroid and a long-acting inhaled anti-cholinergic like tiotropium is equally effective. Early results from the Canadian OPTIMAL study suggests that there may be clinical advantages from combining a LABA/inhaled corticosteroid and anti-cholinergic treatment but larger and longer studies will be needed before this concept is properly established. In practice, many patients with severe COPD and a history of severe exacerbations and/or hospitalisations are now receiving all three types of treatment when they or their healthcare assistant can afford this.

Although unproven, it would seem sensible to ensure that patients taking inhaled corticosteroids receive pneumovax, which reduces the incidence of pneumonia in more severe COPD [47] while the identification of important co-morbidities, like bone and eye disease, should be part of a comprehensive management of any symptomatic COPD patient irrespective of their need for inhaled corticosteroids.

Conclusion

The last 20 years have seen a wealth of data reported about the role of inhaled corticosteroids in COPD. This has taught us much about the disease, its impact on the health status of patients, the nature, frequency and quantification of exacerbations and most recently, the nature and causes of death from COPD. Inhaled corticosteroids are no longer regarded as suitable for monotherapy along with intermittent short-acting bronchodilators but when given together with a long-acting beta-agonist they augment the effectiveness of the latter drug and have set a new standard for the pharmacological care of this condition. Happily this has been achieved without the formidable and intrusive side effects that characterise the use of oral corticosteroids which was widespread before this research was undertaken. Evidence from randomised controlled trials suggests that inhaled steroids improve lung function, reduce exacerbation frequency and improve health status. There is evidence from one randomised controlled trial that inhaled steroids alone do not impact on mortality. Evidence from randomised controlled trials suggest that inhaled steroids carry topical side effects, but there is no consistent evidence of an effect on increased frequency of cataracts or decreased bone mineral density. The TORCH study, however, demonstrated significantly higher rates of pneumonia in COPD patients who remained on inhaled steroids. Experience from randomised controlled trials has led to most bodies recommending inhaled steroids in the form of combination therapy with a long-acting beta-agonist, rather than alone.

References

1. Barnes PJ (2000) Inhaled corticosteroids are not beneficial in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161(2 I):342–344
2. Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM et al (2005) Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 352(19):1967–1976
3. Carpagnano GE, Kharitonov SA, Foschino-Barbaro MP, Resta O, Gramiccioni E, Barnes PJ (2004) Supplementary oxygen in healthy subjects and those with COPD increases oxidative stress and airway inflammation. Thorax 59(12):1016–1019
4. Montuschi P, Collins JV, Ciabattoni G, Lazzeri N, Corradi M, Kharitonov SA et al (2000) Exhaled 8-isoprostane as an in vivo biomarker of lung oxidative stress in patients with COPD and healthy smokers. Am J Respir Crit Care Med 162(3 Pt 1):1175–1177
5. Keatings VM, Barnes PJ (1997) Granulocyte activation markers in induced sputum: comparison between chronic obstructive pulmonary disease, asthma, and normal subjects. Am J Respir Crit Care Med 155(2):449–453
6. Llewellyn-Jones CG, Harris TAJ, Stockley RA (1996) Effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema. Am J Respir Crit Care Med 153(2):616–621
7. Sin DD, Lacy P, York E, Man SF (2004) Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170(7):760–765
8. Hattotuwa KL, Gizycki MJ, Ansari TW, Jeffery PK, Barnes NC (2002) The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: a double-blind, placebo-controlled biopsy study. Am J Respir Crit Care Med 165(12):1592–1596
9. Hogg JC, Chu FS, Tan WC, Sin DD, Patel SA, Pare PD et al (2007) Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. Am J Respir Crit Care Med 176(5):454–459
10. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J et al (2002) Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment

of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med 165(5):698–703, JID – 9421642
11. Renkema TE, Schouten JP, Koeter GH, Postma DS (1996) Effects of long-term treatment with corticosteroids in COPD. Chest 109(5):1156–1162
12. Bourbeau J, Rouleau MY, Boucher S (1998) Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax 53(6):477–482
13. Dompeling E, van Schayck CP, van Grunsven PM, van Herwaarden CL, Akkermans R et al (1993) Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids. A 4-year prospective study [see comments]. Ann Intern Med 118(10):770–778
14. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum (1999) Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 353(9167):1819–1823
15. Pauwels RA, Lofdahl C-G, Laitinen LA, Schouten JP, Postma DS, Pride NB et al (1999) Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med 340(25):1948–1953
16. The Lung Health Study Research Group (2000) Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 343:1902–1909
17. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK (2000) Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. Br Med J 320(7245):1297–1303
18. Calverley PM, Spencer S, Willits L, Burge PS, Jones PW (2003) Withdrawal from treatment as an outcome in the ISOLDE study of COPD. Chest 124(4):1350–1356
19. Van Grunsven PM, Van Schayck CP, Derenne JP, Kerstjens HAM, Renkema TEJ, Postma DS et al (1999) Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. Thorax 54(1):7–14
20. Alsaeedi A, Sin DD, McAlister FA (2002) The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. Am J Med 113(1):59–65
21. Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ (2003) Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. Thorax 58(11):937–941
22. Soriano J, Sin D, Zhang X, Anderson J, Anthonisen N et al (2007) A pooled analysis of FEV_1 decline in COPD patients randomized to inhaled corticosteroids or placebo. Chest 131(3):682–689
23. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins C, Jones PW et al (2008) Effect of pharmacotherapy on rate of decline of lung function in COPD: results from the TORCH study. Am J Respir Crit Care Med 178:332–338
24. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins CR, Jones PW et al (2007) Salmeterol and fluticasone propionate and survival in COPD: the TORCH Trial. N Engl J Med 356:775–789
25. Vestbo J, Pauwels R, Anderson JA, Jones P, Calverley P (2005) Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. Thorax 60(4):301–304
26. Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T et al (2002) Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166(8):1084–1091
27. Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S et al (2003) The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 124(3):834–843

28. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S et al (2003) Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 21(1):74–81
29. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A et al (2003) Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 361(9356):449–456
30. Calverley PMA, Pauwels RA, Jones PW, Anderson JA, Vestbo J (2006) The severity of airways obstruction as a determinant of treatment response in COPD. Int J Chron Obstruct Pulm Dis 1(3):209–218
31. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW (1987) A measure of quality of life for clinical trials in chronic lung disease. Thorax 42(10):773–778
32. Jones PW, Quirk FH, Baveystock CM, Littlejohns P (1992) A self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. Am Rev Respir Dis 145(6):1321–1327
33. Jones PW (2001) Health status measurement in chronic obstructive pulmonary disease. Thorax 56(11):880–887
34. Spencer S, Calverley PMA, Burge PS, Jones PW (2001) Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163(1):122–128
35. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H (2003) Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 22(6):912–919
36. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C (2002) Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. Am J Respir Crit Care Med 166(10):1358–1363
37. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF et al (2005) Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax 60(6):480–487
38. Donaldson GC, Wedzicha JA (2006) COPD Exacerbations 1: epidemiology (Review). Thorax 61:164–168
39. Jones PW, Willits LR, Burge PS, Calverley PM (2003) Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease. Eur Respir J 21(1):68–73
40. Sin DD, Tu JV (2001) Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164(4):580–4, 164(4):580–584
41. Suissa S (2003) Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. Am J Respir Crit Care Med 168(1):49–53
42. Burney P, Suissa S, Soriano JB, Vollmer WM, Viegi G, Sullivan SD et al (2003) The pharmacoepidemiology of COPD: recent advances and methodological discussion. Eur Respir J Suppl 43:1s–44s
43. Sin DD, Wu L, Anderson JA, Anthonisen NR, Buist AS, Burge PS et al (2005) Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. Thorax 60(12):992–997
44. Kiri VA, Pride NB, Soriano JB, Vestbo J (2005) Inhaled corticosteroids in chronic obstructive pulmonary disease: results from two observational designs free of immortal time bias. Am J Respir Crit Care Med 172(4):460–464
45. Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC (2002) Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. Eur Respir J 20(4):819–825
46. Chronic obstructive pulmonary disease (2004) National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 59(Suppl 1):1–232
47. Alpagene I, Vazquer R, Reyes N,Munoz J, Fernárdez M et al (2006) clinical efficacy of antipreunoca vacciration in patients with COPD. Thorax 61:189–195

8

Pharmacological Therapy: Novel Approaches

Stephen I. Rennard

Key points:

- COPD is a preventable and treatable disease
- Goal for novel treatments will include:
  - Primary prevention
  - Symptom management
  - Disease modification
  - Restoration of function
  - Management and control of comorbidities
- Modalities being explored include:
  - Improved pharmacology and formulations of bronchodilators and inhaled corticosteroids
  - Anti-inflammatory agents
  - Cough and muco-active drugs
  - Stimulators of lung repair

Keywords Anti-inflammatory • antiprotease • smoking cessation • anti-oxidant

Introduction

Currently available pharmacologic treatments for chronic obstructive pulmonary disease (COPD) were developed primarily to improve airflow and thereby to improve symptoms. Oftentimes, agents found to have efficacy in COPD were originally developed to treat asthma. Gratifyingly, some currently available treatments can not only improve airflow and symptoms in COPD patients, but also reduce exacerbation frequency [1–3]. Even more exciting, several studies suggest that currently available treatments may slow the rate at which lung function declines [4, 5], although the clinical importance of the very modest effects observed remains uncertain.

Currently the fourth leading cause of death in the USA, COPD is projected to become the third leading cause of death in the USA and worldwide by the year 2020 [6]. While currently available treatments can help symptomatic patients with COPD, improved therapies are desperately needed. In part because of the large market represented by

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_8,

COPD patients, there is currently a rich and varied research program developing novel therapies for the COPD patient. The current chapter will provide an overview of novel approaches for the practicing clinician.

There are several reasons for the active clinician to be familiar with novel therapeutic approaches. First, and most importantly, COPD has for far too long been regarded as a relentlessly progressive condition for which therapy has little to offer. This opinion is incorrect, but remains widespread. The potential for novel therapies helps reinforce the message that COPD is a treatable condition and can help develop a positive approach to the treatment of the COPD patient. In addition, many patients with COPD are enthusiastic to participate in novel clinical trials. Clinical investigation is no longer solely the purview of academic centers. Increasingly, clinical trials are being conducted in general and specialty practices. Development of novel treatments, therefore, represents an opportunity both for the clinician and for patients. Finally, many COPD patients are well informed about novel approaches, and the active clinician needs to be as well. The current chapter will review approaches to advance currently existing therapies, the rationale and strategy for novel approaches, including approached designed to alter lung inflammation, lung tissue repair, the pulmonary vasculature and cough and sputum production (Table 8.1). In addition, while smoking cessation is discussed in Chap. 9,

Table 8.1 Targets for Improved Intervention in COPD[a].

Smoking cessation
Nicotine
Replacement
Vaccine
Receptor
Dopamineregic signaling pathway
CB1 receptor
Inhaler technology
Ease of use
Flexibility in dosing
Bronchodilators
Improved pharmacokinetics
Onset
Duration
Reduced side effects
Inhaled corticosteroids
Increased duration of action
Reduced side effects
Combinations
Multiple agents in a single inhaler device
Anti-inflammatory agents
Phosphodiesterase inhibitors
PDE4
PDE5[b]
Inhibitors of recruitment
Chemotaxis factors
LTB4
IL-8
Complement
Chemtotaxis factor receptors
CXCR2
Adhesion factors

(continued)

Table 8.1 (continued)

- Proteases
  - Serine proteases
    - α1 protease inhibitor
    - Neutrophil elastase
  - Metallo-proteases
  - Cysteine proteases
- Oxidant
- Cytokine
  - Antibody
  - Receptor antagonist
- Signal transduction
  - Intermediates
  - p38
  - Transcription factors/regulators of gene expression
    - HDAC2

Cough and muco-active agents
- Airway neural activity
  - D2 dopamine receptor
  - Irritant receptor
  - Neurokinin receptor
- Mucus release
  - Anti-proteases
  - Anti-oxidant
  - Neurokinin receptor
  - Mucus structure

Pulmonary vasculature

Lung repair
- Retinoid receptors
- Growth factors

[a] General categories are listed. Most include multiple, often very many, specific molecular targets. Selected individual targets are listed to cite specific examples
[b] PDE5 is not an anti-inflammatory, but may have utility as a pulmonary vasodilator. Other pulmonary vasodilator targets are not listed

novel pharmacological approaches to smoking cessation will also be discussed briefly. These will be discussed from the perspective of general approaches, although specific agents will also be discussed.

Advances in Current Therapeutic Strategies

Improvement in Delivery

Delivery of agents by the inhaled route is preferred to treat lung disease. Inhalation results in direct deposition on the airways resulting in high local levels and minimal systemic side effects. Administration via inhalation, however, creates a number of specific problems and opportunities. First, it is generally more difficult to use an inhalational device than it is to take an orally active agent. The metered-dose inhalers, which were widely used in the early 1990s, delivered a high-speed jet of nebulized droplets when activated by pressing on the canister. As a result, patients were obliged to coordinate inhalation with canister activation, while positioning the canister properly. Even with effective use, much of the delivered drug was deposited in the mouth or pharynx. If absorbed systemically, this could result in side effects without therapeutic benefit. Moreover, the use of these devices requires considerable education, and several studies

documented the difficulty patients had with the technique required [7]. Finally, these "classic" metered-dose inhalers utilized chlorofluorocarbon compounds as propellants. Because these compounds deplete ozone in the stratosphere, their use is now banned. While alternative propellants have been developed [8], a number of alternative strategies for delivery of inhaled drugs have been and are being developed [9, 10]. These offer a number of therapeutic advantages, including improved ease of use and greater delivery of active drug to the lung. The most widely used devices, at present, are dry powder inhalers, of which there are a number of variations [11, 12]. The development of these novel devices is rapidly evolving and offers a number of opportunities to improve convenience, ease of use, and efficiency and targeting of delivery.

Bronchodilators

Rationale: Currently, bronchodilators are first-line therapy for patients with COPD frequency [1–3]. It is likely that these agents, by improving expiratory airflow even modestly, allow more complete emptying of the lungs during each expiratory cycle [13]. As a result, lung volumes decrease. This can result in improved function and symptoms in the basal resting state. Importantly, increasing respiratory rate, whether due to exercise, anxiety, fever or any other cause, can result in further hyperinflation that is believed to be a major reason for dyspnoea in the COPD patient [14]. By facilitating lung emptying, bronchodilators minimize this hyperinflation and help mitigate symptoms.

Currently available bronchodilators fall into three classes of frequency [1–3]: beta-agonists, anticholinergics and methyl xanthenes. Beta-agonist bronchodilators, by stimulating ß$_2$ adrenergic receptors present on airway smooth muscle, increase intracellular cyclic AMP, which, in turn, causes airway smooth muscle to relax. Anticholinergic bronchodilators, in contrast, antagonize the effect of acetylcholine. When released by airway nerves, acetylcholine acts on M3 muscarinic receptors present on airway smooth muscle, increasing intracellular calcium and inducing smooth muscle contraction. By blocking this activity, anticholinergic bronchodilators antagonize the endogenous "tone" present in airway smooth muscle and can improve airflow. The only methyl xanthene currently used is theophylline. Its mechanism of action as a bronchodilator is controversial. However, it may act in this regard by inhibiting the breakdown of cyclic AMP.

There are several approaches for improving the currently available bronchodilators. First, currently available agents vary in their onset and duration of action. Agents with prolonged duration are highly desirable, as they optimize lung function throughout the day and night. While onset of action is less important than duration when a bronchodilator is used regularly, most patients prefer an agent with a rapid onset. This is believed to improve compliance and has advantages for patients who benefit from the acute peak effects or who have forgotten a dose of medication. In this context, several beta-agonist bronchodilators that have a duration of action significantly longer than the currently available medications are in development [15]. These novel agents may be appropriate for once-daily dosing. At least one of these agents, indacaterol, has an onset of action as rapid as the "rapidly acting" agent albuterol [16]. Novel, long-acting anticholinergic agents are also in development. Whether these will have more rapid onset of action remains to be established.

Reduction in Toxicity

Currently available inhaled bronchodilators have a relatively low adverse effect profile. Nevertheless, side effects do occur [3]. ß$_2$-adrenergic agonists, for example, are associated with tremor and tachycardia. These are felt to be due to action on ß$_2$-adrenergic

receptors located outside the lung. Thus, increasing the selectivity of the already highly selective agents is unlikely to reduce the adverse effect profile. The development of formulations and delivery systems that minimize systemic absorption, however, raises the possibility of reducing these adverse effects. In addition, many $ß_2$-adrenergic agonists are chiral compounds. In general, only one of the enantiomers accounts for the therapeutic benefits. A racemic mixture may have increased propensity for adverse effects. In this regard, *S*-albuterol has been suggested to induce pro-inflammatory mediator release and thus may contribute to the adverse effects of chronic albuterol use [17]. It is possible, therefore, that beta-adrenergic agonist formulations that contain only active enantiomers may minimize adverse effects [18]. The clinical significance of this approach for the treatment of COPD remains to be established, however.

The currently used anticholinergic bronchodilators are quaternary amines [19]. As a result, they are relatively poorly absorbed across epithelial surfaces and are very ineffective at crossing the blood–brain barrier. CNS effects, which are common with anticholinergics that are not charged such as atropine, are generally not observed. Dry mouth is a relatively common adverse effect associated with tiotropium. Other systemic effects such as difficulty with micturition are uncommon. It is possible that novel anticholinergics may minimize these adverse effects.

Inhaled glucocorticoids have the potential for both local and systemic adverse effects. Topical effects in the throat, including candidiasis and dysphonia depend on the amount of drug deposited locally. Systemic effects depend on the amount of drugs absorbed systemically. Both can be minimized by formulations and devices that deliver relatively larger amounts of the drug to the lung. In addition, it is possible to exploit glucocorticoid drug metabolism to optimize therapeutic benefit. Agents that are very rapidly metabolized, such as fluticasone, mometasone and ciclesonide are very rapidly cleared from the circulation, minimizing systemic effects [20, 21]. In addition, ciclesonide is a pro-drug that is activated in the airway reducing its oral availability, potentially contributing to a further increase in its therapeutic ratio [22].

Inhaled glucocorticoids, particularly when used in combination with a long-acting beta-agonist, have been demonstrated to provide additional therapeutic benefit for the COPD patient. Improvements in inhaled glucocorticoid therapy, particularly the development of agents that can be administered once daily, are also being pursued.

Advantages of Combinations

Several studies have documented the clinical benefit of bronchodilator combinations [23–25]. While early studies suggested that a single bronchodilator could achieve the "maximally possible" bronchodilator effect, when administered in combination, an anticholinergic and a beta-agonist bronchodilator consistently demonstrate improved bronchodilator effect [25]. There are several possible mechanisms to account for this. First, proximal airways are more richly endowed with cholinergic receptors, and anticholinergic bronchodilators have a greater effect in the proximal airways. Conversely, beta-adrenergic agonists are relatively more effective in the distal airways. In addition, there are several studies that suggest "cross talk" of the adrenergic and cholinergic signaling mechanisms.

As noted above, the combination of long-acting beta-agonist bronchodilators and inhaled glucocorticoids has added benefit in COPD patients compared to either agent alone [26, 27]. The mechanism by which inhaled glucocorticoids benefit patients in COPD remains controversial. Actions of the glucocorticoid on airway inflammation and oedema have been suggested, as have interactions between glucocorticoids and beta-adrenergic signaling pathways. Because inhaled glucocorticoids have a very

modest effect on their own, they have not been approved as sole agents for the treatment of patients with COPD. In addition, because of recent concerns about pneumonia when these agents are used alone [28], their off-label use as sole agents is discouraged in patients with COPD. However, as they provide added benefit in combination with long-acting beta-agonists, their use is encouraged [1–3].

Administration of inhaled drugs in a combination device offers a number of potential advantages. As inhaled medications are somewhat more difficult to use than orally active agents, reduction in the number of inhalations required and in the number of devices needed is likely to improve adherence. In addition, for agents such as inhaled glucocorticoids that are best used in combination, availability of a combination helps prevents misuse. Consistent with these practical advantages, the various combination inhalers developed have generally been very successful. It is likely, therefore, that novel bronchodilators will be developed in combination formulations.

Of the agents currently used to treat COPD, theophylline is not used by inhalation. While active orally, theophylline derivatives have been found to be locally irritating, although modestly effective as inhaled bronchodilators [29]. Other novel compounds including the PDE4 inhibitors (see below), however, may be effective by inhalation. If found to be effective in COPD, it seems likely that combinations containing these agents will also be developed.

Smoking Cessation

Cigarette smoking is the most important risk factor for the development of COPD. In the USA, 80% of patients with COPD are current or former smokers. While other risk factors also contribute to the development of COPD, targeting cigarette smoking is the most important preventative and prophylactic measure. In this context, the Lung Health Study clearly demonstrated that smoking cessation early in the course of COPD alters the natural history of the disease [30]. Specifically, the accelerated rate of decline in lung function that characterizes smokers with COPD is mitigated. After a modest improvement over the first year, lung function declines, but does so at a rate comparable to that of a non-smoker. Smoking cessation later in the course of the disease is not associated with reversal of lower respiratory tract inflammation [31, 32]. Nevertheless, patients' symptoms are improved following smoking cessation, despite persistence of lower respiratory tract inflammation [32, 33]. Whether the rate of decline in lung function is altered with cessation later in the course of COPD remains undetermined. Smoking cessation, therefore, should be an important goal for all patients with COPD. The earlier cessation is achieved, the better.

Novel therapeutic approaches for smoking cessation are being actively pursued. This is being facilitated by advances in understanding the psychopharmacology of nicotine, the most important addictive compound present in cigarette smoke [34, 35]. A number of agents that are active on pathways that interact with nicotine induced signaling, particularly with the dopamine pathway, are being explored. Importantly, the psychoactive addictive effect of nicotine on its receptors depends in large part on the pharmacokinetics of delivery to receptors in the brain. The relatively slow delivery of nicotine by replacement therapy, such as the nicotine patch, appears to work through this mechanism. Nicotinic receptor partial agonists such as varenicline also appear to work through this mechanism. The same mechanism underlies the concept behind the nicotine vaccine [36]. When coupled to a carrier protein, it is possible to induce antibody formation to nicotine. The antibodies in the circulation then bind nicotine reversibly.

The binding, however, greatly slows delivery of nicotine to the brain, reducing its addiction potential. Clinical trials with nicotine vaccine are currently underway, and early studies show promise [36].

A second effect of the nicotine partial agonists is to block the full activity of nicotine. Through such an action, varenicline has been reported to reduce the hedonic effects of nicotine [37]. Such an action has the potential to forestall the reinforcing effects of nicotine that occur when a smoker who has quit has a lapse. The nicotine vaccine, by slowing nicotine delivery, may have a similar action. These activities raise the exciting possibility that therapies may be available not only to help smokers quit, but help prevent relapse. A relatively short term study with varenicline supports such an action [38].

One particularly instructive agent, previously in development for smoking cessation is rimonabant. Rimonabant is a canabinoid receptor antagonist that alters release of gamma amino butyric acid release which, in turn, modulates the release of dopamine that is the main downstream mediator of nicotine effects [39]. Clinical trials with rimonabant have suggested efficacy for smoking cessation, although the FDA declined to approve rimonabant because of concerns for potential suicide risk. Nevertheless, having demonstrated that this pathway is an appropriate target for facilitating smoking cessation raises the possibility that other agents can be developed.

Anti-inflammatory Therapies

Rationale and General Considerations

Current concepts suggest that the tissue alterations that result in reduced airflow in COPD are the consequence of tissue damage due to inflammation [1, 40]. In this regard, an inflammatory response characterized by activated alveolar macrophages, neutrophils and the presence of lymphocytes, particularly CD8+ lymphocytes, is present in the airways, the mucus glands and the alveolar structures of the lung. This inflammation worsens as disease progresses [41]. Moreover, numerous animal and in vitro studies support the potential pathogenic role for inflammation in COPD. This body of evidence has contributed to the rationale supporting anti-inflammatory therapy in COPD.

The goals of such therapy would include mitigation of the tissue damage and the consequent structural alterations that result in airflow. Such an action could prevent the progressive loss of lung function that characterizes COPD. While this may benefit the COPD patient in the long run, whether an anti-inflammatory agent would have shorter term benefits for the COPD patient remains undetermined. Since COPD progresses relatively slowly, the development of anti-inflammatory therapies that could alter natural history would require relatively large studies conducted for extended periods of time [42]. As a consequence, such studies would be expensive. This has resulted in exploration of several clinical strategies to identify alternative biological or physiological end points that could serve as surrogates for lung function or could be used directly to accelerate the evaluation of novel therapies. In this context, CT scanning of the chest can provide a quantitative measure of pulmonary emphysema. It has been suggested that this may be a better measure of therapeutic efficacy for α-1 PI replacement than measurements of airflow [43, 44]. The development of novel end points to be used in clinical trials is an important issue for the clinician, as these same end points are likely to provide diagnostic information that can guide therapy [43].

The inflammatory process in COPD offers a plethora of opportunities for therapeutic intervention. Multiple cell types are modulated by a variety of signaling molecules

that act on a number of receptors that, in turn, signal through a variety of intracellular pathways. Once activated, inflammatory cells are stimulated to migrate, a process that involves several distinct steps with several levels of regulation. Once recruited to sites of inflammation, inflammatory cells release a number of mediators that both amplify the inflammatory process and lead to tissue damage. Each of these steps represents a potential therapeutic target. As a result, there are many potential novel anti-inflammatory therapies that could be active in COPD [45]. A large number of these potential therapeutic targets have found interest in both large pharmas and biotechs and, as a result, many novel agents have been explored at basic levels. To date, clinical trials have been conducted with relatively few. As noted above, agents that primarily act by altering the natural history of COPD may require a very long and expensive clinical development program [42]. As exacerbations of COPD, however, are felt to be characterized by acutely worsening inflammation [46], exacerbations may represent a target for a more rapid drug development paradigm. Similarly, neutrophil-derived proteases are highly potent mucus secretagogues [47]. This raises the possibility that targeting neutrophils, which are found in increased numbers in airway mucus glands [48], may have a beneficial effect in mitigating cough and sputum production. It is possible, therefore, that anti-inflammatory therapies could be developed for shorter term benefits, such as cough and sputum and/or exacerbations.

Several approaches that may selectively target neutrophils in COPD have been explored [49]. They includes targeting interleukin-8 and, analogously, targeting leukotriene B4, both potent neutrophil chemotactic factors. The possibility that there are multiple pathways that could recruit and activate inflammatory cells, however, creates the very real potential problem that inhibiting a single pathway may be insufficient to result in therapeutic benefit.

PDE Inhibitors

The first novel class of agents that is likely to reach approval for the treatment of COPD is the class of phosphodiesterase (PDE) inhibitors [50, 51], a class of enzymes that catalyzes the degradation of cyclic nucleotides, cyclic AMP, or cyclic GMP. The PDEs consist of at least 50 members in 14 classes.

PDE5

Inhibitors of PDE5, which catalyze the degradation of cyclic GMP, relax vascular smooth muscle. These agents have been approved for use in erectile dysfunction. They may also reduce pulmonary arterial pressure and may have utility in pulmonary hypertension [52, 53]. An effect in pulmonary hypertension secondary to COPD, therefore, is a potential application of these agents, but whether improved cardiac output will be offset by worsening ventilation-perfusion matching by these agents (or any other pulmonary vasodilators) remains to be determined.

PDE4

PDE4 inhibitors have been specifically developed as therapeutics for COPD and are the novel agents nearest to approval. PDE4s, of which there are four isoforms, each the product of a distinct gene, are prominent in a number of cells, including inflammatory cells [50, 51]. Since cyclic AMP generally inhibits inflammatory cell responses, inhibitors of PDE4 have the potential to increase inflammatory cell cyclic AMP, resulting in inhibition of inflammation. Consistent with this, PDE4 inhibitors have demonstrated anti-inflammatory action in a number of in vitro and animal model systems.

Several PDE4s have entered clinical trials, and results with several have been published. Both cilomilast and roflumilast have demonstrated clinical benefits [54–56],

resulting in modest improvements in airflow, together with a reduction in exacerbation frequency. While these effects have been observed in some studies, several clinical trials have been less impressive. Both agents remain under investigation.

The major adverse effect of PDE4 inhibitors is nausea, which may be associated with vomiting. This appears to be due to a direct effect on PDE4 in the central nervous system emesis center. The sub-type PDE4D appears to be particularly important in mediating this response [57]. In this regard, cilomilast has some selectivity for PDE4D. As a result, its maximally tolerated dose may be limited and may be sub-optimal. Roflumilast, which is not selective among the PDE4 species, may be slightly more effective clinically, at least in part because it can be dosed at a relatively higher level because of its increased tolerability. Whether selective PDE4s that minimize the GI side effects can be developed remains to be seen. Interestingly, in contrast to theophylline, PDE4 inhibitors may be effective by the inhaled route [58]. This raises the possibility that they could be delivered via inhalation allowing increased local concentrations without adverse systemic effects. If PDE4 inhibitors could be combined with other inhaled products, this could represent an important novel strategy.

Consistent with an anti-inflammatory mechanism of action, PDE4 inhibitors result in airflow limitation that increases gradually over the first few weeks of therapy [54–56]. In addition, in a study using bronchoscopy and endobronchial biopsy, the PDE4 inhibitor cilomilast was associated with a reduction in inflammatory cells present on endobronchial biopsy [59].

The anti-inflammatory effect of PDE4 inhibitors raises the possibility that they could alter the natural history of COPD. Such an effect has not been tested clinically. As pulmonary structural cells, including fibroblasts, also express PDE4, it is possible that PDE4 inhibitors could modulate tissue remodeling through actions on structural cells as well as by targeting airway inflammation [60].

Anti-oxidants

Among the mediators released by inflammatory cells in COPD, oxidants have received considerable attention [61]. Oxidative stress damages lung extracellular matrix components directly contributing to tissue structural alterations. In addition, oxidative stress can inactivate anti-proteolytic defenses, including α-1 PI that may result in a functional α-1 PI deficiency [62]. Oxidative stress can, moreover, lead to inactivation of HDAC2 and, thereby, may lead to an inflammatory response that is resistant to glucocorticoid down regulation. A number of anti-oxidant strategies have been suggested. In a relatively large study of 523 subjects, the anti-oxidant *N*-acetylcysteine (NAC) was assessed [63]. No effect was observed on the rate of FEV_1 decline over a 3-year interval. Similarly, there was no effect on rate of COPD exacerbations in the study as a whole. There was, however, a reduction in exacerbation frequency in subjects who were not concurrently treated with glucocorticoids. While the results of this trial were negative, it remains possible that anti-inflammatory agents more effective than NAC may have benefit in COPD patients. Moreover, it may be possible to identify a subset of patients in whom anti-oxidant therapy can have therapeutic benefit.

Anti-proteases

Alpha-1 Protease Inhibitor

Alpha-1 protease inhibitor (α-1 PI, α-1 antitrypsin) is a serum protein that inhibits the activity of serine proteases. Severe deficiency of this protein, which is made primarily in the liver, can greatly increase the risk for the development of pulmonary emphy-

sema [64]. α-1 PI deficiency is a relatively common, inherited disorder occurring in approximately 1 in 2,500 Americans. It is more common in northern than in southern Europe. In the USA, α-1 PI has been approved for replacement therapy in individuals with severe genetic deficiency under the Orphan Drug Act. Since approval, registry studies suggest that drug administration can slow the rate at which lung function is lost [64, 65]. While not yet approved in Europe, a randomized, prospective controlled trial is currently underway.

Patients receiving α-1 PI replacement have also been reported to have a reduction in the frequency of acute exacerbations [66]. This raises the possibility that α-1 PI may have additional benefits and is consistent with an anti-inflammatory role for α-1 PI [67]. It has been suggested that α-1 PI may benefit patients with cystic fibrosis and patients with COPD with normal α-1 PI levels.

Other Protease Inhibitors

The increased risk of emphysema in patients deficient in α-1 PI served to focus attention on the role of proteases and antiproteases. It is now clear that several families of proteases including serine, metallo-, and cysteine proteases, each of which contains many members, likely play a role in the development of COPD [68]. The activity of these proteases is regulated by several families of anti-proteases, and these enzymes interact with each other to comprise a complex network [69]. Considerable preclinical evidence suggests that these proteases are appropriate targets for therapeutic intervention [40]. A major problem with this type of agent, however, is specificity. Since there are many proteolytic enzymes released by inflammatory and structural cells, it may be necessary to use a "broad spectrum" anti-protease. On the other hand, broad specificities increase the potential for adverse effects. Nevertheless, proteolytic inhibitors are being explored for use in COPD and it is likely that some compounds will enter clinical trials.

Anti-TNF-α

Of the inflammatory mediators present in COPD, tumor necrosis factor alpha (TNF-α) has attracted considerable attention [70]. Increased levels of TNF-α have been reported in sputum [71] and in peripheral blood of patients with COPD [72]. TNF-α, moreover, has been suggested to contribute to the systemic effects that characterize COPD, including weakness and loss of lean body mass [72, 73]. TNF-α is believed to contribute to the malaise and systemic effects associated with rheumatoid arthritis. In this context, blockade of TNF-α with anti-TNF antibodies or a TNF receptor derivative can rapidly and dramatically improve general well being as well as local inflammation in rheumatoid arthritis [74]. Based on these observations, infliximab, an anti-TNF antibody with demonstrated efficacy in rheumatoid arthritis and Crohn's disease [74], was assessed in a clinical trial of more than 200 subjects with moderate-to-severe COPD [70]. No therapeutic benefit was observed in the primary outcome variables: health status (quality of life) or walking distance. This study was designed to assess unselected individuals with COPD. Whether this therapy would have been effective in a subset of individuals is undetermined. In addition, a larger number of malignant tumors were observed following therapy with anti-TNF antibodies than were observed in a placebo group. While it is likely that many of these were present, but not clinically recognizable at the time of study entry, current data do not support the use of anti-TNF antibodies for the treatment of COPD.

Currently Available Drugs That May Have Anti-inflammatory Actions in COPD

Macrolides

The recognition that inflammation plays a major role in the pathogenesis of COPD has led to the reassessment of a number of traditionally used therapies. Macrolide antibiotics, for example, are now recognized as having anti-inflammatory as well as anti-microbial effects [75]. The anti-inflammatory effects were discovered largely as a consequence of the action of these drugs in treating diffuse panbronchiolitis, an inflammatory lung disease that, prior to macrolide therapy, was most commonly progressive and fatal [76]. Anti-inflammatory effects of macrolides in COPD, both during acute exacerbations and during stable disease, are now being explored. The concept that macrolides may act by modulating inflammation may justify the once common clinical practice of using macrolide antibiotics during COPD exacerbations despite the likelihood that any micro-organism present would not be sensitive. This would represent an excellent example of theoretical medicine following clinical observation rather than driving clinical practice.

Theophylline

Similarly, theophylline was, at one time, widely used for the treatment of COPD. At target blood levels of 10–20 μg/mL that were previously recommended, theophylline frequently results in nausea and can also result in serious arrhythmias and seizures. As a result, theophylline use requires frequent blood monitoring and clinical caution. The complexity of theophylline's drug–drug interactions, moreover, makes it a relatively difficult pharmaceutical in many clinical settings. As noted above, theophylline has a number of biological activities. Among these appears to be induction of the activity of histone deacetylas-2 [77]. The histone deacetylases (HDAC) are enzymes involved in modifying DNA structure and regulating gene expression. HDAC2 plays an important role in suppressing pro-inflammatory genes in response to glucocorticoids. A deficiency in HDAC2 has been reported in COPD patients [78]. The ability of theophylline to increase HDAC2 activity, therefore, raises the possibility that theophylline may have an important anti-inflammatory action, particularly, in combination with glucocorticoids.

Statins

Statins are agents that are widely used because of their ability to inhibit cholesterol synthesis and lower circulating lipid levels. These agents have been associated with the reduction in risk of myocardial infarction. The statins inhibit cholesterol synthesis at a relatively early step in the pathway: the conversion of acetyl-CoA to mevalonate. Importantly, several of the intermediates between mevalonate and cholesterol play an important role in regulation of signaling processes. It appears that statins, by inhibiting the production of mevalonate, may have anti-inflammatory actions [79, 80]. This raises the possibility that statins, independent of their effects on cholesterol, may have the potential for therapeutic efficacy.

Consistent with an action in COPD are clinical observations of patients with COPD who have been treated with statins. In one clinical database study, Mancini and colleagues demonstrated that patients treated with statins had lower risk of mortality as well as hospitalization [81]. This was true for both cardiac events and for COPD-related events.

When the patients in the database were stratified by cardiac risk, those patients with low cardiac risk still showed a therapeutic benefit from statins. The benefit among these individuals was entirely due to a reduction in COPD-related events, as might be expected since the risk for cardiac events was low. Interestingly, benefits, although to a lesser degree, were also observed with angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors. The effect observed with statins has been supported in an independent database review [82]. It is likely, therefore, that agents currently used to treat cardiac disease will be assessed for therapeutic benefit, specifically in patients with COPD.

Cough and Mucus

Despite the fact that cough is among the most common conditions for which patients seek medical advice, there are no evidence-based therapies currently available and approved for treating this common symptom in COPD [1–3]. Although the pathophysiology of cough and mucus secretion in COPD remains incompletely understood, it is likely that neural reflexes play an important role [83]. Agents that target neural signaling in the airways, therefore, are appealing to therapeutic agents to address this unmet need. This was the rationale behind the development of sibenadet, an agonist on the D2 dopaminergic receptor. In addition, sibenadet has activity on the $ß_2$ adrenergic receptor [84]. Consistent with actions on this receptor, sibenadet resulted in bronchodilation. In animal studies, when the beta receptor was blocked, sibenadet continued to suppress cough, and this activity was blocked by inhibition of the D2 receptor [84]. Clinical trials with sibenadet were undertaken, and early short-term studies demonstrated an improvement in cough [85]. Unfortunately, this was not sustained during longer term studies, suggesting the possibility of tachyphylaxis [86]. While the development of sibenadet was discontinued, the clinical experience with this compound supports the concept that neurally active agents have the potential to improve cough and possibly sputum production in patients with COPD.

In addition to neural stimulation, a number of other stimulatory pathways can lead to mucus hypersecretion in patients with COPD [87, 88]. These pathways include both cellular effects, that is induction of goblet cell metaplasia in the airways together with glandular hypertrophy, as well as regulation of glandular secretion. With the delineation of these pathways, a number of potential targets that could mitigate mucus hypersecretion have been identified. It is likely that clinical trials with agents targeting these pathways will be undertaken.

Pulmonary Vasculature

Agents that modify the pulmonary vasculature are being developed for the treatment of primary pulmonary hypertension [52]. Many of these agents can also be effective vasodilators in secondary forms of pulmonary hypertension, including COPD. For patients with COPD who have secondary pulmonary hypertension as a result of hypoxemia, oxygen is the therapy of choice. However, for other individuals with COPD, pulmonary vasodilators may have the potential for therapeutic benefit. In this regard, many patients with COPD develop pulmonary hypertension with exercise. Exercise, moreover, may be limited in COPD because of compromise in cardiac output. While this may result from increased intrathoracic pressure consequent to dynamic hyperinflation [89], acute

increases in pulmonary systolic blood pressure could also play a role [90]. However, since pulmonary vasoconstriction serves to maintain ventilation-perfusion balance, and preserve oxygenation, pulmonary vasodilators also have the potential to worsen oxygenation. Whether these agents will prove useful to treat patients with COPD remains to be determined.

Systemic Effects

As noted in Chap. 1, COPD is characterized not only by airflow limitation, but also by systemic effect. Often these systemic effects contribute more to the clinical compromise of individual patients than do limitations in expiratory airflow. These systemic manifestations of COPD, therefore, become important targets for clinical intervention. These include reduction in risk of acute cardiac events, prevention of accelerated loss of bone density, treatment of depression and restoration of skeletal muscle strength [91].

At the present time, it is unknown if patients with COPD should be treated for cardiovascular disease, depression or osteoporosis in a manner that differs from the treatment of these conditions in general. To date, relatively few studies have been conducted in this regard. A number of studies, however, have been conducted addressing the loss of skeletal muscle mass and compromise exercise performance that characterizes patients with COPD.

It is likely that several factors contribute to reduced skeletal muscle mass in patients with COPD, including detraining, systemic effects of inflammation, under nutrition due to increased caloric requirements and decreased appetite and a deficiency in anabolic androgens [91]. Exercise training in COPD patients has been demonstrated to improve muscle performance, consistent with a role for detraining [92]. In addition, nutritional supplementation has been demonstrated to lead to weight gain in at least a subset of COPD patients [93]. Anabolic androgens have, in addition, been shown to result in increased muscle mass [94]. The clinical benefits of the latter two interventions remain controversial. The benefits of exercise training, however, are well established [92]. Importantly, the benefits of an exercise training program appear to depend on the intensity of the exercise training. Since exercise is often limited by dynamic hyperinflation [14], the concurrent use of a bronchodilator during pulmonary rehabilitation appears to result in a synergistic benefit [95]. The pharmacologic strategies and agents that will best augment pulmonary exercise rehabilitation programs remain to be defined. It is likely that a number of novel approaches will be investigated in this regard.

Lung Regeneration

In 1997, Massaro and Massaro demonstrated that, following the development of emphysema, administration of all-trans retinoic acid stimulates the formation of new alveolar wall in a rat model [96]. This experiment clearly demonstrated that pulmonary emphysema was not, as was once believed, entirely irreversible. Those original experiments have been repeated in the mouse, but not in other species [97, 98]. Two limited trials with all-trans retinoic acid, which is approved for the treatment of certain forms of leukemia, have been conducted in patients with COPD [99, 100]. Although no untoward adverse effects were observed, no therapeutic benefits were observed either.

Retinoic acid acts on three intracellular receptors: RAR-α, RAR-β and RAR-γ. It appears that the RAR-γ receptor may be particularly important in stimulating

new alveolar wall formation. Based on this, agonists active at the RAR-γ receptor have been developed and are undergoing clinical trials both in patients with α-1 PI deficiency-associated emphysema and in smokers with normal levels of α-1 PI with emphysema.

Based on animal studies, there are a number of other potential therapeutic strategies that could stimulate tissue repair and potentially restore lung function in COPD including hepatocyte growth factor [101] and granulocyte colony stimulating factor [102]. It seems likely that novel strategies targeting these pathways will also be pursued. In addition, the concept that fibrosis is irreversible has also been refuted in a number of clinical and animal model settings [103]. Thus, it is possible that the peribronchiolar fibrosis that contributes to airflow limitation in the small airways may also be reversible through therapeutic interventions [104]. A number of potential agents targeting pathways that regulate repair and remodeling are currently under investigation.

One potential reason for failure of all-trans retinoic acid to stimulate alveolar repair in non-rodent species might be lack of an appropriately responding cell. In this context, rodent growth, which can continue throughout life, differs in many respects from that of other mammalian species. One possible mechanism to account for this difference would be the persistence of a stem/progenitor cell population capable of responding to retinoic acid and inducing the formation of new alveolar wall in rodents. This raises the very interesting possibility that lung regeneration in the human may be facilitated by concurrent cell-based therapies [102], although the development of such therapeutic strategies would require many questions to be addressed [105].

Conclusion

COPD is currently regarded as a treatable and preventable disorder frequency [1, 2]. Advances in prevention, particularly in smoking cessation, will help to prevent the development of COPD. In addition, advances in the treatment of patients with COPD hold the promise to improve symptomatic treatment beyond the goals achievable with current therapy, to alter the natural history of the disease including restoration of lost function, and to address the systemic features of the disorder.

References

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J (2006) Global strategy for diagnosis, management and prevention of COPD. Am J Respir Crit Care Med 174:867–874
2. Celli BR, MacNee W (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23(6):932–946
3. Rennard SI (2004) Treatment of stable chronic obstructive pulmonary disease. Lancet 364(9436):791–802
4. Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ (2003) Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. Thorax 58(11):937–941
5. Anzueto A, Tashkin D, Menjoge S, Kesten S (2005) One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. Pulm Pharmacol Ther 18(2):75–81
6. Murray CJL, Lopez AD (1996) The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Harvard University Press, Cambridge

7. Rubin BK, Fink JB (2005) Optimizing aerosol delivery by pressurized metered-dose inhalers. Respir Care 50(9):1191–1200
8. Leach CL (2005) The CFC to HFA transition and its impact on pulmonary drug development. Respir Care 50(9):1201–1208
9. Smaldone GC (2005) Assessing new technologies: patient-device interactions and deposition. Respir Care 50(9):1151–1160
10. Labiris NR, Dolovich MB (2003) Pulmonary drug delivery. Part II: the role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol 56(6):600–612
11. Newman SP, Busse WW (2002) Evolution of dry powder inhaler design, formulation, and performance. Respir Med 96(5):293–304
12. Frijlink HW, De Boer AH (2004) Dry powder inhalers for pulmonary drug delivery. Expert Opin Drug Deliv 1(1):67–86
13. O'Donnell DE (2006) Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 3(2):180–184
14. O'Donnell DE, Banzett RB, Carrieri-Kohlman V, Casaburi R, Davenport PW, Gandevia SC, Gelb AF, Mahler DA, Webb KA (2007) Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proc Am Thorac Soc 4(2):145–168
15. Matera MG, Cazzola M (2007) Ultra-long-acting beta2-adrenoceptor agonists: an emerging therapeutic option for asthma and COPD? Drugs 67(4):503–515
16. Naline E, Trifilieff A, Fairhurst RA, Advenier C, Molimard M (2007) Effect of indacaterol, a novel long-acting beta2-agonist, on isolated human bronchi. Eur Respir J 29(3):575–581
17. Agrawal DK, Ariyarathna K, Kelbe PW (2004) (S)-Albuterol activates pro-constrictory and pro-inflammatory pathways in human bronchial smooth muscle cells. J Allergy Clin Immunol 113(3):503–510
18. Costello J (1999) Prospects for improved therapy in chronic obstructive pulmonary disease by the use of levalbuterol. J Allergy Clin Immunol 104(2 Pt 2):S61–S68
19. Rennard SI (2000) Anticholinergic bronchodilators. In: Martin RJ, Kraft M (eds) Combination therapy for asthma and chronic obstructive pulmonary disease. Marcel Dekker, New York, pp 159–180
20. Hubner M, Hochhaus G, Derendorf H (2005) Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids. Immunol Allergy Clin North Am 25(3):469–488
21. Meltzer EO, Derendorf H (2006) The systemic safety of inhaled corticosteroid therapy: a focus on ciclesonide. Ann Allergy Asthma Immunol 97(2):149–157
22. Humbert M (2004) Ciclesonide: a novel inhaled corticosteroid. Expert Opin Investig Drugs 13(10):1349–1360
23. Group, C. I. A. S. (1994) In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 105:1411–1419
24. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, Mueller A, Cornelissen PJ (2005) Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 26(2):214–222
25. Rennard SI (1999) Anticholinergics in combination bronchodilator therapy in COPD. In: Spector SL (ed) Anticholinergic agents in the upper and lower airways. Marcel Dekker, Inc., New York, pp 119–136
26. Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, Shah T (2003) The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 124(3):834–843
27. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H (2003) Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 21(1):74–81
28. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356(8):775–789

29. Cushley MJ, Holgate ST (1985) Bronchodilator actions of xanthine derivatives administered by inhalation in asthma. Thorax 40(3):176–179
30. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA, Enright PL, Kanner RE, O'Hara P, Owens GR, Scanlon PD, Tashkin DP, Wise RA (1994) Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. JAMA 272:1497–1505
31. Rutgers SR, Postma DS, ten Hacken NH, Kauffman HF, van Der Mark TW, Koeter GH, Timens W (2000) Ongoing airway inflammation in patients with COPD who do not currently smoke. Thorax 55(1):12–18
32. Willemse BW, ten Hacken NH, Rutgers B, Lesman-Leegte IG, Postma DS, Timens W (2005) Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. Eur Respir J 26(5):835–845
33. Romberger DJ, Spurzem JR, Von Essen SG, Horstman D, Toso J, Hepp L, Stoner JA, Ullrich FA, Minton R, Matthews K, Rennard SI (2006) Impact of smoking cessation on quality of life measures in COPD. PATS 3:A811
34. Schnoll RA, Lerman C (2006) Current and emerging pharmacotherapies for treating tobacco dependence. Expert Opin Emerg Drugs 11(3):429–444
35. Lerman C, Patterson F, Berrettini W (2005) Treating tobacco dependence: state of the science and new directions. J Clin Oncol 23(2):311–323
36. Hatsukami DK, Rennard S, Jorenby D, Fiore M, Koopmeiners J, de Vos A, Horwith G, Pentel PR (2005) Safety and immunogenicity of a nicotine conjugate vaccine in current smokers. Clin Pharmacol Ther 78(5):456–467
37. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR (2006) Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 296(1):47–55
38. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR (2006) Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 296(1):64–71
39. Fagerstrom K, Balfour DJ (2006) Neuropharmacology and potential efficacy of new treatments for tobacco dependence. Expert Opin Investig Drugs 15(2):107–116
40. Shapiro SD, Snider GL, Rennard SI (2005) Chronic Bronchitis and Emphysema. In: Mason RJ, Broadus VC, Murray JF, Nadel JA (eds) Textbook of respiratory medicine, 4th edn. Elsevier, Philadelphia, pp 1115–1167
41. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Pare PD (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350(26):2645–2653
42. Anthonisen N, Connett J, Friedman B, Glass M, Kilday DP, Mingo TS, Rudolphus A, Williams GW (1991) Design of a clinical trial to test a treatment of the underlying cause of emphysema. Ann NY Acad Sci 624:31–34
43. Gross NJ (2004) Outcome measures for COPD treatments: a critical evaluation. COPD 1(1):41–57
44. Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, Skovgaard LT, Kok-Jensen A, Rudolphus A, Seersholm N, Vrooman HA, Reiber JH, Hansen NC, Heckscher T, Viskum K, Stolk J (1999) A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med 160(5 Pt 1):1468–1472
45. Barnes PJ (2004) Mediators of chronic obstructive pulmonary disease. Pharmacol Rev 56(4):515–548
46. White AJ, Gompertz S, Stockley RA (2003) Chronic obstructive pulmonary disease. 6: the aetiology of exacerbations of chronic obstructive pulmonary disease. Thorax 58(1):73–80
47. Sommerhoff CP, Nadel JA, Basbaum CB, Caughey GH (1990) Neutrophil elastase and cathepsin G stimulate secretion from cultured bovine airway gland serous cells. J Clin Invest 85:682–689
48. Saetta M, Turato G, Facchini F, Corbino L, Maestrelli P, Mapp CE, Cavallesco G, Ciaccia A, Fabbri LM (1997) Macrophage and neutrophil infiltration in the bronchial glands of subjects with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:A595

49. Barnes PJ (2007) New molecular targets for the treatment of neutrophilic diseases. J Allergy Clin Immunol 119(5):1055–1062, quiz 1063–1064
50. Giembycz MA (2002) Development status of second generation PDE4 inhibitors for asthma and COPD: the story so far. Monaldi Arch Chest Dis 57(1):48–64
51. Liu X, Rennard SI (2003) Therapeutic potential of PDE4 inhibitors in chronic obstructive pulmonary disease. Medscape
52. Rosenkranz S (2007) Pulmonary hypertension: current diagnosis and treatment. Clin Res Cardiol 96(8):527–541
53. Lewis GD, Semigran MJ (2004) Type 5 phosphodiesterase inhibition in heart failure and pulmonary hypertension. Curr Heart Fail Rep 1(4):183–189
54. Compton CH, Gubb J, Nieman R, Edelson J, Amit O, Bakst A, Ayres JG, Creemers JP, Schultze-Werninghaus G, Brambilla C, Barnes NC (2001) Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study. Lancet 358(9278):265–270
55. Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbroker D, Bethke TD (2005) Roflumilast – an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 366(9485):563–571
56. Rennard SI, Schachter N, Strek M, Rickard K, Amit O (2006) Cilomilast for COPD: results of a 6-month, placebo-controlled study of a potent, selective inhibitor of phosphodiesterase 4. Chest 129(1):56–66
57. Giembycz MA (2002) 4D or not 4D – the emetogenic basis of PDE4 inhibitors uncovered? Trends Pharm Sci 23:548
58. Gutke HJ, Guse JH, Khobzaoui M, Renukappa-Gutke T, Burnet M (2005) AWD-12–281 (inhaled) (elbion/GlaxoSmithKline). Curr Opin Investig Drugs 6(11):1149–1158
59. Gamble E, Grootendorst DC, Brightling CE, Troy S, Qiu Y, Zhu J, Parker D, Matin D, Majumdar S, Vignola AM, Kroegel C, Morell F, Hansel TT, Rennard SI, Compton C, Amit O, Tat T, Edelson JD, Pavord ID, Rabe KF, Barnes NC, Jeffery PK (2003) Antiinflammatory effects of the phosphodiesterase 4 ihibitor cilomilast (Ariflo) in COPD. Am J Respir Crit Care Med 168:976–982
60. Kohyama T, Liu X, Wen FQ, Zhu YK, Wang H, Kim HJ, Takizawa H, Cieslinski LB, Barnette MS, Rennard SI (2002) PDE4 inhibitors attenuate fibroblast chemotaxis and contraction of native collagen gels. Am J Respir Cell Mol Biol 26(6):694–701
61. MacNee W (2005) Oxidants and COPD. Curr Drug Targets Inflamm Allergy 4(6): 627–641
62. Janoff A (1982) Reduction of the elastase in inhibitory capacity of alpha-1-antitrypsin by peroxides in cigarette smoke. An analysis of the brands and the filters. Am Rev Respir Dis 126:25–30
63. Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, van Schayck CP, Olivieri D, Del Donno M, De Backer W, Lankhorst I, Ardia A (2005) Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 365(9470):1552–1560
64. Stoller JK, Aboussouan LS (2005) Alpha1-antitrypsin deficiency. Lancet 365(9478):2225–2236
65. Abusriwil H, Stockley RA (2006) Alpha-1-antitrypsin replacement therapy: current status. Curr Opin Pulm Med 12(2):125–131
66. Lieberman J (2000) Augmentation therapy reduces frequency of lung infections in antitrypsin deficiency: a new hypothesis with supporting data. Chest 118(5):1480–1485
67. Brantly M (2002) Alpha1-antitrypsin: not just an antiprotease: extending the half-life of a natural anti-inflammatory molecule by conjugation with polyethylene glycol. Am J Respir Cell Mol Biol 27(6):652–654
68. McElvaney NG, Crystal RG (1997) Proteases and lung injury. In: The lung: scientific foundations. Lippincott-Raven, Philadelphia
69. McElvaney NG, Crystal RG (1997) Antiproteases and lung defense. In: Crystal RG, West JB, Weibel ER, Barnes PJ (eds) The lung: scientific foundations. Lippincott-Raven, Philadelphia, pp 2219–2235

70. Rennard SI, Fogarty C, Kelsen S, Long W, Ramsdell J, Allison J, Mahler D, Saadeh C, Siler T, Snell P, Korenblat P, Smith W, Kaye M, Mandel M, Andrews C, Prabhu R, Donohue JF, Watt R, Lo KH, Schlenker-Herceg R (2007) The safety and efficacy of Infliximab in moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175:926–934
71. Keatings VM, Jatakanon A, Worsdell YM, Barnes PJ (1997) Effects of inhaled and oral glucocorticoids on infalmmatory indices in asthma and COPD. Am J Respir Crit Care Med 155:542–548
72. Di Francia M, Barbier D, Mege JL, Orehek J (1994) Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 150:1453–1455
73. de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM (1996) Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. Am J Respir Crit Care Med 153(2):633–637
74. Keating GM, Perry CM (2002) Infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis. BioDrugs 16(2):111–148
75. Tamaoki J, Kadota J, Takizawa H (2004) Clinical implications of the immunomodulatory effects of macrolides. Am J Med 117(Suppl 9A):5S–11S
76. Azuma A, Kudoh S (2006) Diffuse panbronchiolitis in East Asia. Respirology 11(3):249–261
77. Adcock IM, Ito K, Barnes PJ (2005) Histone deacetylation: an important mechanism in inflammatory lung diseases. COPD 2(4):445–455
78. Barnes PJ (2006) Reduced histone deacetylase in COPD: clinical implications. Chest 129(1):151–155
79. Bonetti PO, Lerman LO, Napoli C, Lerman A (2003) Statin effects beyond lipid lowering – are they clinically relevant? Eur Heart J 24(3):225–248
80. Hothersall E, McSharry C, Thomson NC (2006) Potential therapeutic role for statins in respiratory disease. Thorax 61(8):729–734
81. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM (2006) Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol 47(12):2554–2560
82. SØyseth V, Brekke PH, Smith P, Omland T (2007) Statin use is associated with reduced mortality in COPD. Eur Respir J 29(2):279–283
83. Kollarik M, Undem BJ (2006) Sensory transduction in cough-associated nerves. Respir Physiol Neurobiol 152(3):243–254
84. Dougall IG, Young A, Ince F, Jackson DM (2003) Dual dopamine D2 receptor and beta2-adrenoceptor agonists for the treatment of chronic obstructive pulmonary disease: the pre-clinical rationale. Respir Med 97(Suppl A):S3–S7
85. Ind PW, Laitinen L, Laursen L, Wenzel S, Wouters E, Deamer L, Nystrom P (2003) Early clinical investigation of Viozan (sibenadet HCl), a novel D2 dopamine receptor, beta2-adrenoceptor agonist for the treatment of chronic obstructive pulmonary disease symptoms. Respir Med 97(Suppl A):S9–S21
86. Laursen LC, Lindqvist A, Hepburn T, Lloyd J, Perrett J, Sanders N, Rocchiccioli K (2003) The role of the novel D2/beta2-agonist, Viozan (sibenadet HCl), in the treatment of symptoms of chronic obstructive pulmonary disease: results of a large-scale clinical investigation. Respir Med 97(Suppl A):S23–S33
87. Rogers DF, Barnes PJ (2006) Treatment of airway mucus hypersecretion. Ann Med 38(2):116–125
88. Adler KB, Li Y (2001) Airway epithelium and mucus: intracellular signaling pathways for gene expression and secretion. Am J Respir Cell Mol Biol 25(4):397–400
89. Aliverti A, Ghidoli G, Dellaca RL, Pedotti A, Macklem PT (2003) Chest wall kinematic determinants of diaphragm length by optoelectronic plethysmography and ultrasonography. J Appl Physiol 94(2):621–630
90. Burrows B, Kettel LJ, Niden AH, Rabinowitz M, Diener CF (1972) Patterns of cardiovascular dysfunction in chronic obstructive lung disease. N Engl J Med 286(17):912–918

91. Wouters EF (2002) Chronic obstructive pulmonary disease. 5: systemic effects of COPD. Thorax 57(12):1067–1070
92. Lacasse Y, Goldstein R, Lasserson TJ, Martin S (2006) Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* (4):CD003793
93. Schols AM, Slangen J, Vovovics L, Wouters EF (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797
94. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, Fournier M, Storer TW (2004) Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170(8):870–878
95. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S (2005) Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 127(3):809–817
96. Massaro G, Massaro D (1997) Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats. Nat Med 3:675–677
97. Massaro D, Massaro GD (2006) Toward therapeutic pulmonary alveolar regeneration in humans. Proc Am Thorac Soc 3(8):709–712
98. Meshi B, Vitalis TZ, Ionescu D, Elliott WM, Liu C, Wang XD, Hayashi S, Hogg JC (2002) Emphysematous lung destruction by cigarette smoke. The effects of latent adenoviral infection on the lung inflammatory response. Am J Respir Cell Mol Biol 26(1):52–57
99. Mao JT, Aberle D, Tashkin DP, Goldin J, Roth MD (2000) A phase II pilot study of all-trans retinoic acid for the treatment of human emphysema. Am J Respir Crit Care Med 161:A583
100. Roth MD, Connett JE, D'Armiento JM, Foronjy RF, Friedman PJ, Goldin JG, Louis TA, Mao JT, Muindi JR, O'Connor GT, Ramsdell JW, Ries AL, Scharf SM, Schluger NW, Sciurba FC, Skeans MA, Walter RE, Wendt CH, Wise RA (2006) Feasibility of retinoids for the treatment of emphysema study. Chest 130(5):1334–1345
101. Shigemura N, Sawa Y, Mizuno S, Ono M, Ohta M, Nakamura T, Kaneda Y, Matsuda H (2005) Amelioration of pulmonary emphysema by in vivo gene transfection with hepatocyte growth factor in rats. Circulation 111(11):1407–1414
102. Ishizawa K, Kubo H, Yamada M, Kobayashi S, Numasaki M, Ueda S, Suzuki T, Sasaki H (2004) Bone marrow-derived cells contribute to lung regeneration after elastase-induced pulmonary emphysema. FEBS Lett 556(1–3):249–252
103. Rogers DF, Laurent GJ (1998) New ideas on the pathophysiology and treatment of lung disease. Thorax 53(3):200–203
104. Howell JE, McAnulty RJ (2006) TGF-beta: its role in asthma and therapeutic potential. Curr Drug Targets 7(5):547–565
105. Griffiths MJ, Bonnet D, Janes SM (2005) Stem cells of the alveolar epithelium. Lancet 366(9481):249–260

9

Smoking Cessation

Arunabh Talwar, Virginia Reichert, and Kalpalatha Guntupalli

Key Points:

- Cigarette smoking is an addiction and a chronic relapsing disorder.
- It is the arguably the most important preventable cause of COPD in the developed world.
- Nicotine sustains the addictive tobacco use. The α4β2 nicotine acetylcholine receptor subtype is the main receptor mediating nicotine dependence.
- The clinician must be prepared to address the problem of smoking on a regular basis and to retreat patients who backslide.
- The best hope of improved treatment for smoking cessation occurs from combining existing and new pharmacotherapies with effective behavioral therapy.
- To obtain optimum results the therapy should be individualized for each patient.

Keywords Chronic obstructive pulmonary disease • nicotine • smoking cessation

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive. No therapy other than smoking cessation can affect the survival in this group of patients on a similar scale [1]. Thus the strategy of smoking cessation has been mentioned as the corner stone of therapy for COPD [2, 3].

Cigarette smoke causes an inflammatory response in the lower respiratory tract characterized by the accumulation of pigment-laden alveolar macrophages together with recruitment of smaller numbers of neutrophils [4]. These activated inflammatory cells release a variety of mediators, including proteases, oxidants, and toxic peptides, which can damage lung structures and are believed to be a major cause of the tissue destruction that leads to emphysema [5]. Thus, prevention and treatment of COPD by a broad approach, such as smoking cessation education should also be an important goal for healthcare professionals.

The present chapter mainly focuses on the smoking cessation strategies according to the recommendations, with particular reference to patients with COPD.

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_9,

Epidemiology of Cigarette Smoking

Cigarette smoking is an addiction and a chronic relapsing disorder, and is regarded as a primary disorder by the Department of Health and Human Services Guidelines in the USA and by the World Health Organization (WHO) [6]. Therefore, treating tobacco use and dependence should be regarded as a primary and specific intervention. Smoking should be routinely evaluated whenever a patient presents to a healthcare facility, and all smokers should be offered the best chance to treat this disorder. Successful treatment of this addiction can have a substantial benefit in reducing incidence and complications of COPD.

World Health Organization (WHO) estimates the total number of tobacco smokers at 1.1 billion [7]. Approximately 47% of men and 12% of women in the world smoke at this time [8]. Approximately one third to half of these die of smoking related diseases [9].

Tobacco use in the United States exacts profound human and economic costs. These costs argue eloquently for bold, scientifically grounded strategies to curb tobacco use [10]. The 1999 National Health Interview Survey (NHIS) estimated that, in the US, 46.5 million adults smoke (25.7% of men and 21.5% of women). According to the recent Surgeon General's report, smoking kills an estimated 440,000 Americans each year. On average, men who smoke cut their lives short by 13.2 years, and female smokers lose 14.5 years. The economic toll exceeds $157 billion each year in the United States – $75 billion in direct medical costs and $82 billion in lost productivity [6].

Tobacco dependence is a complex behavior problem involving pharmacological, psychological and social components. Cigarette smoking is an addiction and a chronic relapsing disorder. Smoking should be routinely evaluated whenever a patient presents to a healthcare facility and all smokers should be offered the best chance to treat this disorder. Nicotine is the main alkaloid found in tobacco and is responsible for its addictive potential.

The most comprehensive of the guidelines prepared on smoking cessation is the Tobacco Use and Dependence evidence based guidelines sponsored by the US Department of Health and Homan Services and released in 2000 [11]. The guidelines and the meta analyses on which they are based are available online (Office of the Surgeon General. Tobacco Cessation Guideline. http://www.surgeongeneral.gov/tobacco/.htm). The key findings of this report are summarized in Table 9.1.

Brief Intervention

An estimated 70% of smokers see a physician each year, providing physicians with a substantial opportunity to influence smoking behavior [6]. Given that so many tobacco users visit a primary care clinician each year, it is important that these clinicians be prepared to intervene with tobacco users who are willing to quit. The five major steps (the "5 A's") to intervention in the primary care setting are listed in Table 9.2. It is important for the clinician to *ask* the patient if he or she uses tobacco, *advise* him or her to quit, *assess* willingness to make a quit attempt, *assist* him or her in making a quit attempt, and *arrange*

Table 9.1 The key recommendations of the updated guideline, *Treating Tobacco Use and Dependence*, guidelines.

1. Tobacco dependence is a chronic condition that often requires repeated intervention until long-term or even permanent abstinence is achieved.
2. Effective tobacco dependence treatments are available, and every patient who uses tobacco should be offered these treatments
   - Patients *willing* to try to quit tobacco use should be provided treatment
   - Patients *unwilling* to try to quit tobacco use should be provided a brief intervention designed to increase their motivation to quit.
3. It is essential that clinicians and health care delivery systems (including administrators, insurers, and purchasers) institutionalize the consistent identification, documentation, and treatment of every tobacco user seen in a health care setting.
4. Brief tobacco dependence treatment is effective, and every patient who uses tobacco should be offered at least brief treatment.
5. There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness. Treatments involving person-to-person contact (via individual, group, or proactive telephone counseling) are consistently effective, and their effectiveness increases with treatment intensity (e.g., minutes of contact).
6. Three types of counseling and behavioral therapies were found to be especially effective and should be used with all patients attempting tobacco cessation:
   - Provision of practical counseling (problem solving/skills training);
   - Provision of social support as part of treatment (intra-treatment social support); and
   - Help in securing social support outside of treatment (extra-treatment social support).
7. Effective pharmacotherapies for smoking cessation now exist. Except in the presence of contraindications, these should be used with all patients attempting to quit smoking.
   - *First-line* pharmacotherapies were identified that reliably increase long-term smoking abstinence rates:
     – Bupropion SR
     – Varenicline[b]
     – Nicotine gum
     – Nicotine inhaler
     – Nicotine nasal spray
     – Nicotine patch
     – Nicotine Lozenges[a]
   - Two *second-line* pharmacotherapies were identified as efficacious and may be considered by clinicians if first-line pharmacotherapies are not effective:
     – Clonidine
     – Nortriptyline
   - Over-the-counter nicotine patches are effective relative to placebo, and their use should be encouraged.
8. Tobacco dependence treatments are both clinically effective and cost-effective relative to other medical and disease prevention interventions.

[a]Lozenges approved in October 2002
[b]Varenicline approved in October 2006

Table 9.2 The "5 A's" for brief intervention.

Ask about tobacco use.	Identify and document tobacco use status for every patient at every visit.
Advise to quit.	In a clear, strong and personalized manner urge every tobacco user to quit
Assess willingness to make a quit attempt.	Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempt.	For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit
Arrange follow-up.	Schedule follow-up contact, preferably within the first week after the quit date

Table 9.3 Enhancing motivation to quit tobacco with the 5 R's.

Relevance	Encourage the patient to indicate why quitting smoking is personally relevant being as specific as possible
Risks	Encourage the patient to identify possible negative consequences of tobacco use. This can be elaborated into acute risks, long term risks, and environmental risks
Rewards	Ask the patient to identify potential benefits of stopping tobacco use
Roadblocks	Ask the patient to identify barriers of impediments to quitting and offer treatments to address these barriers
Repetition	The motivational intervention should be repeated with every visit of an unmotivated patient

for follow-up contacts to prevent relapse. The strategies are designed to be brief, requiring 3 min or less of direct clinician time. Permanent remission can be achieved in a substantial number of smokers with the currently available treatments. Another useful method is called the 5 R's: relevance, risks, rewards, roadblocks, and repetition (Table 9.3).

Smokers unwilling to make a quit attempt should be offered a brief motivational intervention. Tobacco control programs should build motivation to quit smoking and address salient barriers to cessation, such as emotional distress, post cessation weight gain problem, and access to and coverage for treatment, and should also educate smokers regarding the specific health benefits of cessation. Smokers interested in quitting should be informed of the variety of effective interventions available to them and provided with assistance in selecting the most appropriate option for their circumstances and needs. The effectiveness of counseling increases with the intensity of treatments, but even brief interventions are of benefit [6, 11]. Regardless of intensity, all interventions should involve three key components: pharmacologic treatment, clinician-provided social support and information on problem- solving/ skills training. Clinicians should also identify and discuss barriers to quitting smoking.

Patients who are interested in quitting within the next month should be helped to set a quit date, offered pharmacotherapy with nicotine replacement or bupropion or Varenicline, and referred to a counseling program. The choice of pharmacotherapy should be based on the patient's preferences, needs, tolerability and any prior experience. Symptoms of nicotine withdrawal (tension, agitation, depression, disturbed sleep) and side effects of nicotine replacement therapy, bupropion and Varenicline should be explained to patients. If the smoker has severe withdrawal symptoms, cravings, or difficulty maintaining abstinence, a general approach is to start with one NRT agent and add another NRT agent if needed. Adding pharmacotherapy to in-person or telephone behavioral counseling doubles the cessation rate, but counseling is also effective by itself. Follow-up visits should be arranged to prevent relapse. All relapses should be followed up with discussions of new strategies for the next attempt to quit. Clinicians should monitor the progress of patients who are trying to quit, and view relapses not as failures but as opportunities to learn from what happened and to change tactics [12]. This more aggressive and continuous focus on smoking might be particular relevance in COPD patients who seem to be more hard core smokers with greater difficulty in quitting [13]. The educational component of smoking cessation prepares patients and significant others to be actively involved in providing care, improves their understanding of the smoking cessation process, and teaches practical ways of dealing

Table 9.4 Recommendations for smoking cessation in patients with chronic obstructive pulmonary disease (COPD) (Modified from [1]).

Address smoking at every visit
Use lung function as a risk factor, as well as other individual risk factors
Use carbon monoxide measurements as a natural opportunity to talk about smoking
Help the patient develop a quit plan
Set a quit date – ideally within the next 2 weeks
Provide behavioral support
Anticipate challenges, including withdrawal
Remove all tobacco products. Prior to quitting, avoid smoking in places where you spend a lot of time (e.g., work, house, car)
Use pharmacotherapeutic agents with frequent clinic visits
Give frequent motivation and support at follow-up visits
Reconsider smoking status every 3–5 months
Use carbon monoxide monitoring as a surrogate for quit status
Smoking cessation should be included in all COPD rehabilitation programs
Arrange follow-up clinic visits in smokers to start a new course of smoking cessation

with disabling relapsing symptoms; this reliance on patients and supportive others to assume charge is known as a collaborative self management [14].

It might be advantageous to use lung function testing and carbon dioxide monitoring to motivate the COPD patients [1].All rehabilitation programs must include smoking cessation as this is the only factor that affects survival in COPD (except for oxygen therapy in the end stage COPD). Given that the number of providers delivering a message may have an important impact on outcomes, the addition of counseling by allied health professionals (e.g., nurses, respiratory therapist), who typically have more contact with patients, may be more effective than counseling by physicians alone. Table 9.4 summarizes recommendations for smoking cessation in patients with COPD.

Basic Neurobiology of Smoking

The major physiological obstacle to quitting is the addictive nature of nicotine. When tobacco use is stopped there is a withdrawal syndrome characterized by irritability, anger, impatience, restlessness, difficulty concentrating, insomnia, increased appetite, anxiety, and depressed mood. These symptoms usually begin a few hours after the last cigarette, peak 2–3 days later, and wane over a period of several weeks or months.

After inhaling smoke from a modern cigarette, arterial nicotine levels increase markedly within 15 s [15]. This nicotine activates the brain reward center (in nucleus accumbens) by increasing the dopamine release [16]. This brain reward system is a common pathway for pleasurable activities and most drug addiction. This peak in plasma nicotine level, and the transient activation of the reward system, is followed by a gradual fall in nicotine levels into a state of withdrawal [17] which in turn is relieved by the next cigarette. Dependence arises from the temporal association of the ritual and sensory inputs with the repeated stimulation and relief of withdrawal.

A greater part of difficulty in quitting is craving for tobacco combined with nicotine withdrawal syndrome and the pharmacological treatments available so far claim to relieve craving as well as the withdrawal syndrome.

Table 9.5 Fagerstrom test for level of nicotine dependence.

How soon after waking do you smoke first cigarette? Less than 5 min: 3 points 5–30 min: 2 points 31–60 min: 1 point	– Points
Do you find it difficult to refrain from smoking in places where it is forbidden Yes: 1 point No: 0 point	– points
Which cigarette would you most hate to give up? First one in the morning: 1 point Any other: 0 point	– points
How many cigarettes do you smoke per day? More than 30 per day: 3 points 21–30 per day: 2 points 11–20 per day: 1 point	– Points
Do you smoke more frequently during the first hours after waking than during the rest of the day Yes: 1 point No: 0 point	– points
Do you smoke if you are so ill that you are in bed most of the day Yes: 1 point No: 0 point	– points **Total Points**

Interpretation

Total points	**Level of dependence**	**Nicotine replacement therapy**
5–6 points	heavy nicotine dependence	consider 21-mg nicotine patch
3–4 points	moderate nicotine dependence	consider 14-mg nicotine patch
0–2 points	light nicotine dependence	consider 7-mg nicotine patch or no patch

Assessment of Nicotine Dependence

In counseling smokers about the optimal means to achieve cessation, clinicians should make an assessment of the nicotine dependence, which can be measured via the Fagerstrom Test of Nicotine Dependence Scale score [18] (greater than or equal to 5) (see Table 9.5). The two questions that most strongly correlate with the dependence are the time to first cigarette in the morning (<30 vs > 30 min) and the number of cigarettes smoked per day. Decisions about the best form of therapy can be based on patient preference, on degree of nicotine dependence measured via the Fagerstrom Test of Nicotine Dependence Scale score, or habitually smoking the first cigarette within 30 min of awakening) or nicotine replacement therapy history, which includes number and outcome of previous quit attempts, specific method used, duration, side effects, and proper usage.

Pharmacological Treatment

Nicotine Replacement Therapy

At present, –Nicotine Replacement Therapy is the most common form of medication used for the treatment of tobacco dependence. Nicotine medications improve cessation efforts through one or more of the following five mechanisms: [19] (a) Reducing the withdrawal symptoms, (b) Reducing the cravings, (c) reducing the reinforcing effects of tobacco delivered nicotine, (d) providing the reinforcing coping strategy at times when

Table 9.6 Pharmacological smoking cessation interventions.

Pharmacological intervention	Estimated OR (95% CI)	Dose	Duration	Adverse effects/ contraindications
Varenicline	3.85 (2.43–4.27)	1 mg bid	12 weeks if quit attempt can be extended, for another 12 weeks	Nausea, Insomnia
Bupropion SR	2.1 (1.5–3.0)	150 mg every morning for 3 days. then 150 mg BID (begin treatment 1–2 weeks pre-quit)	7–12 weeks, maintenance up to 6 months	Insomnia, dry mouth Caution: history of seizures, eating disorders
Nicotine gum	1.5 (1.3–1.8)	1–24 cigarettes/day: 2 mg gum (up to 24 pieces); >25 cigarettes/day: 4 mg gum (up to 24 pieces)	Up to 12 weeks	Mouth soreness, dyspepsia
Nicotine inhaler	2.5 (1.7–3.6)	6–16 cartridges/day	Up to 6 months	Local irritation of mouth and throat
Nicotine nasal spray	2.7 (1.8–4.1)	8–40 doses/day	3–6 months	Nasal irritation
Nicotine patch	1.9 (1.7–2.2)	1–25 cigarettes/day 21 mg/24 h 14 mg/24 h 7 mg/24 h >25 cigarettes/day can start with 21–42 mg/24 h	4 weeks 2 weeks 2 weeks	Local skin irritation, insomnia
Nicotine Lozenges	NR	Smoke 1st cigarette >30 min after awakening – 2 mg (min 9 mg/max 20 lozenges/day) Smoke 1st cigarette within 30 min after awakening – 4 mg (min 9 mg/max 20 lozenges/day)	8 weeks	Mouth soreness, dyspepsia
Clonidine	2.1 (1.4–3.2)	0.15–0.75 mg/day	3–10 weeks	Dry mouth, dizziness, sedation Caution: rebound hypertension
Nortriptyline	3.2 (1.8–5.7)	75–100 mg/day	12 weeks	Sedation, dry mouth Caution: risk of arrhythmias

OR odds ratio, *CI* confidence interval, *BID* twice daily, *NR* not reported

The information contained within this table is not comprehensive. Please see the package insert for additional information

Nicotine nasal spray and Nicotrol inhaler are available by prescription only. Others (patches, gums, and lozenges) are available over the counter

Clonidine and Nortriptyline are second-line pharmacotherapeutics (not approved for use for smoking cessation by the FDA)

Varenicline data from reference [68]

craving may occur e.g., stress etc, and (e) providing an alternate source of reinforcing nicotine effect.

Studies have demonstrated that the use of NRT can significantly increase the abstinence rate compared to a placebo group, almost doubling the long-term success rate (Table 9.6) [20]. The initial doses of NRT should be sufficiently high to allow complete suppression of nicotine withdrawal symptoms, then gradually reduced (usually over 2–6 weeks)

as tobacco abstinence becomes established. The average 12-month success rate reported in most studies is about 15–25% [6]. The US Public Health Service recommends that except in special circumstances (medical contraindications, smoking <10 cigarettes daily, pregnancy, or breastfeeding), all smokers attempting to quit should be offered nicotine replacement therapy (strength of recommendation) [6]. When smokers use these products they must cease all tobacco use before starting the NRT because of concerns about nicotine toxicity with concurrent NRT and tobacco use.

Food and Drugs Administration (FDA) has approved five types of NRT for use by smokers to help in quitting. These are Nicotine gum (2 and 4 mg). Nicotine patch (7–21 mg), nicotine oral inhaler, nicotine nasal spray and nicotine polacrilex lozenge (2 and 4 mg). In USA, Nicotine Gum, patches, and lozenges are available over the counter, whereas the inhaler and spray can only be obtained with a physician's prescription. The faster acting NRT's (e.g., spray, gum, inhaler) are self dosing systems to be used ad libitum and help reduce craving [21] and in contrast, the patch supplies constant, low level of nicotine which can help relieve nicotine withdrawal symptoms [22]. Nicotine sublingual tablets are also available in some countries outside USA. A number of other products, including nicotine water, and lollipops are available to public in other countries without having been properly evaluated to obtain medicine license [23].

In a review of 108 trials, the odds ratio for abstinence with NRT compared to control was 1.73 (95% confidence interval 1.62–1.85). The odds ratios for the different forms of NRT were 1.66 for gum, 1.76 for patches, 2.27 for nasal spray, 2.08 for inhaled nicotine and 1.73 for nicotine sublingual tablet. These odds were largely independent of the duration of therapy, the intensity of additional support provided, or the setting in which the NRT was offered. In highly dependent smokers, there was a significant benefit of 4 mg gum compared with 2 mg gum (odds ratio 2.67, 95% confidence interval 1.69–4.22) [20].

Nicotine Product Choices

Use of nicotine replacement therapy should be preferentially directed to smokers who are motivated to quit, and have high levels of nicotine dependency. Choice of which form to use should reflect patient needs, tolerability and cost considerations. Patches are likely to be easier to use than gum or nasal spray in primary care settings [20]. Patients report a preference for patches over gums, sprays or the inhaler and tend to use patches nearer to the fashion recommended, but these differences do not affect cessation rate [24]. Comparative studies suggest that all the available forms of NRTs are roughly equally efficacious [25, 26].

Smokers unwilling to give up oral and behavioral rituals of smoking may perceive the inhaler as being more helpful [27]. Higher doses of nicotine gum or lozenge (4 mg vs 2 mg) increase quit rates in heavy smokers. Use of high-dose patches (>21 mg) may benefit heavy smokers or those who relapse due to nicotine withdrawal [11].

Patients who have a stomach ulcer or diabetes should not use gum or lozenges, but may use patches. However, patients who have an allergy to adhesive tape or preexisting skin problems should not choose nicotine patch. Nicotine gum 2 mg is for those who smoke fewer than 25 cigarettes daily, but Nicotine gum 4 mg is for those who smoke 25 or more daily. Lozenges use a different index for the initial choice. Those who smoke their first cigarette more than 30 min after waking should begin with the 2-mg lozenge, and those who smoke their first cigarette within 30 min of waking up should begin by using the 4-mg lozenge [28]. All nicotine replacement therapies delay but do not prevent weight gain. There is a dose-response relationship between nicotine gum

and weight gain: smokers who use more gum gain less weight [11]. NRT has been used in COPD patients as well. In the lung health study, 3,094 smokers with mild COPD were followed for 5 years. The use of 2 mg gum appeared safe with no significant side effects [29].

Safety of NRT

Continued smoking whilst on NRT is likely to cause adverse effects due to higher nicotine levels. These may include headache, heartburn, hiccoughs, nausea, vomiting, coughing, irritation in the mouth and throat, aphthous ulcers, acne, confusion, abdominal pain, back pain, myalgia, flatulence, and more rarely, palpitations, sleep disturbance, and dizziness. Some have questioned the possibility of oral cancer from close contact of the lozenges with oral mucosa. While oral cancer results from the use of chewing tobacco and snuff, lozenges (like Nicorette Gum) are free of the carcinogens that are formed from nicotine during curing, aging, and fermentation of tobacco [30].

Cardiovascular risk and the use of NRT have been systematically studied since the nicotine patch was released in 1991. The doses of nicotine from cigarette smoking are generally higher and more rapid than from the slower NRT delivery [31]. There are also other cardiotoxic substances apart from nicotine in cigarette smoke. The flat dose response relation for nicotine ensures that the effects of smoking along with NRT are similar to that of smoking alone. Trials apparently suggest that NRT use in those with stable CV disease does not increase CV risk [32]. Separate analyses have documented the lack of an association between use of the nicotine patch and acute cardiovascular events, even in patients who continue to smoke intermittently while using the nicotine patch [33]. Others have advocated the use of a lower dose patch in post MI patients who are at risk for resuming smoking [34].

Nicotine is metabolized more quickly in pregnancy [35]. Plasma clearances of nicotine and cotinine (its principal metabolite) are increased by 60% and 140%, respectively, and the half life of cotinine is reduced in pregnant women (9 vs 17 h in non-pregnant women). Among continuing smokers this could, in theory, lead to compensatory smoking to maintain desired nicotine concentrations, and hence increase fetal harm. It may also reduce the efficacy of nicotine replacement since conventional doses will provide less nicotine substitution. To date, however, the efficacy of nicotine replacement therapy in pregnancy is not known. The only completed and published randomized controlled trial of nicotine replacement (delivered by transdermal patches) showed no difference from placebo, but the numbers studied were small, and the trial was underpowered to determine whether nicotine replacement was effective [36]. Nevertheless, babies born to women in the nicotine treatment group had significantly higher birth weights than those in the placebo group (mean difference 186 g (95% confidence interval 35 to 336 g)), indicating that the intrauterine growth restriction caused by smoking is probably not attributable to nicotine. Pregnant patients should be encouraged to quit on their own. Those who fail and make an informed choice about the NRT should probably be advised to use shorter acting products (Nasal sprays and chewing gum) to minimize fetal exposure to nicotine overnight [37].

Combination Nicotine Products

A strategy for further improving the efficacy of NRT is the combination of one medication that allows for passive nicotine delivery (e.g., transdermal patch) with another medication that permits ad libitum nicotine delivery (e.g., gum, nasal spray, and inhaler)

[38, 39]. The rationale for combining NRT medications is that smokers may need both a slow delivery system to achieve a constant concentration of nicotine to relieve cravings and tobacco withdrawal symptoms, as well as a faster acting preparation that can be administered on demand for immediate relief of breakthrough cravings and withdrawal symptoms [40]. Patients should be encouraged to use combined treatments if unable to quit using a single form of first-line pharmacotherapy [11, 41].

Bupropion

There are at least two reasons to believe antidepressants might help in smoking cessation. Depression may be a symptom of nicotine withdrawal, and smoking cessation sometimes precipitates depression. In some individuals, nicotine may have antidepressant effects that maintain smoking [42].Antidepressants may substitute for this effect. Sustained release bupropion (Bupropion SR) is the only antidepressant currently approved by the FDA for smoking cessation in USA; although it is not licensed for that purpose in many other countries. It is a dopamine and norepinephrine reuptake inhibitor and ameliorates the extent of withdrawal symptoms during abstinence [43]. It may also act as a nicotine receptor antagonist, reducing the reinforcing potential of nicotine [44, 45], Typically, bupropion is initiated 1 week before the target quit date, with dosing at 150 mg/day for 3 days and then 150 mg twice daily for the remainder of the duration. Unlike the NRTs, there is no absolute requirement that smokers should quit before the target quit date. At this dose abstinence rate of up to 44% has been reported at 7 weeks after the treatment [46]. Recent studies have extended its use to preventing smoking relapse after initial achievement of smoking cessation [47]. Treatment for as long as a year has been reported, but an inability to maintain abstinence after 4 weeks would warrant termination of treatment with bupropion [48]. Meta analysis published by the Cochrane groups reveals that bupropion doubles quit rates as compared to placebo (OR 1.97, 95% CI 1.67–2.34) [49]. Bupropion SR seems particularly more effective in individuals who smoke more than 10–15 cigarettes per day and are motivated to quit [50]. The primary side effects are headache, jitteriness, dry mouth, initial insomnia, and gastrointestinal symptoms. The drug is contraindicated in patients with seizures but otherwise appears safe [51]; the rate of *de novo* seizures is very low (approximately 0.1%) and observed mainly when the dose exceeds 450 mg/day. There are few studies that have used bupropion successfully for smoking cessation treatments in subjects with COPD [52, 53].

When combined with the nicotine patch, the control of cravings is better in groups using bupropion plus nicotine patch than in groups with bupropion or the patch alone [54]. However, the most appropriate place of such combination treatment in the therapeutic armamentarium requires further study and consideration.

Varenicline

Varenicline affects the central nicotine receptors by binding to the specific α4β2 receptors as a partial nicotine agonist and selective nicotinic receptor modulator. As a partial agonist, it is believed to eliminate the reward from smoking and prevent withdrawal symptoms. Varenicline is well absorbed and primarily excreted unchanged (92%) in urine. It has a half-life of 17 h and takes 4.3 h to reach maximum concentration. Smokers are asked to up-titrate their dose to Varenicline 1 mg twice daily during the first 7 days of treatment, to stop smoking on day 8, and to continue treatment for 12 weeks.

In two studies ($n = 1{,}025$ and 1,027) with similar design, Varenicline 1 mg bid was compared with buropion SR 150 mg BID versus placebo for 3 months. The quit rate after 1 year was 22% (and 23%) for Varenicline, 16.4% (and 15%) for bupropion, and 8.4 (and 10.3%) for placebo, i.e., quit rates for Varenicline were significantly higher versus placebo and bupropion [55, 56]. The major side effects were nausea and abnormal dreams. Varenicline employs a new and interesting mechanism for the treatment of tobacco dependence. In a maintenance study, 1,927 smokers were treated open-label with Varenicline for 3 months, with a 3-month point prevalence quit rate of 64.1%. Successful quitters continued with Varenicline for another 3 months in a double-blind design, with a quit rate from week 13–52 of 43.6 *versus* 36.9% ($p = 0.02$), suggesting that some smokers may benefit from 6 months' therapy with varenicline to maintain abstinence [57].It is expected that with more documentation and experience, Varenicline will be a first-line drug in smoking cessation [58].

Second Line Medications for Smoking Cessation

There has been a general surge of interest in the use of other antidepressants for aiding long-term smoking cessation. Tricyclic antidepressants (TCA) such as nortriptyline inhibit the reuptake of norepinephrine and 5 HT, and may help in smoking cessation. However TCAs have significant side effects such as anticholinergic activity and possibility of overdose. Five trials of nortriptyline for smoking cessation have demonstrated its efficacy, with a pooled odds ratio of 2.8 (95% confidence interval = 1.8–4.3) [49]. Doses used in smoking cessation trials have initiated treatment at a dose of 25 mg/day, increasing gradually to a target dose of 75–100 mg/day. Therapy is initiated 10–28 days before the quit date to allow nortriptyline to reach steady state at the target dose. Duration of treatment used in smoking cessation trials has been approximately 12 weeks. Most commonly reported side effects of Nortriptyline include sedation, dry mouth, blurred vision, urinary retention, lightheadedness, and shaky hands. In view of the risk of arrhythmias, nortriptyline should be used with extreme caution in patients with cardiovascular disease. Similarly, Selegiline – a monoamine oxidase type B (MAO–B) inhibitor that increases presynaptic dopaminergic concentration has shown promise in initial trials [59]. Other drugs that have been studied include doxepin [60] (e.g., fluoxetine, paroxetine), moclobemide, Buspar, and venlafaxine. While the results of the trials of these drugs is outside the scope of this article, none of these drugs have the strength of evidence to make them realistic contenders for the first-line treatments for tobacco dependence.

Clonidine

Clonidine is a α 2-adrenoreceptor agonist used as a hypertension receptor, but it is also found useful in the treatment of opioid withdrawal. The Surgeon General's report and the Cochrane review rank clonidine as a second-line agent [61]. Meta analyses of published studies suggest that it nearly doubles the quit rate [62]. Usually, it is initiated on the quit date or shortly before (up to 3 days) the quit date. Initial dosing is typically 0.10 mg twice daily or 0.10-mg/day transdermal patch, increasing by 0.10 mg/day/week if needed. The dose duration has varied across the clinical trials, ranging from 3 to 10 weeks. The most commonly reported side effects include dry mouth, drowsiness, dizziness, sedation, and constipation. As an antihypertensive medication, clonidine can be expected to lower blood pressure in most patients. Therefore, clinicians may need to monitor blood pressure when using this medication. Abrupt cessation can cause rebound hypertension.

Table 9.7 Summary of cognitive and behavioral tobacco cessation counseling strategies [69, 70].

Strategy	Comment
Cognitive approaches	
Commitment to quit	Have patients verbalize out loud that they want to be a nonsmoker and that they will overcome temporary temptations
Distract thought pattern	Encourage patients to think about something else when the urge to smoke occurs
Think positive	Smokers should give themselves "pep talks" to keep on track despite obstacles they face
Relaxation through imagery	Focus thinking on positive, relaxing images
Rehearse responses to possible scenarios	Practice how to react when temptations arise, such as if at a social gathering where there are other smokers, or if someone offers a cigarette
Behavioral approaches	
Coping with Stress	Rehearse coping strategies to deal with work, school, or with family stresses, e.g., taking a walk, deep breathing, calling a friend for support, or massaging
Alcohol	Alcohol use can lead to relapse so patients should be advised to limit or abstain from drinking, especially in the early stages of trying to quit
Other tobacco users	Try to limit exposure to fellow family members, co-workers, and friends who are smoking. Encourage them to not smoke in your presence
Satisfying oral gratification urges	Keep non-tobacco oral substitutes on hand, including gum, sugarless candy, straws, bottled water, or NTR
Break automatic smoking routines	Identify situations when smoking is often part of an everyday activity and try to displace the smoking behavior from the routine. For example, smoking while drinking morning coffee – take a walk after breakfast; driving – have car detailed and aired out to remove all signs of cigarettes in the vehicle such as ashtrays, etc. and have some gum handy when they drive; telephone – keep hands busy, walk and talk, limit length of call; after meals – don't linger at the table, call a friend
Post-cessation weight gain	Can be a barrier to quitting so address the issue, encouraging healthful eating with increased fruits and vegetables, adequate water intake and a modest exercise program; moderation is the key
Tobacco cravings	Usually temporary, 5–10 min in duration; encourage distractive behavior and thinking

Recent Advances in Smoking Cessation Therapy

A cornerstone of effective treatment is tobacco dependence counseling, for which there is a dose response relation between the intensity of counseling (total minutes of contact) and its effectiveness. A broad range of non pharmacologic support strategies are available, including behavioral, cognitive and motivational interventions (Table 9.7). There are clear synergies when behavioral support and pharmacotherapy are used in combination. The best results occur when clinicians individualize a specific therapeutic program for each patient. In addition, recognizing that smoking is a relapsing disorder, the clinician must be prepared to readdress the problem of smoking on a regular basis and retreat patients who relapse.

The recent interest in smoking cessation has triggered a rapid increase in development of potential new non-nicotine pharmacotherapies, including, anabasine, reboxetine, and rimonabant. Successful new products need to have excellent side-effect profiles in addition to proven efficacy.

The drug rimonabant (Acomplia) is effective for weight loss and smoking cessation; Rimonabant has been called the anti-marijuana. CB1 blockers act on the endocannabinoid

system (the EC system), a natural system that modulates the body's energy balance and nicotine dependence. An over-stimulated EC system is thought to play a role in obesity and in tobacco dependence, and CB1 blockers are supposed to reduce this overstimulation. Results from a recently presented trial shows that rimonabant is effective for smoking cessation and post cessation weight gain. The 10-week trial enrolled nearly 800 men and women who smoked an average of 23 cigarettes a day before the study began. The goal was no smoking for at least 4 consecutive weeks. Of those who completed the study, 36.2% of those who received a 20-mg dose of rimonabant quit smoking compared with about one fifth of those who received placebo. None of these smokers were obese. But participants in the placebo group gained 6.6 lb, while those in the rimonabant group gained only 1.5 lb [63].

Anabaseine is a compound that binds selectively to a subtype of nicotinic receptors, the α7 nicotinic acetylcholinergic receptors (nAChR). In addition, it is also an antagonist of α4-β2 receptors. The α7- may be an important modulator of neurons in brain that control both the reward and aversive properties of nicotine [64]. Its role in impacting smoking cessation is still being studied.

Other formulations under development include a nicotine buccal adhesive tablet [65], rapid release nicotine gum [21] and nicotine solution drops [66]. These new faster delivery nicotine replacement products have the promise of addressing a broader list of indications, including treatment of nicotine withdrawal during temporary abstinence and long-term nicotine maintenance. Phase I trials of Trials of nicotine vaccine [67] have been completed but any future nicotine vaccine will need to demonstrate clinical efficacy and also improve certain consumer acceptability characteristics (e.g., frequency of injections required) before they can become widely used and successful therapies [19].

Conclusion

Smoking cessation is a low cost intervention; it is of proven benefit in patients with COPD. Smoking cessation activities and support for its implementation should be integrated into the health care system. Despite evidence that physicians can impact smoking habits, this component of intervention remains underutilized. The outcome of smoking cessation has improved with the availability of proper behavior approaches and medications. Incorporating these guidelines into daily clinical practice ensures that as health care providers we provide the opportunity for our patients to quit smoking. The best hope of improved treatment comes from combining existing and new pharmacotherapies with effective behavioral therapy [19].

NRT and bupropion SR are first-line treatments for smoking cessation. Smokers attempting to quit should be encouraged to use these drugs to aid cessation, except in the presence of contraindications. Different NRTs (gum, patch, inhaler, nasal spray, lozenge and sublingual tablets) are equally effective as smoking cessation treatments. Combining the nicotine patch with a self-administered form of NRT can be more effective than a single form of NRT. NRT should be used to aid cessation in all smokers with COPD, regardless of disease severity and number of cigarettes smoked). Combined treatment with bupropion SR and NRT might be more effective in heavy smokers. Both NRT and bupropion SR are effective and well tolerated in smokers with stable cardiovascular disease and in COPD patients (evidence level A). There is no evidence that selective serotonin re-uptake inhibitors (SSRIs) have any effect in smoking cessation. Varenicline might have an additional therapeutic effect as smoking cessation treatment.

However until more documentation and experience is needed in patients with occur. Regular follow-up visits are important and are linked with longer-term successful outcome. The best hope of improved treatment comes from combining existing and new pharmacotherapies with effective behavioral therapy [58]. Table 9.6 summarizes the data on efficacy of various pharmacological agents used for smoking cessation.

References

1. Gratziou C, Tonnesen P (2006) Smoking cessation and prevention. Eur Respir Mon 38:242–57
2. Celli BR, MacNee W (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23(6):932–46
3. GIfCOLDG (2005) Workshop Report: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Update 2005: Available at: www.goldcopd.com
4. Rennard SI, Togo S, Holz O (2006) Cigarette smoke inhibits alveolar repair: a mechanism for the development of emphysema. Proc Am Thorac Soc 3(8):703–8
5. Repine JE, Bast A, Lankhorst I (1997) Oxidative stress in chronic obstructive pulmonary disease. Oxidative stress study group. Am J Respir Crit Care Med 156(2 Pt 1):341–57
6. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report (2000) The tobacco use and dependence clinical practice guideline panel, staff, and consortium representatives. J Am Med Assoc 283(24):3244–54
7. Karnath B (2002) Smoking cessation. Am J Med 112(5):399–405
8. Fagerstrom K (2002) The epidemiology of smoking: health consequences and benefits of cessation. Drugs 62(Suppl 2):1–9
9. Doll R, Peto R (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 2(6051):1525–36
10. Fiore MC, McCarthy DE, Jackson TC et al (2004) Integrating smoking cessation treatment into primary care: an effectiveness study. Prev Med 38(4):412–20
11. Fiore MC, Bailey WC, Cohen SJ (2000) Treating tobacco use and dependence: clinical practice guideline. US Department of Health and Human Services, Public Health Service, Rockville, June 2000
12. Talwar A, Jain M, Vijayan VK (2004) Pharmacotherapy of tobacco dependence. Med Clin North Am 88(6):1517–34
13. Chronic obstructive pulmonary disease (2004) National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 59(Suppl 1):1–232
14. Tougaard L, Krone T, Sorknaes A, Ellegaard H (1992) Economic benefits of teaching patients with chronic obstructive pulmonary disease about their illness. The PASTMA group. Lancet 339(8808):1517–20
15. Stauffer HP, Riedwyl H (1977) Interaction and pH dependence of effects of nicotine and carbon monoxide in cigarette smoke inhalation experiments with rats. Agents Actions 7(5–6):579–88
16. Zhou FM, Liang Y, Dani JA (2001) Endogenous nicotinic cholinergic activity regulates dopamine release in the striatum. Nat Neurosci 4(12):1224–9
17. Pontieri FE, Tanda G, Orzi F, Di Chiara G (1996) Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 382(6588):255–7
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br J Addict 86(9):1119–27
19. Foulds J, Burke M, Steinberg M, Williams JM, Ziedonis DM (2004) Advances in pharmacotherapy for tobacco dependence. Expert Opin Emerg Drugs 9(1):39–53
20. Silagy C, Lancaster T, Stead L, Mant D, Fowler G (2001) Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev (3):CD000146

21. Shiffman S, Shadel WG, Niaura R et al (2003) Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. Psychopharmacology (Berl) 166(4):343–50
22. Hughes JR, Goldstein MG, Hurt RD, Shiffman S (1999) Recent advances in the pharmacotherapy of smoking. J Am Med Assoc 281(1):72–6
23. Foulds J, Russell MA, Jarvis MJ, Feyerabend C (1998) Nicotine absorption and dependence in unlicensed lozenges available over the counter. Addiction 93(9):1427–31
24. West R, Hajek P, Nilsson F, Foulds J, May S, Meadows A (2001) Individual differences in preferences for and responses to four nicotine replacement products. Psychopharmacology (Berl) 153(2):225–30
25. Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A (1999) Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. Arch Intern Med 159(17):2033–8
26. Hughes JR, Shiffman S, Callas P, Zhang J (2003) A meta-analysis of the efficacy of over-the-counter nicotine replacement. Tob Control 12(1):21–7
27. Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K (1996) Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. Addiction 91(9):1293–306
28. Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR (2002) Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med 162(11):1267–76
29. Murray RP, Bailey WC, Daniels K et al (1996) Safety of nicotine polacrilex gum used by 3, 094 participants in the lung health study. Lung Health Study Research Group. Chest 109(2):438–45
30. Hoffmann D, Djordjevic MV (1997) Chemical composition and carcinogenicity of smokeless tobacco. Adv Dent Res 11(3):322–9
31. Benowitz NL, Gourlay SG (1997) Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol 29(7):1422–31
32. Keeley EC, Pirwitz MJ, Landau C et al (1996) Intranasal nicotine spray does not augment the adverse effects of cigarette smoking on myocardial oxygen demand or coronary arterial dimensions. Am J Med 101(4):357–63
33. Nicotine replacement therapy for patients with coronary artery disease (1994) Working group for the study of transdermal nicotine in patients with coronary artery disease. Arch Intern Med 154(9):989–95
34. Benowitz NL (1993) Nicotine replacement therapy. What has been accomplished – can we do better? Drugs 45(2):157–70
35. Dempsey D, Jacob P 3rd, Benowitz NL (2002) Accelerated metabolism of nicotine and cotinine in pregnant smokers. J Pharmacol Exp Ther 301(2):594–8
36. Wisborg K, Henriksen TB, Jespersen LB, Secher NJ (2000) Nicotine patches for pregnant smokers: a randomized controlled study. Obstet Gynecol 96(6):967–71
37. Molyneux A (2004) Nicotine replacement therapy. Br Med J 328(7437):454–6
38. Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE (2001) Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. CNS Drugs 15(6):453–67
39. Fagerstrom KO, Schneider NG, Lunell E (1993) Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. Psychopharmacology (Berl) 111(3):271–7
40. Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G (1995) Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. Prev Med 24(1):41–7
41. Bohadana A, Nilsson F, Rasmussen T, Martinet Y (2000) Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. Arch Intern Med 160(20):3128–34
42. Kassel JD, Stroud LR, Paronis CA (2003) Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. Psychol Bull 129(2):270–304
43. Ascher JA, Cole JO, Colin JN et al (1995) Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 56(9):395–401

44. Slemmer JE, Martin BR, Damaj MI (2000) Bupropion is a nicotinic antagonist. J Pharmacol Exp Ther 295(1):321–7
45. Rauhut AS, Neugebauer N, Dwoskin LP, Bardo MT (2003) Effect of bupropion on nicotine self-administration in rats. Psychopharmacology (Berl) 169(1):1–9
46. Hurt RD, Sachs DP, Glover ED et al (1997) A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 337(17):1195–202
47. Hays JT, Hurt RD, Rigotti NA et al (2001) Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. Ann Intern Med 135(6):423–33
48. Hays JT, Ebbert JO (2003) Bupropion sustained release for treatment of tobacco dependence. Mayo Clin Proc 78(8):1020–4, quiz 4
49. Hughes JR, Stead LF, Lancaster T (2003) Antidepressants for smoking cessation. Cochrane Database Syst Rev (2):CD000031
50. Coleman T (2001) Smoking cessation: integrating recent advances into clinical practice. Thorax 56(7):579–82
51. Martinez-Raga J, Keaney F, Sutherland G, Perez-Galvez B, Strang J (2003) Treatment of nicotine dependence with bupropion SR: review of its efficacy, safety and pharmacological profile. Addict Biol 8(1):13–21
52. Tashkin D, Kanner R, Bailey W et al (2001) Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet 357(9268):1571–5
53. Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, van Schayck CP (2005) Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med 165(19):2286–92
54. Jorenby DE, Leischow SJ, Nides MA et al (1999) A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 340(9):685–91
55. Gonzales D, Rennard SI, Nides M et al (2006) Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. J Am Med Assoc 296(1):47–55
56. Jorenby DE, Hays JT, Rigotti NA et al (2006) Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. J Am Med Assoc 296(1):56–63
57. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR (2006) Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. J Am Med Assoc 296(1):64–71
58. Tonnesen P, Carrozzi L, Fagerstrom KO et al (2007) Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. Eur Respir J 29(2):390–417
59. George TP, Vessicchio JC, Termine A, Jatlow PI, Kosten TR, O'Malley SS (2003) A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. Biol Psychiatry 53(2):136–43
60. Edwards NB, Murphy JK, Downs AD, Ackerman BJ, Rosenthal TL (1989) Doxepin as an adjunct to smoking cessation: a double-blind pilot study. Am J Psychiatry 146(3):373–6
61. Gourlay SG, Stead LF, Benowitz NL (2000) Clonidine for smoking cessation. Cochrane Database Syst Rev (2):CD000058
62. Gourlay SG, Benowitz NL (1995) Is clonidine an effective smoking cessation therapy? Drugs 50(2):197–207
63. Anthenelli RM (2004) Effects of rimonabant in the reduction of major cardiovascular risk factors. Results from the STRATUS-US trial (Smoking cessation in smokers motivated to quit). In: American college of cardiology 53rd annual scientific meeting, New Orleans, 9 March 2004
64. Laviolette SR, van der Kooy D (2004) The neurobiology of nicotine addiction: bridging the gap from molecules to behaviour. Nat Rev Neurosci 5(1):55–65
65. Park CR, Munday DL (2002) Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int J Pharm 237(1–2):215–26

66. Westman EC, Tomlin KF, Perkins CE, Rose JE (2001) Oral nicotine solution for smoking cessation: a pilot tolerability study. Nicotine Tob Res 3(4):391–6
67. Lindmayer K, Horwith G, Fattom A, et.al (2003) Results of phase I double-blinded controlled safety and immunogenicity trial of NICVAX, a nicotine conjugated vaccine. Society for Research on Nicotine and Tobacco, 9th Annual Meeting, New Orleans (Abstract)
68. Cachill K, Stead LF, Lancaster T (2007) Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev (January 24) (1):CD006103
69. Rigotti NA (2002) Clinical practice. Treatment of tobacco use and dependence. N Engl J Med 346(7):506–12
70. Villano LM, White AR (2004) Alternative therapies for tobacco dependence. Med Clin North Am 88(6):1607–21

10

Pulmonary Rehabilitation

Charlie K. Lan, Linda Nici, and Richard Zu Wallack

Key Points:

Pulmonary Rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases.

Consequences of COPD include:

- Respiratory limitation
- Reripheral muscle dysfunction
- Respiratory muscle dysfunction
- Cardiac abnormality
- Nutritional abnormality
- Skeletal abnormality
- Psychosocial issue

Recent studies have unraveled mechanistic reasons why pulmonary rehabilitation works.

The components of pulmonary rehabilitation include:

- Assessment/re-assessment
- Exercise training
- Education and self-management strategies
- Nutritional intervention
- Psychological and social consideration

Pulmonary rehabilitation has emerged as an evidence-based science showing its effectiveness across multiple outcome areas. However, pulmonary rehabilitation does not improve forced expiratory volume at 1 s (FEV1).

Pulmonary rehabilitation has now become one of the standard therapies for chronic obstructive pulmonary disease.

The major goals of pulmonary rehabilitation are:

- To reduce burden of symptoms such as dyspnoea and fatigue
- To improve functional status
- To increase participation in physical and social activities
- To improve health related quality of life
- To reduce health care utilization

The following are general criteria for pulmonary rehabilitation referral:

- Severe dyspnoea and/or fatigue
- Decreased exercise ability

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_10,

- Interference with performing physical activities of daily living
- Impaired health status
- Decreased occupational performance
- Nutritional depletion
- Frequent respiratory exacerbations
- Increased medical resource consumption

Pulmonary rehabilitation should be administered throughout the course of COPD, be an integral part of COPD therapy, and complement pharmacological intervention for COPD.

Pulmonary rehabilitation is still under-utilized due to combination of under-awareness of its effectiveness by health care providers, unavailability of programs in some area, and insufficient third-party reimbursement.

Keywords Muscle dysfunction • exercise training • depression

Introduction

Pulmonary rehabilitation has been accepted by clinicians for decades as an effective therapy for patients with COPD [1]. However, over the past 15 years there has been the unraveling of some of the mechanistic reasons why pulmonary rehabilitation works and the emergence of an evidence-based science showing its effectiveness across multiple outcome areas. With this new scientific information, pulmonary rehabilitation has risen to prominence as a standard therapy for COPD. In fact, the positive signals from this therapy in exercise performance, dyspnoea relief, and health status usually exceed those from other treatments such as bronchodilators. In this regard, pulmonary rehabilitation should be considered complementary to pharmacologic therapy for COPD.

Pulmonary rehabilitation is now prominently placed in treatment guidelines for COPD: both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and the American Thoracic Society – European Respiratory Society Statement on the Diagnosis and Treatment of COPD recommend it for COPD of moderate severity or greater [2, 3]. Figure 10.1 [2] outlines the treatment algorithm for COPD, placing pulmonary rehabilitation alongside regular bronchodilator therapy. A summary of some of the scientific developments leading to these guideline recommendations is given in Table 10.1.

Definition and Rationale of Pulmonary Rehabilitation

The American Thoracic Society and the European Respiratory Society define pulmonary rehabilitation as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease" [4].

The Statement goes on to describe the process of pulmonary rehabilitation: "Although there is considerable variability among pulmonary rehabilitation programs, most provide patient assessment, exercise training, education and self management strategies. These interventions address the primary and the secondary impairments

<table>
<tr><td>Stage</td><td>I: Mild</td><td>II: Moderate</td><td>III: Severe</td><td>IV: Very Severe</td></tr>
<tr><td>Characteristics</td><td>FEV1/FVC < 70%
FEV1 >= 80% predicted</td><td>FEV1/FVC < 70%
50% <= FEV1 < 80% predicted</td><td>FEV1/FVC < 70%
30% <= FEV1 < 50% predicted</td><td>FEV1/FVC < 70%
FEV1 < 30% predicted or FEV1 < 50% predicted plus chronic respiratory failure</td></tr>
<tr><td rowspan="4">Therapy</td><td colspan="4">Avoidance of Risk Factors
Influenza Vaccination
Add Short-acting bronchodilator when needed</td></tr>
<tr><td rowspan="3"></td><td colspan="3">Add regular treatment with one or more long-acting bronchodilators when needed
Add Pulmonary Rehabilitation</td></tr>
<tr><td rowspan="2"></td><td colspan="2">Add inhaled glucocorticosteroids if repeated exacerbations</td></tr>
<tr><td></td><td>Add long-term oxygen if chronic respiratory failure and consider surgical treatment</td></tr>
</table>

Fig. 10.1. Gold report on chronic obstructive pulmonary disease (*COPD*) management [2]. The Global initiative for chronic obstructive lung disease (*GOLD*) published a report on global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease in placing pulmonary rehabilitation a part of standard therapy for COPD alongside regular bronchodilator therapy in their outlines of treatment algorithm for COPD

Table 10.1 A brief history of pulmonary rehabilitation.

1980s	Pulmonary rehabilitation is recognized as effective by clinicians and is successfully utilized without much evidence base
1987	Guyatt reports on the Chronic Respiratory Disease Questionnaire (CRQ), a COPD-specific health status [140]. Health status improves substantially with pulmonary rehabilitation despite the fact that there is usually no measurable change in FEV1
1991	Casaburi and colleagues [117] demonstrate that exercise training produces a physiologic training effect in patients with COPD, and this effect is dose (intensity) dependent
1994	Reardon and colleagues [141] show that pulmonary rehabilitation improves dyspnoea during exercise testing and associated with activities
1995	Ries and colleagues [136] report on the first large randomized trail of pulmonary rehabilitation, with demonstrated benefits over multiple outcome areas
1996	Maltais demonstrates biochemical alterations in muscles of COPD patients, and their changes following exercise training
1998	O'Donnell and colleagues demonstrate some of the physiologic underpinnings to the reduction in dyspnoea associated with exercise training
2000	Griffiths and colleagues demonstrate the positive effects of pulmonary rehabilitation on health care utilization
2003	Bourbeau and colleagues demonstrate that a self management strategy has measurable benefits in COPD outpatients

associated with the respiratory disease" [4]. Nutritional intervention and psychosocial support are also provided, when required. Pulmonary rehabilitation is usually provided by an interdisciplinary team in collaboration with the patient and family, and is specifically tailored to the unique needs of the individual. Its components are listed in Table 10.2.

Table 10.2 Components of comprehensive pulmonary rehabilitation programs [142].

1. Education, emphasizing self-management strategies
2. Upper and lower extremity endurance and resistance exercise training
3. Psychosocial support
4. Nutritional assessment and intervention
5. Outcome assessment
6. Promotion of long-term adherence through encouragement of activity and exercise in the home setting

The above components are tailored to the specific needs of the individual patient

Table 10.3 Positive outcomes associated with pulmonary rehabilitation.

1. Decreased exertional dyspnoea and dyspnoea associated with daily activities [143]
2. Increased exercise performance [144]
3. Improved health related quality of life [145]
4. Enhanced functional status [146]
5. Reduced health care utilization [147–149]

Pulmonary rehabilitation has proven beneficial effects over multiple outcome areas, [5] as outlined in Table 10.3. In most cases, the positive signal from pulmonary rehabilitation in areas such as dyspnoea relief and exercise performance enhancement is appreciably greater than that from other conventional treatments, including long acting bronchodilators. However, pulmonary rehabilitation and pharmacologic therapy should be considered complementary: (1) if a COPD patient remains symptomatic despite bronchodilators, pulmonary rehabilitation would likely provide additional benefit, and (2) optimal bronchodilation allows for higher intensity exercise training during pulmonary rehabilitation, thereby enhancing its effects.

Respiratory and Systemic Consequences of COPD

COPD is a respiratory disease with prominent systemic consequences. Table 10.4 lists some of these systemic consequences. Systemic abnormalities, especially peripheral muscle dysfunction, play a prominent role in the exercise intolerance and dyspnoea in this disease [3, 4, 6].

Respiratory Limitations

Ventilatory limitation is probably the most proximate factor that contributes to exercise intolerance in COPD [7, 8]. In most cases, dyspnoea relates to a combination of increased resistive and elastic work of breathing. During exercise, the increased ventilatory demand and resultant increase in respiratory rate lead to dynamic lung hyperinflation. This further increases ventilatory constraint, intensifies the sensation of dyspnoea, and contributes to exercise limitation [9]. Techniques like pursed-lip breathing, which is often part of breathing re-training in pulmonary rehabilitation, reduce end-expiratory chest wall volume and breathlessness by lengthening total expiratory time [10].

Both hypoxemia and hypercapnia may directly or indirectly cause exercise limitation. Hypoxemia increases the output from peripheral chemoreceptors in the carotid body to

Table 10.4 Consequences of chronic respiratory disease.

Respiratory limitation
Air-flow obstruction
Static and dynamic hyperinflation
Increased dead-space ventilation
Impaired gas exchange
Peripheral Muscle Dysfunction
Due to inactivity
Steroid myopathy
Inflammatory state
Increased oxidative stress
Early onset of lactic acidemia
Respiratory Muscle Dysfunction
Cardiac Impairment
Cardiovascular deconditioning
Cor pulmonale
Nutritional and body composition abnormalities
Skeletal Disease
Osteoporosis
Psychosocial Issues
Depression, anxiety

the respiratory center, resulting in increased ventilatory drive [11–13]. This increased ventilatory drive adds to dynamic lung hyperinflation, further aggravating breathlessness and exercise intolerance. Hypoxia also decreases anaerobic threshold, causing lactic acid production at a relatively low work-load. Lactic acid increases the production of carbon dioxide (which must be eliminated) and requires increased ventilation to overcome metabolic acidosis [12].

Peripheral Muscle Dysfunction

Skeletal muscle dysfunction is well recognized in COPD patients. Abnormalities include atrophy [14], decreases in oxidative enzymes [15], and decreased ratio of type I to type II muscle fibers. [14] These result in decreased strength [16], reduced endurance [14], impaired oxidative capacity [14, 15], increased fatigability [14], and reduced aerobic capacity [15]. Exercise training, as part of pulmonary rehabilitation, tends to reduce the severity of these abnormalities [41].

An important factor contributing to peripheral muscle abnormalities in COPD is a sedentary lifestyle [17]. Inactivity results in deconditioning and skeletal muscle atrophy [18]. However, inactivity is not the only factor in muscle dysfunction. For example, 6 months of high-intensity exercise training does not completely normalize skeletal muscle strength in COPD [19]. Furthermore, the abnormal type I to type II muscle fibers ratio in COPD remains, even after controlling for the level of activity [20].

The systemic inflammatory process in COPD, especially mediated through increased level of tumor necrosis factor alpha (TNF-α), undoubtedly contributes to skeletal muscle abnormalities [21]. Through its catabolic effect, TNF-α reduces muscle mass and function. This systemic inflammatory response is most prominent during and following the COPD exacerbation [22].

Skeletal muscle dysfunction is also caused by chronic corticosteroid use [23]. Additionally, there is evidence for oxidative stress in muscles of patients with COPD [24].

Both exercise and acute exacerbation of COPD increase the mitochondrial activity, which results in generation of large amount of free radicals. This imbalance of oxidant-antioxidant activity causes oxidative damage to contractile proteins in COPD.

Respiratory Muscle Dysfunction

The mechanisms that contribute to peripheral skeletal muscle dysfunction discussed previously (with exception of inactivity) undoubtedly also apply to the diaphragm. As an adaptation, the diaphragm has a greater resistance to fatigue and the ability to generate greater force at the same lung volume compared to normal individuals [25]. However, static and dynamic hyperinflation requires the COPD patient to breath at a higher lung volume, placing the diaphragm at a great mechanical disadvantage.

Cardiac Abnormalities

Inactivity associated with chronic lung disease results in cardiovascular deconditioning and contributes to exercise limitation. As COPD progresses to chronic respiratory failure, increased right ventricular after-load from hypoxia-mediated pulmonary vasoconstriction leads to cor pulmonale. This eventually leads to decreased stroke volume and increased heart rate, further limiting exercise tolerance [26]. Finally, dynamic hyperinflation during exercise increases intrapleural pressure and right atrial pressure; this leads to a reduction of venous return and a decrease in cardiac output, further limiting exercise performance.

Nutritional Abnormalities

Nutritional abnormalities, especially decreased muscle mass, contribute to the morbidity and mortality of COPD [27]. For example, decreased fat-free mass is associated with decreased peripheral muscle strength, independent of disease severity [28]. Nutritional intervention associated with pulmonary rehabilitation results in improvement of fat-free mass loss, exercise tolerance, and decreases mortality [29].

Skeletal Abnormalities

There is an increased risk of decreased bone mineral density in COPD patients: two-thirds have radiological evidence of either osteoporosis or osteopenia [30]. The underlying etiology may be related to combination of smoking, vitamin D deficiency, inactivity, low-body mass index, hypogonadism, and use of glucocorticoids [30]. Consequently, the risk of vertebral fracture in COPD patients is a great concern. Kyphoscoliosis and pain caused by thoracic vertebral fracture further compromise the mechanical disadvantage of the thoracic cage and contribute to dyspnoea and exercise limitation.

Psychosocial Factors

Depression is very common in patients with COPD, with prevalence as high as 50% in some series [31, 32]. Consequently, the assessment for psychosocial problems such as depression and anxiety (and treatment when indicated) is an important component of comprehensive pulmonary rehabilitation. Treatment for depression and anxiety can improve the overall quality of life, help in smoking cessation, medication compliance, and adherence to pulmonary rehabilitation [33]. Even without specific psychological

intervention, pulmonary rehabilitation can lead to some improvement in depressive symptoms in some individuals [34]. Patients with significant psychosocial problems should be referred to a specialist.

Why Pulmonary Rehabilitation Works

Pulmonary rehabilitation has no substantial effect on the primary lung impairment, such as the FEV1, of patients with COPD. This fact, plus the incorrect perception that these patients are often ventilatory-limited before a physiologic training effect can be achieved, has delayed the widespread acceptance of pulmonary rehabilitation as a therapeutic option. This paradox is explained by the often-pronounced beneficial effects of pulmonary rehabilitation on the multi-systemic manifestations of this disease [35]. These manifestations include peripheral muscle dysfunction due to deconditioning and structural muscle abnormalities (decreased oxidative enzymes and changes in muscle fibers), nutritional and body composition abnormalities, sub-optimal self-management strategies (especially for the exacerbation), fear of dyspnoea-producing activities, inefficient pacing, and anxiety and depression.

Selection Criteria for Pulmonary Rehabilitation

Pulmonary rehabilitation should be considered for patients with chronic respiratory disease, who have persistent symptoms or reductions in functional status or health status despite otherwise standard medical therapy. COPD is the most common disease leading to pulmonary rehabilitation, although all respiratory patients with the above indications might be candidates. This is based on the rationale that the reversible co-morbidities are also present in other chronic respiratory diseases. In general, the referral to pulmonary rehabilitation is based on the following inclusion criteria [36]:

1. Severe dyspnoea and/or fatigue
2. Decreased exercise ability
3. Interference with performing physical activities of daily living
4. Impaired health status
5. Decreased occupational performance
6. Nutritional depletion
7. Frequent respiratory exacerbations
8. Increased medical resource consumption

Persistent symptoms or limitation in functional or health status in an individual with chronic respiratory disease determine the need for pulmonary rehabilitation, not a specific physiologic abnormality such as a reduced FEV1. Furthermore, markers of physiologic abnormalities such as the FEV1 correlate relatively poorly with clinical variables such as dyspnoea, exercise capacity, activity limitation, or quality of life. Therefore, the FEV1 should not be used as a surrogate for assessment in these areas and or as the sole criterion for referral.

Referral to pulmonary rehabilitation has been all too often reserved for patients with advanced lung disease. While these patients improve with pulmonary rehabilitation [37], referral at an earlier stage might allow for greater benefit, with emphasis on preventative strategies, such as smoking cessation or activity promotion, exercise at higher intensities.

As such, current COPD guidelines place referral to pulmonary rehabilitation at moderate disease stage, where regular bronchodilator therapy is also recommended.

Contraindications fall into two major categories. Patients with co-morbid conditions that, in the clinician's opinion, would substantially interfere with the rehabilitative process are not candidates for pulmonary rehabilitation. Examples include disabling arthritis, or severe neuropsychiatric disease. Patients with a condition that might place them at undue risk during exercise training, such as severe pulmonary hypertension and unstable cardiovascular disease, are also not candidates. Since many COPD patients have these conditions to some degree, an assessment by a physician experienced in pulmonary rehabilitation is essential to determine the appropriateness and safety of this intervention.

Poor motivation is a relative contraindication to pulmonary rehabilitation, since the process requires active collaboration among the patient and health care providers. This is especially relevant the area of incorporating activity and exercise into the home situation. However, seemingly low levels of motivation might improve over the course of pulmonary rehabilitation, especially if patients perceive a demonstrable benefit from the therapy. Active cigarette smokers may be reasonable candidates for pulmonary rehabilitation providing that behavioral and/or pharmacologic smoking cessation intervention is given.

Goals of Pulmonary Rehabilitation

The specific goals of pulmonary rehabilitation vary with morbidity and needs of individual patients. In general, its goals include a reduced burden of symptoms such as dyspnoea and fatigue, improved functional status, and improve health related quality of life. The latter is reflected by decreased bothersome symptoms and increased participation in physical and social activities. The reduction in health care utilization is an additional goal of pulmonary rehabilitation.

Components of Pulmonary Rehabilitation

Assessment

A thorough patient assessment lays the framework for successful pulmonary rehabilitation. This assessment is necessary to determine the appropriateness of the referral, recognize safety issues, ensure optimal medical management, address supplemental oxygen requirements, identify exercise, educational, nutritional, and psychosocial needs, create the exercise prescription, and establish patient-specific goals. This process involves the collaborative efforts of the medical director, the rehabilitation coordinator, and other staff. The patient assessment may also include a maximal cardiopulmonary exercise test, which can assess the safety of exercise, and the factors contributing to exercise limitation [38]. The exercise test can also help with the exercise prescription.

Exercise Training

Exercise training is the cornerstone of pulmonary rehabilitation. As the most effective means of improving muscle function in COPD [39–41], it is indicated for patients with decreased exercise performance, disabling dyspnoea or fatigue, or impairment of physical activities of daily living. Most COPD patients referred for pulmonary rehabilitation

are in a relatively stable state; however the post-exacerbation period is an opportune time to begin this intervention [42]. Exercise training must address the individual patient's limitation to exercise, which may include ventilatory limitations, gas exchange abnormalities, and skeletal or respiratory muscle dysfunction. Exercise training may also improve motivation for exercise, reduce mood disturbance [43, 44], decrease symptoms [45], and improve cardiovascular function. Although COPD patients may be ventilatory-limited, most can sustain the necessary training intensity and duration for skeletal muscle adaptation.

While exercise training is a necessary component of pulmonary rehabilitation, the optimal frequency and duration are not known. Outpatient exercise training with 2 or 3 sessions per week for 4 weeks showed less benefit than similar training for 7 weeks [46, 47]. Additionally, 20 sessions leads to greater positive outcomes than 10 sessions [48]. It is generally believed that longer programs yield larger and more sustained training effects [49]. Patients should perform exercises at least three times per week, and regular supervision of exercise sessions is necessary to achieve optimal physiological benefits [50, 51]. If there are program constraints, twice-weekly supervised exercise training plus one or more unsupervised sessions at home may be an acceptable alternative.

In general, the goal of exercise training in pulmonary rehabilitation is to achieve maximal physiological training effects, which is best attained at high intensities [52]. While an intensity that exceeds 60% of peak capacity is sufficient to elicit physiological training effects [53], in clinical practice, symptom scores can be used to adjust training load [54] – a Borg score of 4–6 for dyspnoea is a reasonable target [52]. Many COPD patients can train at relatively high percentages of their maximal work-rate. However, this approach may not be suitable to all patients because of symptom limitation, substantial co-morbidities, or low motivation. These patients still stand to benefit from lower intensity training, since this training also improves symptoms, health status, and activities of daily living [55, 56]. Low intensity targets may be important in long-term adherence to the exercise prescription. Interval training can be considered for patients who cannot sustain long uninterrupted periods of endurance training. It is a modification where the longer exercise session is replaced by several smaller sessions separated by periods of rest or lower intensity exercise [57].

Exercise training in pulmonary rehabilitation has traditionally focused on the lower extremities, with most of supervised whole body exercise usually performed on a treadmill or cycle ergometer. Rehabilitation programs also using encourage walking. However, since many activities of daily living involve upper extremities and improvement is specific to those muscles trained, upper limb exercises should also be incorporated into the program [58]. Upper extremity exercises can include training on an arm cycle ergometer, free weights, and elastic bands. Upper limb exercise training reduces dyspnoea during upper limb activities and reduces ventilatory requirements for arm elevation [59, 60].

Strength (resistance) training in COPD [61] has a greater effect in increasing muscle mass and strength than endurance training [40, 62, 63]. As this type of exercise results in less dyspnoea, it may be better tolerated than endurance training. The combination of endurance and strength training is probably the optimal approach to treat peripheral muscle dysfunction in COPD.

Education and Self-management Strategies

Patient education is a core component of pulmonary rehabilitation [4, 64]. Its emphasis has changed from traditional, didactic lectures to the promotion of self-management strategies. The latter emphasize illness control through increasing self efficacy.

In this context, self-efficacy is the belief that one can successfully execute particular behaviors in order to produce certain outcomes [65]. The desired result is health behavior change that leads to improved clinical outcomes, including adherence [66, 67]. Self-management interventions emphasize ways to integrate the demands of the disease and its treatment into a daily routine. Important areas include the prevention and early treatment of COPD exacerbations, informed end-of-life decision making, smoking cessation strategies (when indicated), promotion of adherence to the treatment plan, and breathing strategies and bronchial hygiene techniques.

Prevention and early treatment of COPD exacerbations is especially important as they can result in a more rapid decline of lung function [68], increased peripheral muscle weakness [69], decreased health status [70], increased health care utilization [71, 72], and increased mortality [73]. Early therapy speeds recovery [74] and reduces health care costs [75]. COPD patients should be educated to respond early in the exacerbation by activating an action plan. This usually includes initiating a predetermined medication regimen and alerting the health care provider. Pulmonary rehabilitation is an appropriate setting for the discussion of advance care planning and palliative care [76, 77].

Breathing strategies may provide benefit in some patients [78]. These techniques include pursed-lip breathing, active expiration, diaphragmatic breathing, adapting specific body positions, and coordinating paced breathing with activities. In some COPD patients, mucus hypersecretion and difficulty mobilizing secretions adds to the burden of the disease. Instruction in the importance of bronchial hygiene and training in drainage techniques are appropriate for these patients [79].

Recent evidence [75] demonstrates that a multi-component, skill-oriented, self-management program that incorporates an exacerbation action plan and home exercise promotion can reduce health care utilization and improve health status.

Patients with COPD are not unique: adherence to therapeutic interventions is crucial to health behavior in all chronic disease [80]. Developing self-management skills, incorporating and promoting exercise into the home setting early in the course of rehabilitation, providing longer lasting programs [81], and offering post-rehabilitation maintenance programs may enhance long term adherence.

Nutritional Intervention

Body composition abnormalities are prevalent in COPD: individuals with moderate-to-severe disease are frequently underweight [82, 83]. Muscle wasting associated with COPD is more common in, but by no means limited to, underweight patients. At a minimum, a body mass index (BMI), defined as the weight in kg divided by the height in meters squared, should be determined. Based on the BMI, patients can be categorized as underweight (<21 kg/m^2), normal weight (21–25 kg/m^2), overweight (25–30 kg/m^2) and obese (>30 kg/m^2). Recent weight loss (>10% in the past 6 months or >5% in the past month) is also an important independent predictor of morbidity and mortality in COPD. The BMI, however, may not accurately reflect changes in body composition as reductions in fat-free or lean body mass [84, 85] also common in COPD, better correlate with exercise limitation, reduced health status, increased health care utilization, and reduced survival [86–89].

The rationale for evaluating and treating nutritional/body composition abnormality in COPD is based primarily on its high prevalence and association with morbidity and mortality. Several physiological and pharmacological interventions may potentially improve body composition abnormalities in COPD. These interventions include

caloric replacement [90, 91], strength training [40, 92], anabolic hormonal therapy [93, 94], or their combinations. It remains to be determined whether improvement in body composition will translate into real functional benefits and or increased survival.

Psychological and Social Considerations

Chronic respiratory disease is commonly associated with anxiety, depression and other mental health disorders [95]. Psychosocial support provided within pulmonary rehabilitation can improve mood disorders by encouraging adaptive behaviors, diminishing negative emotions, and providing a supportive environment.

Depressive symptoms are common in patients with moderate to severe COPD, with an approximate prevalence rate of 45% [96]. Sub-clinical depression can be seen in up to 25% of elderly COPD patients [97], yet both depression and anxiety in the elderly are significantly under-treated [98]. Impaired gas exchange may also lead to mild to moderate neuropsychological impairments such as difficulties in concentration, memory disturbances, cognitive dysfunction, difficulty solving common problems in daily living, missed office or clinic appointments, or failure to adhere to the medical and self-management plans [44]. Oxygen supplementation should be considered those patients with documented hypoxemia.

The initial patient assessment should include a psychosocial evaluation. Screening questionnaires such as the Hospital Anxiety and Depression Questionnaire or Beck Depression Inventory may aid in the recognition of significant anxiety and depression [99, 100]. While moderate levels of anxiety or depression may be addressed in the pulmonary rehabilitation program, patients identified as having significant psychosocial disturbances should be referred to an appropriate mental health practitioner prior to the start of the program.

Settings of Pulmonary Rehabilitation

The success of pulmonary rehabilitation depends more on how it is given rather than where it is provided. In general, pulmonary rehabilitation can be in three settings, inpatient, outpatient, and home-based. Clinical efficacy has been demonstrated in all three settings [5, 101, 102]. The choice of pulmonary rehabilitation setting often depends on patient factors such as disease severity and co-morbidities, availability and distance to the pulmonary rehabilitation programs, and third-party reimbursement.

Although clinical efficacy has been shown with pulmonary rehabilitation program regardless of the setting, there are certain advantage and disadvantage associated with each setting. Table 10.5 outlines some advantages and disadvantages of each setting [101].

Pulmonary Rehabilitation as Part of Integrated Care

Optimal medical care for individuals with COPD generally requires combining pharmacologic and non-pharmacologic therapies. The latter include the promotion of a healthy lifestyle (smoking cessation, optimal nutrition, regular exercise, and promotion of physical activity), vaccinations, adherence with medical therapy, collaborative self-management strategies (an action plan for the early and effective treatment of exacerbations), and advance directives as part of end-of-life planning.

Table 10.5 Advantages and disadvantages of pulmonary rehabilitation in different settings (Adapted from [101]).

	Advantages	Disadvantages
Inpatient	Closer medical monitoring Intensive nursing care available 24 h/day Fewer transpor tation issues Ideal for patients requiring higher level of care	Cost Difficulty in third-party reimbursement Limited availability of programs
Outpatient	By far, the most widely available Least costly, efficient use of staff resources Least intrusive to the family	Potential transportation issues Little opportunity to observe home activities
Home-based	Convenience to patient and family Transportation generally is not an issue Providing exercise training and instruction in a familiar environment may promote long-term adherence	Cost Little group support Logistically difficult to provide multidisciplinary care Limited access to exercise equipment

The incorporation of the above interventions is simply good medical practice. This concept has been emphasized in the recent Statement on Pulmonary Rehabilitation developed by the American Thoracic Society and the European Respiratory Society: "In a broader sense, pulmonary rehabilitation includes a spectrum of intervention strategies integrated into the lifelong management of patients with chronic respiratory disease and involves a dynamic, active collaboration among the patient, the family, and health care providers" [4]. The most efficient and effective method of providing these therapies for patients with moderate to severe COPD is comprehensive pulmonary rehabilitation. However, not all individuals are candidates for pulmonary rehabilitation or even have access to this therapy, so efforts should be given to foster its application across the spectrum of COPD.

Developing Areas in the Science and Application of Pulmonary Rehabilitation

Activity and Exercise in COPD

The progression of COPD is often characterized by deteriorating respiratory physiology (such as a declining FEV1) and progressive limitation in exercise capacity and physical activity levels. In response to the dyspnoea and fatigue associated with physical exertion, patients often subconsciously adopt a more sedentary lifestyle, limiting or giving up strenuous physical activities [103]. While this strategy reduces distressing symptoms (one cannot have exertional dyspnoea without exertion), the activity limitation is itself detrimental, being associated with higher mortality and increased hospital resource utilization [104].

Although clinicians have long recognized that COPD patients are quite sedentary, only recently was this proven with direct activity assessment [105], as illustrated in Fig. 10.2 [105]. Compared to healthy elderly subjects, COPD patients walk and stand considerably less over the course of the day. Physical activities appear to be particularly reduced in the period following the exacerbation of COPD [106], and when the disease has reached the stage when long-term oxygen therapy is required [107].

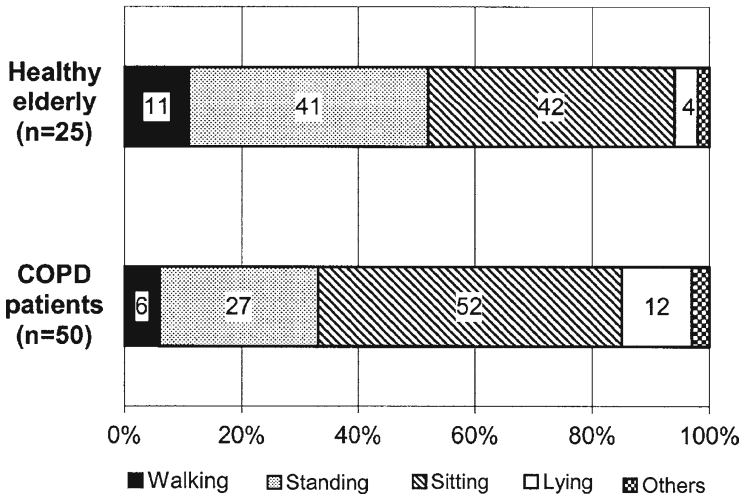


Fig. 10.2. Difference in the activities of healthy elderly versus chronic obstructive pulmonary disease (*COPD*) patients [105]. Percentages of time spent in each of the activities or body positions in healthy subjects compared to patients with COPD during the day (others = cycling or undetermined activity)

It is reasonable to assume that improved exercise tolerance from pulmonary rehabilitation will lead to increased physical activities in COPD patients. While this has yet to be proven unequivocally, one recent study did find increased activity levels following outpatient pulmonary rehabilitation [108]. However, pulmonary rehabilitation is more than just exercise training; alternately, it could increase physical activities of daily living, independent of its effect on exercise performance. For example, improved pacing and increased self-efficacy for walking may increase activity despite no demonstrable improvement in exercise testing.

Decreases in both functional exercise capacity and physical activity appear to be related to increased health care utilization and mortality in COPD [109–111]. It remains to be determined whether improvements in exercise or physical activity resulting from pulmonary rehabilitation will lead to improved outcomes in these important areas – although this is certainly plausible.

Initiating Pulmonary Rehabilitation Immediately Following the COPD Exacerbation

COPD patients are usually sent to pulmonary rehabilitation when they still have bothersome symptoms or physical activity limitation despite otherwise optimal medical therapy. While the referral might be made at discharge following a hospitalization for an exacerbation, patients are commonly sent to rehabilitation in a relatively stable state [112]. However, as recent studies indicate, referring patients to pulmonary rehabilitation shortly after hospitalization for a COPD exacerbation may substantially reduce subsequent health care utilization and – possibly – mortality risk [113]. New self-management strategies, such as early treatment of subsequent exacerbations, plus enhanced exercise capacity and physical activity probably underlie these beneficial health benefits.

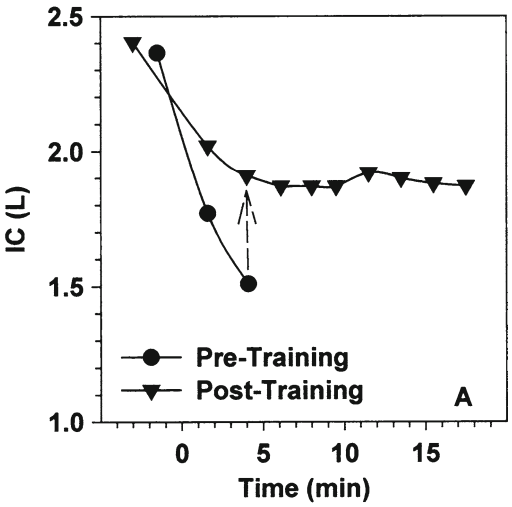


Fig. 10.3. The effect of exercise training on lung volumes [116]. Higher inspiratory capacity (*IC*) values reflect lower end-expiratory lung volumes. IC dropped rapidly at baseline (line with circle symbols) during exercise in untrained chronic obstructive pulmonary disease (*COPD*) subjects, indicating the rapid development of dynamic hyperinflation. Following exercise training, not only was exercise endurance time (*x*-axis) prolonged, there was considerably less dynamic hyperinflation (line with triangle symbols)

Lung Hyperinflation and Exercise Training in COPD

Exercise capacity in patients with COPD is limited in large part by dyspnoea resulting from static and dynamic hyperinflation [114]. At increased lung volumes, the elastic work of breathing is increased and the respiratory muscles are placed at a mechanical disadvantage [115]. Furthermore, exercising de-conditioned muscles of ambulation requires disproportionate increases in minute ventilation, resulting in part from early lactic acid production. The need for an increased respiratory rate in response to the above, coupled with a prolonged expiratory time causes the patient to breathe in before the preceding breath is fully exhaled. The resultant dynamic hyperinflation plays a large role in the exertional dyspnoea of COPD.

Exercise training in COPD *indirectly* reduces dynamic hyperinflation because of its beneficial effects on peripheral muscles, especially the muscles of ambulation. Trained muscles produce less lactate at any given work rate, resulting in a decreased respiratory rate [116]. The lower respiratory rate during exercise will allow for more complete lung emptying with each breath – thereby reducing dynamic hyperinflation. Fig. 10.3 [116] depicts this indirect beneficial effect on lung volumes. The reduction in hyperinflation undoubtedly contributes to the positive effects pulmonary rehabilitation exercise training has on exercise performance.

Enhancing Exercise Training Effects in Pulmonary Rehabilitation

Substantial improvement in exercise performance is often attained following a supervised exercise training program for patients with COPD. However, similar to that with healthy individuals, beneficial effects are dose-dependent – higher levels of training lead to greater physiologic gains [117–119]. Two strategies that would allow COPD patients to train at higher intensities, bronchodilators and supplemental oxygen therapy, will be discussed below.

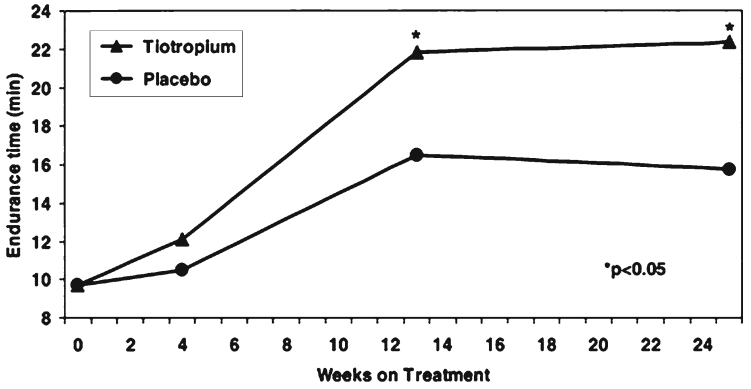


Fig. 10.4. Long-acting bronchodilator therapy and exercise training in chronic obstructive pulmonary disease (*COPD*) patients [126]. COPD patients referred to pulmonary rehabilitation were randomized to the long-acting anticholinergic bronchodilator, tiotropium, or placebo at week 0 in this double-blind trial. Short acting bronchodilators were used in all patients, as-needed. From weeks 5 to 13 both groups participated in high-intensity exercise training as part of pulmonary rehabilitation. After rehabilitation they continued their maintenance pharmacologic therapy (tiotropium or placebo) until week 25. Exercise endurance (*y*-axis) improved in both groups during pulmonary rehabilitation, but those taking the long-acting bronchodilator therapy improved more. Moreover, this beneficial effect appeared to be sustained after the formal exercise training. This study underscores the complementary effects of bronchodilators and exercise training in COPD

Bronchodilators

Bronchodilator therapy in COPD reduces dyspnoea and improves exercise tolerance [120–122]. Dilating airways decreases the resistive work of breathing and reduces dyspnoea. Additionally, lessening static and dynamic hyperinflation decreases the elastic work of breathing, further alleviating dyspnoea [123, 124]. Through these mechanisms, bronchodilators may allow COPD patients to exercise at higher intensities, thereby increasing the likelihood of a substantial gain in exercise performance.

Bronchodilator therapy may even change the primary cause of exercise limitation from exertional dyspnoea to leg fatigue; the latter being particularly amenable to exercise training [125]. The additive effects of combining these two modalities are shown in Fig. 10.4 [126]. This study underscores the complementary effects of bronchodilators and exercise training in COPD.

Supplemental Oxygen

Long-term oxygen therapy prolongs survival in COPD patients with severe hypoxemia [127, 128]. Because of this, there is rationale for continuing oxygen therapy in hypoxemic patients during exercise training. It is also reasonable (both from a safety perspective and to enhance outcome) to administer supplemental oxygen during exercise and activity in patients who do not require continuous O_2 therapy but have exercise-induced hypoxemia [129].

COPD patients for whom ambulatory oxygen therapy is prescribed are very sedentary, and the oxygen prescription does not significantly increase activity [130]. Referring COPD patients to pulmonary rehabilitation when oxygen therapy is started might help both with adherence with oxygen therapy and promotion of activity.

Supplemental oxygen therapy can also be considered an adjunct to exercise training in pulmonary rehabilitation: through reducing dyspnoea, it may allow for greater intensities of exercise training in symptom-limited COPD patients. This effect – which may be present even for those without exercise-induced hypoxemia – may be mediated through a reduction in dynamic hyperinflation [131]. A rationale behind this intriguing effect is that oxygen therapy promotes lower respiratory rates during exercise (due in part to effects on chemoreceptors and reductions in dyspnoea), leading to a more complete emptying of the lungs during exhalation.

In the laboratory setting, administering supplemental oxygen therapy during exercise testing increases exercise capacity [129]. However, use of supplemental oxygen to enhance exercise training in pulmonary rehabilitation has had mixed results [132–134]. Supplemental oxygen therapy would probably have its greatest effect with strategies incorporating high-intensity exercise as it would allow patients to train at higher levels [135]. It has become standard of care in the United States to administer supplemental oxygen during exercise or activity in COPD patients with documented hypoxemia. The routine use of supplemental oxygen for non-hypoxemic COPD patients in the pulmonary rehabilitation setting remains to be determined.

Maintaining the Benefits of Pulmonary Rehabilitation

The beneficial effects of pulmonary rehabilitation – while often substantial –gradually decrease over time [136]. Gains made in health status are often longer lasting than exercise performance. While this drop-off in effectiveness probably has multiple reasons, failure to maintain long-term adherence with the post-rehabilitation plan is usually considered most important: COPD patients decrease structured exercise over time. This is particularly relevant in the period following the COPD exacerbation, when patients revert to a more sedentary lifestyle [137]. Interventions designed to improve long term adherence so far have not had much success [137, 138]. Longer lasting pulmonary rehabilitation programs may result in more sustained improvement [139], but this is probably not practical in our current health care system. Further research is necessary in this area, especially through transferring principles of pulmonary rehabilitation to the home setting.

Combination Therapy for COPD

COPD is not simply a lung disease. Its pervasive systemic manifestations profoundly affect the individual's ability to function within the environment. Therefore, pulmonary rehabilitation must be viewed within the continuum of care for COPD. True combination therapy incorporates both pharmacologic and non-pharmacologic therapy, with the goal to reduce symptoms, increase functional status, have a health economic benefit, and – ultimately – prolong survival.

Summary

Pulmonary rehabilitation has emerged as a standard of care for patients with chronic respiratory disease who remain symptomatic or have reduced functional status despite otherwise standard medical therapy. As such, it is placed prominently in current guidelines for COPD. Pulmonary rehabilitation reduces dyspnoea, and improves exercise performance, functional status, and quality of life. Recent studies demonstrate that it also decreases health care utilization. This multidisciplinary approach, which includes

exercise training, the promotion of self-management strategies, nutritional intervention, and psychosocial support, works predominately through the reducing systemic effects of the disease. Components of pulmonary rehabilitation can be administered throughout the course of COPD as part of integrated care. Pulmonary rehabilitation and pharmacological therapy are complementary: optimizing bronchodilator therapy increases the effectiveness of pulmonary rehabilitation, and pulmonary rehabilitation enhances the benefits of pharmacological therapy. Pulmonary rehabilitation is currently underutilized, due to combinations of under-awareness of its effectiveness by some health care providers, unavailability of programs in some areas, and often insufficient third-party reimbursement.

The Global initiative for chronic obstructive lung disease (GOLD) published a report on global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease in 2006 placing pulmonary rehabilitation a part of standard therapy for COPD alongside regular bronchodilator therapy in their outlines of treatment algorithm for COPD.

Percentage of time spent in each of the activities or body positions in healthy subjects compared to patients with chronic obstructive pulmonary disease (COPD) during the day. (Others = cycling or undetermined activity).

Higher inspiratory capacity (IC) values reflect lower end-expiratory lung volumes. IC dropped rapidly at baseline (line with circle symbols) during exercise in untrained COPD subjects, indicating the rapid development of dynamic hyperinflation. Following exercise training, not only was exercise endurance time (*x*-axis) prolonged, there was considerably less dynamic hyperinflation (line with triangle symbols).

COPD patients referred to pulmonary rehabilitation were randomized to the long-acting anticholinergic bronchodilator, tiotropium, or placebo at Week 0 in this double-blind trial. Short acting bronchodilators were used in all patients, as needed. From Weeks 5–13, both groups participated in high-intensity exercise training as part of pulmonary rehabilitation. After rehabilitation they continued their maintenance pharmacologic therapy (tiotropium or placebo) until Week 25. Exercise endurance (*y*-axis) improved in both groups during pulmonary rehabilitation, but those taking the long-acting bronchodilator therapy improved more. Moreover, this beneficial effect appeared to be sustained after the formal exercise training. This study underscores the complementary effects of bronchodilators and exercise training in COPD.

References

1. Haas A, Cardon H (1969) Rehabilitation in chronic obstructive lung disease: a 5-year study of 252 male patients. Med Clin North Am 53:593–606
2. Global Initiative for Chronic Obstructive Pulmonary Disease Workshop Report. http://www.goldcopd.com
3. ATS-ERS Statement on the Diagnosis and Treatment of COPD www.thoracic.org
4. Nici L, Donner C, ZuWallack R, Wouters E et al (2006) The ATS/ERS statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173:1390–1414
5. ACCP-AACVPR Pulmonary Rehabilitation Guidelines Panel (1997) Pulmonary rehabilitation: joint ACCP/AACVPR evidence based guidelines. Chest 112:1363–1396
6. Decramer M et al (2005) Systemic effects of COPD. Respir Med 99(Suppl B):S3–10
7. O'Donnell DE (2001) Ventilatory limitations in chronic obstructive pulmonary disease. Med Sci Sports Exerc 33(7 Suppl):S647–55
8. Rodrigues F (2004) Limiting factors of exercise capacity in patients with COPD. Rev Port Pneumol 10(1):9–61

9. Puente-Maestu L et al (2005) Dyspnea, ventilatory pattern, and changes in dynamic hyperinflation related to the intensity of constant work rate exercise in COPD. Chest 128(2):651–6
10. Bianchi R et al (2004) Chest wall kinematics and breathlessness during pursed-lip breathing in patients with COPD. Chest 125(2):459–65
11. Kobayashi S et al (1996) Relationship between breathlessness and hypoxic and hypercapnic ventilatory response in patients with COPD. Eur Respir J 9(11):2340–5
12. Somfay A et al (2002) Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. Chest 121(2):393–400
13. Bee D, Howard P (1993) The carotid body: a review of its anatomy, physiology and clinical importance. Monaldi Arch Chest Dis 48(1):48–53
14. Mador MJ, Bozkanat E (2001) Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Respir Res 2(4):216–24
15. Maltais F et al (2000) Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. Thorax 55(10):848–53
16. Franssen FM et al (2005) Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training. Med Sci Sports Exerc 37(1):2–9
17. Schonhofer B et al (1997) Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. Eur Respir J 10(12):2814–9
18. Bernard S et al (1998) Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158(2):629–34
19. Troosters T, Gosselink R, Decramer M (2001) Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopulm Rehabil 21(1):10–7
20. Maltais F et al (1999) Altered expression of myosin heavy chain in the vastus lateralis muscle in patients with COPD. Eur Respir J 13(4):850–4
21. Schols AM et al (1996) Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 51(8):819–24
22. Spruit MA et al (2003) Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. Thorax 58(9):752–6
23. Decramer M et al (1994) Corticosteroids contribute to muscle weakness in chronic airflow obstruction. Am J Respir Crit Care Med 150(1):11–6
24. Rahman I, Skwarska E, MacNee W (1997) Attenuation of oxidant/antioxidant imbalance during treatment of exacerbations of chronic obstructive pulmonary disease. Thorax 52(6):565–8
25. Levine S et al (2002) Bioenergetic adaptation of individual human diaphragmatic myofibers to severe COPD. J Appl Physiol 92(3):1205–13
26. Berger HJ et al (1979) 1979 Memorial Award Paper. Comparison of exercise right ventricular performance in chronic obstructive pulmonary disease and coronary artery disease: noninvasive assessment by quantitative radionuclide angiocardiography. Invest Radiol 14(5):342–53
27. Faisy C et al (2000) Bioelectrical impedance analysis in estimating nutritional status and outcome of patients with chronic obstructive pulmonary disease and acute respiratory failure. Intensive Care Med 26(5):518–25
28. Vermeeren MA et al (2006) Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med 100(8):1349–55
29. Schols A (2003) Nutritional modulation as part of the integrated management of chronic obstructive pulmonary disease. Proc Nutr Soc 62(4):783–91
30. Jorgensen NR et al (2007) The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease – a cross sectional study. Respir Med 101(1):177–85
31. Guell R et al (2006) Impact of pulmonary rehabilitation on psychosocial morbidity in patients with severe COPD. Chest 129(4):899–904
32. Light RW et al (1985) Prevalence of depression and anxiety in patients with COPD. Relationship to functional capacity. Chest 87(1):35–8
33. Kayahan B et al (2006) Psychological outcomes of an outpatient pulmonary rehabilitation program in patients with chronic obstructive pulmonary disease. Respir Med 100(6):1050–7

34. Emery CF et al (1991) Psychological outcomes of a pulmonary rehabilitation program. Chest 100(3):613–7
35. Nici L, ZuWallack R, Wouters E, Donner (2006) On pulmonary rehabilitation and the flight of the bumblebee. Eur Respir J 28:461–462
36. American Association of Cardiovascular and Pulmonary Rehabilitation (2007). Guidelines for pulmonary rehabilitation programs. In: ZuWallack RZ, Crouch R (eds.) Human Kinetics, Champaign, IL 3rd edn
37. ZuWallack RL, Patel K, Reardon JZ, Clark BA, Normandin EA (1991) Predictors of improvement in the 12-minute walking distance following a six-week outpatient pulmonary rehabilitation program. Chest 99:805–808
38. American Thoracic Society/American College of Chest Physicians (2003) ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211–277
39. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez De Suso JM, Moreno A, Barbera JA, Nadal J, DE Jover L, Rodriguez-Roisin R, Wagner PD (1999) Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:1726–1734
40. Bernard S, Whittom F, LeBlanc P, Jobin J, Belleau R, Berube C, Carrier G, Maltais F (1999) Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:896–900
41. Maltais F, LeBlanc P, Simard C, Jobin J, Berube C, Bruneau J, Carrier L, Belleau R (1996) Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154:442–447
42. Puhan MA, Scharplatz M, Troosters T, Steurer J (2005) Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality – a systematic review. Respir Res 6:54
43. Emery CF, Leatherman NE, Burker EJ, MacIntyre NR (1991) Psychological outcomes of a pulmonary rehabilitation program. Chest 100:613–617
44. Emery CF, Schein RL, Hauck ER, MacIntyre NR (1998) Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. Health Psychol 17:232–240
45. O'Donnell DE, McGuire M, Samis L, Webb KA (1995) The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. Am J Respir Crit Care Med 152:2005–2013
46. Green RH, Singh SJ, Williams J, Morgan MD (2001) A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax 56:143–145
47. Plankeel JF, McMullen B, MacIntyre NR (2005) Exercise outcomes after pulmonary rehabilitation depend on the initial mechanisms of exercise limitation among non-oxygen-dependent COPD patients. Chest 127(1):110–116
48. Rossi G, Florini F, Romagnoli M, Bellatone T, Lucic S, Lugli D, Clini E (2005) Length and clinical effectiveness of pulmonary rehabilitation in outpatients with chronic airway obstruction. Chest 127:105–109
49. Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, Goldstein RS (2002) Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 3:CD003793
50. Ringbaek TJ, Broendum E, Hemmingsen L, Lybeck K, Nielsen D, Andersen C, Lange P (2000) Rehabilitation of patients with chronic obstructive pulmonary disease. Exercise twice a week is not sufficient! Respir Med 94:150–154
51. Puente-Maestu L, Sanz ML, Sanz P, Cubillo JM, Mayol J, Casaburi R (2000) Comparison of effects of supervised versus self-monitored training programs in patients with chronic obstructive pulmonary disease. Eur Respir J 15:517–525
52. Vallet G, Ahmaidi S, Serres I, Fabre C, Bourgouin D, Desplan J, Varray A, Prefaut C (1997) Comparison of two training programmes in chronic airway limitation patients: standardized versus individualized protocols. Eur Respir J 10:114–122

53. Punzal PA, Ries AL, Kaplan RW, Prewitt LM (1991) Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. Chest 100:618–623
54. Horowitz MB, Littenberg B, Mahler DA (1996) Dyspnea ratings for prescribing exercise intensity in patients with COPD. Chest 109:1169–1175
55. Clark CJ, Cochrane L, Mackay E (1996) Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. Eur Respir J 9:2590–2596
56. Normandin EA, McCusker C, Connors M, Vale F, Gerardi D, ZuWallack RL (2002) An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. Chest 121:1085–1091
57. Gosselink R, Troosters T, Decramer M (1998) Effects of exercise training in COPD patients; interval versus endurance training. Eur Respir J 12:2S
58. Lake FR, Henderson K, Briffa T, Openshaw J, Musk AW (1990) Upper-limb and lower-limb exercise training in patients with chronic airflow obstruction. Chest 97:1077–1082
59. Couser JI Jr, Martinez FJ, Celli BR (1993) Pulmonary rehabilitation that includes arm exercise reduces metabolic and ventilatory requirements for simple arm elevation. Chest 103:37–41
60. Epstein SK, Celli BR, Martinez FJ, Couser JI, Roa J, Pollock M, Benditt JO (1997) Arm training reduces the VO_2 and VE cost of unsupported arm exercise and elevation in chronic obstructive pulmonary disease. J Cardiopulm Rehabil 17:171–177
61. Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL (1992) Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax 47:70–7
62. Spruit MA, Gosselink R, Troosters T, De Paepe C, Decramer M (2002) Resistance versus endurance training in patients with COPD and skeletal muscle weakness. Eur Respir J 19:1072–1078
63. O'Shea SD, Taylor NF, Paratz J (2004) Peripheral muscle strength training in COPD: a systematic review. Chest 126:903–914
64. Lareau SC, Insel KC (2000) Chapter 6. Patient and family education. In: Hodgkin JE, Celli BR, Connors GL (eds) Pulmonary rehabilitation, Human Kinetics, Champaign, IL 3rd edn
65. Bandura A (1977) Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev 84:191–215
66. Bodenheimer T, Lorig K, Holman H, Grumbach K (2002) Patient self-management of chronic disease in primary care. JAMA 288(19):2469–2475
67. Bourbeau J, Nault D, Dang-Tan T (2004) Self-management and behaviour modification in COPD. Patient Educ Couns 53:271–277
68. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57:847–852
69. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, Bouillon R, Decramer M (2003) Muscle force during an acute exacerbation in hospitalized patients with COPD and its relationship with CXCL8 and IGF-I. Thorax 59(9):741–2
70. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jefferies DJ, Wedzicha JA (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1418–1422
71. Andersson F, Borg S, Jansson SA, Jonsson AC, Ericsson A, Prutz C et al (2002) The costs of exacerbations in chronic obstructive pulmonary disease. Respir Med 96:700–708
72. Price MJ, Hurrell C (1999) Health care costs of treating exacerbations of COPD. Eur Respir J 14(Suppl 30):S380
73. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA (1996) Outcomes following acute exacerbation of severe chronic obstructive lung disease. Am J Respir Crit Care Med 154(4 pt 1):959–67
74. Wilkinson T, Donaldson G, Hurst J, Seemungal T, Wedzicha J (2004) Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169:1298–1303
75. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, Renzi P, Nault D, Borycki E, Schwartzman K, Singh R, Collet JP (2003) Chronic obstructive pulmonary

disease axis of the respiratory network Fonds de la Recherche en Sante du Quebec. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease. Arch Int Med 163(5):585–91
76. Hefner JE, Fahy B, Hilling L, Barbieri C (1996) Attitudes regarding advance directives among patients in pulmonary rehabilitation. Am J Respir Crit Care Med 154:1735–1740
77. Heffner JE (2000) Role of pulmonary rehabilitation in palliative care. Respir Care 45(11):1371–1375
78. Gosselink R (2003) Controlled breathing and dyspnea in patients with chronic obstructive pulmonary disease. J Rehabil Res Develop 40:25–34
79. Jones AP, Rowe BH (2000) Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis. Cochrane Database Syst Rev 2:CD000045
80. Organization WH (2003) Adherence to long-term therapies: evidence for action. Annex 1:143
81. Troosters T, Gosselink R, Decramer M (2000) Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med 109(3):207–12
82. Engelen MPKJ, Schols AMWJ, Baken WC, Wesseling GJ, Wouters EF (1994) Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in outpatients with COPD. Eur Respir J 7:1793–1797
83. Schols AMWJ, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EF (1993) Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 147:1151–1156
84. Schols AMWJ, Fredrix EW, Soeters PB, Westerterp KR, Wouters EFM (1991) Resting energy expenditure in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 5:983–987
85. Engelen MPKJ, Schols AMWJ, Heidendal GAK, Wouters EFM (1998) Dual-energy X-ray absorptiometry in the clinical evaluation of body composition and bone mineral density in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 68:1298–1303
86. Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM (2000) Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 94(9):859–867
87. Schols AM, Slangen J, Volovics L, Wouters EF (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157(6 Pt 1):1791–1797
88. Wilson DO, Rogers RM, Wright EC, Anthonisen NR (1989) Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis 139(6):1435–1438
89. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP (1999) Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160(6):1856–1861
90. Steiner MC, Barton RL, Singh SJ, Morgan MD (2003) Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. Thorax 58(9):745–751
91. Efthimiou J, Fleming J, Gomes C, Spiro SG (1988) The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 137(5):1075–1082
92. Franssen FM, Broekhuizen R, Janssen PP, Wouters EF, Schols AM (2004) Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. Chest 125(6):2021–2028
93. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF (1995) Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med 152:1268–1274
94. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI et al (2004) Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170(8):870–878
95. Singer HK, Ruchinskas RA, Riley KC (2001) The psychological impact of end-stage lung disease. Chest 120:1246–1252

96. Mills TL (2001) Comorbid depressive symptomatology: isolating the effects of chronic medical conditions on self-reported depressive symptoms among community-dwelling older adults. Soc Sci Med 53:569–578
97. Yohannes AM, Baldwin RC, Connolly MJ (2003) Prevalence of sub-threshold depression in elderly patients with chronic obstructive pulmonary disease. Int J Geriatr Psychiatry 18(5):412–416
98. Lacasse Y, Rousseau L, Maltais F (2001) Prevalence of depressive symptoms and depression in patients with severe oxygen-dependent Chronic Obstructive Pulmonary Disease. J Cardiopulm Rehabil 21(2):80–86
99. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–70
100. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
101. Pulmonary rehabilitation (1999) American thoracic society. Am J Respir Crit Care Med 159(5 Pt 1):1666–82
102. Strijbos JH et al (1996) A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. Chest 109(2):366–72
103. Lareau SC, Meek PM, Press D, Anholm JD, Roos PJ (1999) Longitudinal assessment of dyspnea in patients with chronic obstructive pulmonary disease. Heart Lung 28:65–73
104. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM (2006 Sep) Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 61(9):772–778
105. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R (2005) Characteristics of physical activities in daily life in COPD. Am J Respir Crit Care Med 171:972–977
106. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R (2006 Mar) Physical activity and hospitalization for exacerbation of COPD. Chest 129(3):536–44
107. Garcia-Aymerich J, Felez MA, Escarrabill J, Marrades RM, Morera J, Elosua R, Anto JM (2004 Oct) Physical activity and its determinants in severe chronic obstructive pulmonary disease. Med Sci Sports Exerc 36(10):1667–73
108. Sewell L, Singh S, Williams J, Collier R, Morgan M (2005) Can individualized rehabilitation improve functional indenendence in elderly patients with COPD? Chest 128:1194–1200
109. Bowen JB, Votto JJ, Thrall RS, Campbell M, Stockdale-Woolley R, Bandyopadhyay T, ZuWallack R (2000) Functional status and survival following pulmonary rehabilitation. Chest 118:697–703
110. Ringbaek TJ, Lange P (2005 May) Outdoor activity and performance status as predictors of survival in hypoxaemic chronic obstructive pulmonary disease (COPD). Clin Rehabil 19(3):331–8
111. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM (2006 Sep) Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 61(9):772–8
112. Raskin J, Spiegler P, McCusker C, ZuWallack R, Bernstein M, Busby J, DiLauro P, Griffiths K, Haggerty M, Hovey L, McEvoy D, Reardon JZ, Stavrolakes K, Stockdale-Woolley R, Thompson P, Trimmer G, Youngson L (2006) he effect of pulmonary rehabilitation on healthcare utilization in chronic obstructive pulmonary disease: the northeast pulmonary rehabilitation consortium. J Cardiopulm Rehabil 26:231–6
113. Puhan MA, Scharplatz M, Troosters T, Steurer J (2005) Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality – a systematic review. Respir Res 6:54
114. O'Donnell DE, Revill SM, Webb KA (2001) Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:770–777
115. Cooper CB (2006 Oct) The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 119(10 Suppl 1):21–31

116. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R (2005) Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 128:2025–34
117. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K (1991) Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 143:9–18
118. Puente-Maestu L, Sanz ML, Sanz P, Ruiz de Ona JM, Rodriguez-Hermosa JL, Whipp BJ (2000) Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. Eur Respir J 15:1026–1032
119. Maltais F, LeBlanc P, Jobin J (1997) Intensity of training and physiological adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:555–561
120. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA (2004) Effect of salmeterol on the ventilatory response to exercise in COPD. Eur Respir J 24(1):86–94
121. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, Kesten S, O'Donnell D (2005 Sep) Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest 128(3):1168–78
122. Appleton S, Smith B, Veale A, Bara A (2002) Long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 3:CD001104
123. O'Donnell DE, Lam M, Webb KA (1998) Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:1557–1565
124. O'Donnell DE, Lam M, Webb KA (1999) Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:542–549
125. Saey D, Debigare R, LeBlanc P, Mador MJ, Cote CG, Jobin J, Maltais F (2003) Contractile leg fatigue after cycle exercise. A factor limiting exercise in patients with COPD. Am J Respir Crit Care Med 168:425–430
126. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Kesten S (2005) Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 127:809–817
127. The Nocturnal Oxygen Therapy Group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 93:391–398
128. Medical Research Council Working Party (1981) Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 8222:681–686
129. Bradley JM, O'Neill B (Oct 2005) Short-term ambulatory oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 19(4):CD004356
130. LaCasse Y, Lecours R, Pelletier C, Begin R, Maltais F (2005) Randomised trial of ambulatory oxygenin oxygen-dependent COPD. Eur Respir J 25:1032–1038
131. Somfay A, Porszasz J, Lee SM, Casaburi R (2001) Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxemic COPD patients. Eur Respir J 18:77–84
132. Rooyackers JM, Dekhuijzen PNR, Van Herwaarden CLA, Folgering HTM (1997) Training with supplemental oxygen in patients with COPD and hypoxemia at peak exercise. Eur Respir J 10:1278–1284
133. Garrod R, Paul EA, Wedzicha JA (2000) Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. Thorax 55:539–543
134. Wadell K, Henriksson-Larsen K, Lundgren R (2001) Physical training with and without oxygen in patients with chronic obstructive pulmonary disease adn exercise-induced hypoxaemia. J Rehab Med 33:200–205
135. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R (2003) Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med 168:1034–1042
136. Ries AL, Kaplan RM, Limberg TM, Prewitt LM (1995) Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 122:823–832

137. Brooks D, Krip B, Mangovski-Alzamora S, Goldstein RS (2002) The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. Eur Respir J 20:20–29
138. Ries AL, Kaplan RM, Myers R et al (2003) Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. Am J Respir Crit Care Med 167:880–888
139. Troosters T, Gosselink R, Decramer M (2000) Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med 109(3):207–12
140. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. (1987) A measure of quality of life for clinical trials in chronic lung disease. Thorax 42:773–778.
141. Reardon J, Awad E, Normandin E, Vale F, Clark B, and ZuWallack RL (1994) The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. Chest 105:1046–1052.
142. ZuWallack RZ, Crouch R editors (2004) American Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for pulmonary rehabilitation programs, 3rd edition, Human Kinetics 2004.
143. ZuWallack R, Lareau S, Meek P. (2004) The effect of pulmonary rehabilitation on dyspnea. In Lung biology in health and disease: Dyspnea. Mahler D, editor. New York:Marcel Decker, Inc.
144. Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, Goldstein RS. (2002) Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. (3):CD003793.
145. Lacasse Y, Wong E, Guyatt GH et al. (1996) Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet 348:1115–1119
146. Haggerty MC, Stockdale-Woolley R, ZuWallack R. (1999) Functional status in pulmonary rehabilitation participants. J Cardiopulmonary Rehabil 19:35–42.
147. Griffiths TL, Burr ML, Campbell IA et al. (2000) Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 355:362–368.
148. Griffiths TL, Phillips CJ, Davies S et al. (2001) Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax 56:779-784
149. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life and health care costs in California. J Cardiopulmonary Rehabil 2004; 24:52–62.

11

Exacerbations of COPD

Sandra G. Adams and Antonio Anzueto

Key Points:

- The contemporary definition of an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum beyond the day-to-day variability sufficient to warrant a change in management.
- Acute exacerbations of COPD are associated with enormous cost, increased rate of decline of lung function in continuous smokers, poor quality of life, and high mortality.
- A trial of noninvasive mechanical ventilation (bi-level Positive Airway Pressure or bi-level PAP) should be attempted in patients with progressive respiratory acidosis, impending respiratory failure, or markedly increased work of breathing due to AECOPD because bi-level PAP is associated with success rates of 80–85% due to reduced intubation rates, lower rates of nosocomial infections, and improved mortality.
- Aggressive prevention and management of AECOPD are important to help reduce the cost, morbidity, and mortality associated with these episodes.

Keywords COPD exacerbation • pneumonia • dyspnoea • nosocomial infection

Introduction

Patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) comprise a heterogeneous population and vary widely in their clinical course. This chapter will review (1) the definitions and spectrum of characteristics of patients with AECOPD, (2) how acute exacerbations affect quality of life, lung function, and mortality, (3) common "Do's" and "Don'ts" in AECOPD, (4) factors associated with frequent exacerbations, (5) antibiotic selection and the impact of treatment failure, and (6) clinical parameters to risk stratify patients.

Definitions and Spectrum of Patients with AECOPD

The classic definition of AECOPD is based on the landmark trial by Anthonisen and colleagues and includes the presence one or more of the following respiratory symptoms: increased shortness of breath, increased sputum production, and/or sputum purulence [1]. The more contemporary definition by The European Respiratory

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_11,

Society (ERS) and The American Thoracic Society (ATS) guidelines state that an AECOPD is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum beyond the day-to-day variability sufficient to warrant a change in management [2]. The interpretation of data in the literature is difficult to generalize due to differences in the populations studied. Most of the early trials included patients of all ages with "chronic bronchitis," which was clinically defined as a cough for 3 consecutive months, for 2 years. There was no requirement of a minimum age or smoking history in many of these studies. In addition, there was no requirement for patients to have obstruction by PFTs to be included in these early studies. Because many patients included in these trials were only 20–30 years old and had normal lung function, the results are likely not generalizable or applicable to the most common types of patients with COPD who are treated for acute exacerbations today. In the mid-1990s, the FDA changed the inclusion criteria for patients who are included in therapeutic trials for AECOPD to more appropriately represent the true population of patients with this disease.

Currently, clinical trials for this population include patients older than 40 years of age who have a significant smoking history. In addition to the difficulties with inclusion, the definition of AECOPD was not standardized until the late 1980s, when Anthonisen et al. applied the Winnipeg criteria to a population of patients during his prospective, placebo-controlled trial [1]. According to these criteria, patients who are classified in the severe range include those with all three clinical symptoms (of increased shortness of breath, increased sputum production, and a change in sputum purulence) at initial presentation. In addition, many of the earlier studies do not measure or report the number of previous exacerbations, the presence of co-morbidities such as cardiovascular disease, or other factors that help define the "high-risk" population with AECOPD. Patients with AECOPD are often the most difficult to treat and challenging for healthcare providers.

Cost, Morbidity, and Mortality of Severe AECOPD

Episodes of AECOPD are associated with enormous health care expenditures, high morbidity, and significant mortality [2–6]. Acute exacerbations were nationally responsible for over 725,000 hospitalizations and 1.5 million emergency department visits in the year 2000 [3, 7]. Niederman and colleagues reported that age (patients >65 years) and inpatient treatment are the major determinants contributing to the overall cost of AECOPD [7]. The total cost for a select population was estimated at $1.2 billion for the 207,540 inpatients ≥65 years old versus only $452 million for 5.8 million outpatients in the same age group [7]. The mean length of stay was longer, and the in-hospital mortality rate was significantly higher, for those over the age of 65 years. Therefore, hospitalizations account for the majority of the healthcare expenditures for COPD of over $37 billion annually (Table 11.1). Miravitlles and colleagues estimated the mean total cost of an acute COPD exacerbation was €140 in a recent study of primary care in Spain [8]. Again, inpatient costs comprised the majority of the cost (58% of the total cost), followed by the total drug acquisition cost of 32.2%. These costs may not be applicable to other countries because of the differences in reference prices and management practices and healthcare systems; however, if we

Table 11.1 Cost of treatment of acute exacerbation of chronic bronchitis (Adapted from Ref. [7]).

Age group	Hospital costs (millions of dollars)	Outpatient costs (millions of dollars)
≥65 years	1,141	34
<65 years	408	14
All ages	1,549	48

consider the high prevalence of COPD and the frequency of exacerbations, it is easy to understand the magnitude of the healthcare burden derived from this disease [8]. In addition to the financial burden required to care for these patients, other costs such as days missed from work and severe limitations in quality of life are important features of this condition [8].

Patients with recurrent AECOPD suffer with significant morbidity associated with their condition [2, 6, 9]. Kanner and colleagues evaluated the loss of lung function of 5,887 smokers with obstruction to airflow by PFTs ($FEV_1/FVC < 70\%$, with FEV_1 of 55–90% predicted) in the Lung Health Study [10]. These investigators grouped all of the self-reported illnesses that occurred in this population together as lower respiratory infections (LRI), which included episodes of chest colds, influenza, bronchitis, and pneumonia. Several important findings were reported in this study: (1) continuous smokers had significantly more LRI than sustained quitters ($p = 0.0003$), (2) LRI rates increased with time in continuous smokers, but not in sustained quitters ($p = 0.008$), and (3) in continuous smokers with ≥1.5 LRI per year, over 44% of the mean predicted loss in lung function (measured by FEV_1) per year was attributed to acute exacerbations. Therefore, evaluation of the participants of this study with mild COPD, demonstrated that self-reported LRI were associated with significant long-term adverse effects on lung function in those who continued to smoke cigarettes [10].

Episodes of AECOPD negatively impact patients' quality of life for months following the acute event [11]. As reported by Connors and colleagues, the prospective cohort of 1,016 hospitalized patients with AECOPD who presented with hypercarbia ($PaCO_2 > 50$ mmHg) demonstrated only one fourth of patients to be both alive and able to report either a good, very good, or excellent quality of life 6 months after discharge [11]. Patients were interviewed at 2 and 6 months after their index hospitalization. At 2 months, the *S*ickness *I*mpact *P*rofile (SIP) was used to evaluate perceived health and functional status (high scores indicated worse health). At 6 months, 514 patients were interviewed about their activities of daily living. Approximately 54% required assistance with at least one activity of daily living and 49% considered their health status to be fair or poor. Trade-off scores showed that 64% of patients were willing to trade a year of their current health status for less than a year of excellent health.

The recovery of health related quality of life (HRQL) parameters after an acute COPD exacerbation may be determined by several factors. In a study by Spencer and colleagues, exacerbated patients who did not relapse during follow-up experienced an improvement in the chronic respiratory disease questionnaire (CRDQ) of 11.8 points at 1 month, and 17 points after 5 months of the onset of the exacerbation [12]. A change in score in any domain of the CRDQ of 0.5 or more represents the minimal clinically important difference that is noticeable to patients, and changes of the CRDQ of 1.0 or more and 1.5 or more represent moderate or large improvements, respectively [13]. These results indicate that recovery of health status after an exacerbation may take longer than previously expected. In contrast, median recovery time for lung function after an exacerbation is 6 days and for symptoms is 7 days [14]. However, this recovery

may be influenced by the severity of the exacerbation. The more severe the exacerbation, the longer it takes to recover. Seemungal and colleagues showed that only 75% of patients return to their baseline peak flow values 35 days following the episode [14]. These investigators also reported data on daily peak flow and respiratory symptoms for 1 year in 73 patients with COPD attending outpatient clinics (71% male, mean age 67 ± 8.3 years, mean FEV_1 40% predicted) [15]. Exacerbations were identified from the diary cards and from acute visits for treatment of exacerbations. The *S*t. *G*eorge's *R*espiratory *Q*uestionnaire (SGRQ) and *M*edical *R*esearch *C*ouncil (MRC) questionnaire were completed by patients at the end of the study. During the 1-year observation period, there were 190 exacerbations (mean 2.7 per patient; median, 3; range 1–10). Exacerbations were more frequent in patients with repeated previous exacerbations (OR = 5.5, $p = 0.001$). Using the median number of exacerbations, patients were classified as infrequent exacerbators (0–2) or frequent exacerbators (3–8). SGRQ total score was significantly worse in frequent exacerbators (mean difference 14.8, $p < 0.001$). In multivariable regression analyses, exacerbation frequency was strongly correlated with SGRQ total score and component scores. Miravitlles and colleagues studied a group of 336 patients with moderate-to-severe COPD who were followed over 2 years [16]. This study showed that patients with moderate COPD, who suffered more than 3 exacerbations during the study, had a change in SGRQ score that was 2 points per year worse than that of patients with less than 3 exacerbations ($p = 0.04$). This study confirms the impact of exacerbations on health status, but it is also important to point out that this deterioration in health status was not accompanied by a significant deterioration in lung function parameters [16]. Thus, these studies demonstrated that patients who suffered more exacerbations had significantly worse SGRQ scores than did infrequent exacerbators. They also show that HRQL questionnaires offer complementary information to lung function and respiratory symptoms, which helps monitor the course of recovery of an exacerbation. The slow progress of patients' HRQL after each exacerbation suggests that these patients will not return to their baseline condition and will experience further deterioration of their HRQL over time.

In addition to the cost and morbidity of AECOPD, the mortality rates are also high, particularly for those with severe disease. The Study to Understand Prognosis and Preferences for Outcomes and Rates of Treatment (SUPPORT) that enrolled patients who had severe acute exacerbation of COPD, reported an in-hospital mortality rate of 11% in patients with acute hypercapnic respiratory failure [11]. The 180-day mortality rate was 33% and the 2-year mortality rate was 49% (Fig. 11.1). The predictors of mortality include acute physiology and chronic health evaluation (APACHE III) score, body mass index, age, functional status 2 weeks prior to admission, lower ratio of partial pressure (tension) of oxygen to fraction of inspired oxygen (PO_2 to FiO_2), congestive heart failure, serum albumin level, cor-pulmonale, lower activities of daily living scores, and lower scores on the Duke Activity Status Index [11]. Mortality rates may be significantly higher for older individuals (age over 65 years) and reached 59% at 1 year following an AECOPD episode that required treatment in the intensive care unit in one study by Seneff and colleagues [17]. Another study evaluated clinical indicators of outcomes of 1,400 admissions for AECOPD to 38 British hospitals and was published in 2002 by Roberts and colleagues [18]. These investigators included patients who required mechanical ventilation and reported that the 90-day mortality rate was 14%, with a readmission rate of 34% within this 3-month period. Esteban and colleagues reported the results from their prospective cohort of 5,183 consecutive adult patients admitted to 361 intensive care units (ICU) who received mechanical ventilation for more than 12 h [19]. The ICU mortality rate of the subgroup of 10.1% who had

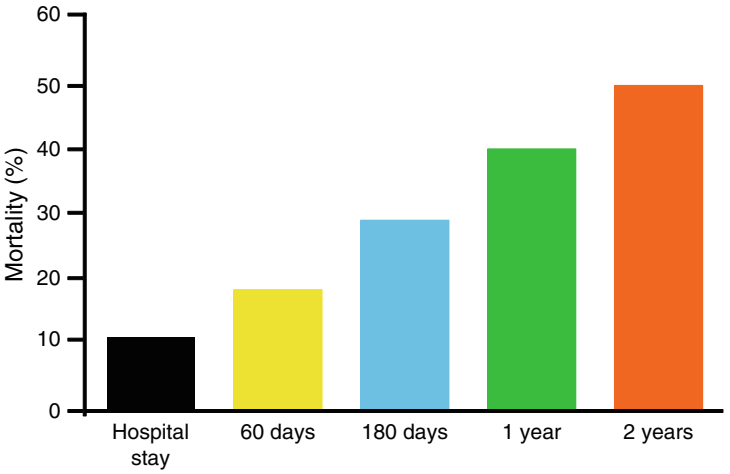


Fig. 11.1. Mortality after COPD exacerbation [11]

AECOPD was 22% (95% Confidence Interval, 19–26%), which was remarkably similar to the ICU mortality rate of 20% reported 27 years earlier by Petty and colleagues for a similar population of mechanically ventilated patients with AECOPD [20]. These and other studies reported in-hospital mortality rates of 11–24% at 1 year and 22–35.6% at 2 years [21, 22]. None of these studies specifically examined the prognostic influence of having only an acute exacerbation of COPD. Soler-Cataluna and colleagues were the first to report that severe exacerbations of COPD have an independent negative prognostic impact [23]. These investigators demonstrated that mortality rates are higher with increased frequency of severe exacerbations and with those requiring hospitalization. Patients with frequent exacerbations had the highest mortality rate ($p < 0.001$), with a risk of death 4.3 times greater (95% CI 2.62–7.02) than for patients requiring no hospital management [23]. Thus, exacerbations alone may be a significant factor associated with increased mortality in COPD, but the severity of the underlying disease may influence the outcomes of patients. Acute exacerbations of COPD are clearly associated with high cost, morbidity, and mortality, and place an enormous burden on the patients and healthcare providers that deal with this disease on a daily basis.

Common "Do's" and "Don'ts" in AECOPD

"Do's": Factors Shown to Be Helpful in Patients with AECOPD

1. Short-acting bronchodilators are useful during episodes of AECOPD and should be administered for acute symptoms.
2. A chest radiograph is useful for patients presenting to the emergency department or the hospital with AECOPD [24, 25]. This does not mean that a chest radiograph should not be obtained if a patient presents to your office; however, data are not clear regarding the utility of obtaining radiographs in this setting. Chest radiography may be helpful in an outpatient clinic setting if the patient appears ill, has crackles or egophony on lung exam (suggesting possible pneumonia), or has fever or pleuritic chest pain.
3. If the patient is hypoxemic, oxygen should be administered. For most patients, a goal of an oxygen saturation of 90% or greater is appropriate. However, if the

patient has a history of hypercapnia or elevated serum bicarbonate, oxygen should be administered to raise the patient's oxygen saturation to between 88% and 92%. Administering high levels of oxygen (that raises the oxygen saturations to >95%) to patients with hypercapnia may cause or worsen the respiratory acidosis (resulting in a reduced pH and markedly increased $PaCO_2$). Having said this, oxygen must be administered to patients who are hypoxemic (saturations <88–90%), even if respiratory acidosis occurs. In other words, the oxygen must NOT be taken away if respiratory acidosis develops; but other interventions, such as noninvasive ventilation (bi-level Positive Airway Pressure – bi-level PAP) or mechanical ventilation must be added to the oxygen to reverse the respiratory acidosis.

4. Patients with progressive respiratory acidosis, impending respiratory failure, or markedly increased work of breathing due to AECOPD benefit from noninvasive mechanical ventilation (bi-level Positive Airway Pressure – bi-level PAP). There have been at least six randomized controlled trials (RCTs) and multiple uncontrolled trials that have demonstrated success rates of 80–85% with bi-level PAP in reducing intubation rates, lowering the occurrence of nosocomial infections, and improving mortality in patients with AECOPD [24–26]. Bi-level PAP should not be utilized in patients with respiratory failure associated with severe pneumonia, acute respiratory distress syndrome, or sepsis however, because it has been associated with increased mortality in these patient populations. But for the respiratory failure associated with AECOPD, bi-level PAP is a very good option [26].
5. Systemic corticosteroids (prednisone) should be utilized for moderate to severe episodes of AECOPD [24, 25]. The optimal dose and duration of therapy have not clearly been defined because most of the trials in this area have been performed in inpatients. Recently, a randomized controlled trial was published that demonstrated improved outcomes in outpatients with AECOPD who were treated with 40 mg of prednisone for 10 days [27]. We know that a prolonged course (8 weeks) is equally effective to a 2 week course, but the longer course is associated with significantly more side effects [28]. Therefore, many experts recommend prescribing relatively low doses of prednisone (30–40 mg) for 7–14 days [29].

"Don'ts": Factors That Are Not Helpful in Patients with AECOPD

1. Measuring peak expiratory flow rates (PEFR) and/or spirometry acutely in patients with AECOPD is not indicated and is not helpful in assessing the severity of these exacerbations or the response to therapy [24, 25]. In contrast, these measurements are critical and very important in patients with acute exacerbations of *asthma*.
2. Mucolytics such as acetylcysteine are generally not beneficial in patients with AECOPD and may be associated with significant bronchospasm [24, 25].
3. Chest physiotherapy (percussion and postural drainage) has no role in patients with AECOPD unless they have documented area(s) of atelectasis on chest radiograph [24, 25].

Factors Associated with Frequent Exacerbations

In order to understand the impact of exacerbations on the natural history of COPD, the frequency of these events and the factors that are more likely associated with increased frequency need to be identified. Several investigators suggested that exacerbation frequency increases with disease severity [30, 31]. Patients with moderate COPD

(mean FEV_1 of 50–55% predicted) have been shown to suffer from a mean number of approximately 2 exacerbations per year [30, 31]. Greenberg and colleagues found that exacerbations defined as acute respiratory illnesses with increased cough, shortness of breath, or sputum production and/or a change in sputum color were more frequent in patients with moderate COPD (3 per year) than in those with mild COPD (1.8 per year) [32]. Using a symptom-based definition, Donaldson and colleagues reported that patients with severe COPD (GOLD Stage III, $n = 38$) had an annual exacerbation frequency of 3.43 per year compared with 2.68 per year in those with moderate COPD (GOLD Stage II, $n = 94$; $p = 0.029$) [33]. In an observational study, patients with mean FEV_1 of 47% predicted also presented a mean of 2 episodes per year, with this number dependent on the degree of functional impairment at baseline [34]. These investigators used a symptom-based definition of exacerbation and patients with FEV_1 >60% had mean 1.6 ± 1.5 exacerbations per year (mean ± SD), compared with 1.9 ± 1.8 with FEV_1 = 59–40% and 2.3 ± 1.9 with FEV_1 < 40%.

The results of follow-up studies show that patients who suffer a high number of exacerbations during a given period will continue to suffer frequent exacerbations in the future [35]. Therefore, frequency of exacerbations will depend on patients underlying severity of lung disease and number of prior exacerbations [36]. The following is a summary of the factors associated with increased frequency of exacerbation [37–42].

- Age 65 years or older
- Daily cough and wheezing
- Persistent symptoms of chronic bronchitis
- Chronic bronchial mucous hypersecretion
- Severity of impairment in FEV_1
- Frequent prior exacerbations

The Use of Antibiotics, the Specific Antibiotic Choice, and the Impact of Treatment Failure

The specific etiology of AECOPD is difficult to determine in an outpatient office setting on the basis of symptoms and signs. Although sputum studies can be potentially useful, they have significant limitations for routine use; including the delay in obtaining the results, cost, and lack of sensitivity and specificity. Bacterial infections can be identified in approximately 50% of patients with AECOPD [43]. Other factors such as pollutants, viruses, allergens, atypical infections, and other noxious stimuli also contribute to episodes of AECOPD. Some episodes of AECOPD will resolve spontaneously and do not require treatment with antibiotics [43]. There have been a number of clinical trials examining the use of antibiotics in the treatment of AECOPD. Many of the earlier studies showed minimal to no benefit of antibiotic prescriptions for acute exacerbations. In 1995 Saint and colleagues published the results of a meta-analysis of nine randomized, placebo-controlled trials (published between 1957 and 1992) examining the role of antibiotics in the treatment of AECOPD [44]. No single common outcome was reported in each of the studies included in this analysis. However, outcomes that were available for analysis and comparison in some of the studies include: (1) the mean number of days of illness, (2) the overall symptom score, and (3) the changes in peak expiratory flow rate. Analysis of the studies that provided data on expiratory flow rates, noted an improvement of 10.75 L/min in the antibiotic-treated groups. The authors concluded that this antibiotic-associated improvement was likely to be clinically significant; particularly in patients with low baseline peak flow rates and limited respiratory reserve.

In general, there are no reliable criteria for an individual patient with AECOPD to definitively distinguish between episodes that are caused by bacteria and those that are not. The currently available evidence supports the use of antibiotics in patients with two or three symptoms of AECOPD (increased shortness of breath, increased sputum production, and/or sputum purulence) [1, 24, 25]. One major problem with the evidence in this area is that the majority of the trials of antibiotics versus placebo in AECOPD were performed before 1990, prior to the development of significant antimicrobial resistance. Therefore, most of the recommendations regarding the use of antibiotics are based on expert opinion [2, 45, 46]. Treatment guidelines for AECOPD reflect the lack of an evidence-base data to provide specific recommendations for the use of antibiotics [24, 25]. More recently, the GOLD, ATS/ERS, and Canadian Thoracic Society guidelines recommend antibiotic choices on the basis of local sensitivity patterns of the most common pathogens associated with this condition [2, 5, 6]. The most common bacterial "core" organisms associated with AECOPD are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. However, some data suggest that patients with severe and very severe COPD have a higher risk for infections with Gram negative organisms (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Stenotrophomonas*, etc.) [47, 48]. A potential benefit of antibiotic therapy for patients with AECOPD is that antibiotics can reduce the burden of bacteria in the airways. Bronchoscopic studies, using sterile protected specimen brush, have demonstrated that approximately 25% of stable COPD patients are colonized (usually $\leq 10^3$organisms) with potentially pathogenic bacteria [49, 50]. However, a much larger percentage (50–75%) of patients with acute exacerbations have potentially pathogenic microorganisms in addition to significantly higher concentrations (frequently $\geq 10^4$ organisms) of bacteria in the large airways [49, 51–53].

Conventional end-points for efficacy of antibiotics treatment in AECOPD include the subjective report of improvement in symptoms and documentation of bacteriological resolution measured at 2–3 weeks after the treatment was started. These endpoints have been used for drug registration purposes, but lack clinical relevance. It has been suggested by several reports that the infection-free interval (i.e., the time to the next episode of AECOPD) may be a more suitable end-point in this patient population [54–56]. Recently, Wilson and colleagues showed a significant increase in the infection-free interval in patients with AECOPD treated with gemifloxacin over clarithromycin [56]. This study showed that a longer infection-free interval was associated with decreased hospitalization rates, which may translate to cost savings, improved quality of life, and potentially slower progression of the underlying airway obstruction. Because treatment with appropriate antibiotics significantly decreases the bacterial burden (and frequently eradicates the organisms that are sensitive) at the 72-h follow-up bronchoscopy, it is speculated that the proper choice of antibiotic reduces the risk of progression to more severe infections, such as pneumonia. The eradication of bacteria by antibiotics is thought to break the vicious cycle of infection (i.e., lung destruction leading to progression of the lung disease). To demonstrate this issue, Noiura and colleagues published a prospective, randomized, double-blind, placebo-controlled trial, evaluating the use of ofloxacin in 90 consecutive patients with AECOPD who required mechanical ventilation [57]. This study also demonstrated that significant a number of patients with severe AECOPD were infected with Gram-negative organisms (including *E. coli*, *P. mirabilis*, and *P. aeruginosa*). In addition to supporting the findings of isolating Gram negative organisms from patients with severe AECOPD, this trial demonstrated that treating these pathogens improves outcomes. The antibiotic-treated group had a significantly lower in-hospital mortality rate (4% vs 22%, $p = 0.01$) and significantly reduced length of hospital stay (14.9 vs 24.5 days, $p = 0.01$) compared

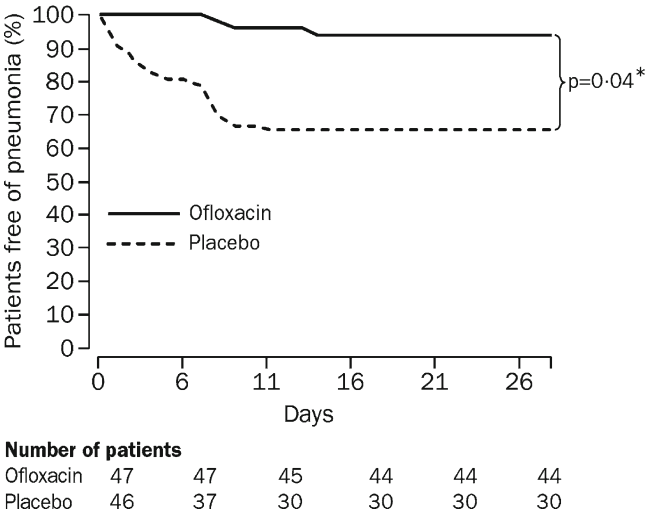


Fig. 11.2. Kaplan-Meir survival analysis of pneumonia free-interval comparing patients hospitalized with acute exacerbation of chronic bronchitis and treated with antibiotics or placebo. The risk of developing pneumonia is significant higher during the first 6 days since admission in the placebo treated patients (Reprinted from [57]. With permission)

with the placebo group. In addition, the patients receiving antibiotics were less likely to develop pneumonia than those receiving placebo, especially during the first week of mechanical ventilation (7.2 ± 2.2 days [range 4–11] vs 10.6 ± 2.9 days [range 9–14], $p = 0.04$ by log-rank test) (Fig. 11.2).

Relapses (treatment failures requiring return visit or hospitalization within 14–28 days of index visit) occur in up to 25% of patients and are associated with high morbidity [39, 51, 58, 59]. Patients who fail their initial outpatient therapy use the largest percentage of total resources spent for COPD, especially when they subsequently require hospitalization [8, 39, 58, 60]. However, many of these patients do not seek medical care despite persistent symptoms. Results of prospective clinical trials show a lower incidence of relapse, usually lower than 10%. These results cannot be extrapolated to everyday practice because patients included in the older clinical trials often consist of those with chronic bronchitis and ages ranging from 18 to 90 years, a significant proportion of nonsmokers, and individuals without ventilatory impairment (not COPD). In comparison, more recent studies address treatment failure in observational "real-life" studies and show a failure rate ranging from 12% to 26% [16, 33, 61]. Therapy failure is an important outcome, particularly since relapses are associated with high cost and morbidity.

If the use of antibiotics to treat AECOPD has all the potential benefits discussed, does the specific antibiotic choice matter? Anthonisen and colleagues assumed that all of the antibiotics were equivalent, thus the specific agent prescribed was not considered important [1]. In addition, most of the antibiotic trials that have been recently published were designed to compare a new antibiotic with an established compound for the purpose of new product registration and licensing. Equivalence is the desired outcome of such trials and therefore, the agent chosen for comparison is not considered important. In addition, these trials frequently include patients with poorly defined disease severity (often without any obstructive lung disease) and acute illness of minor severity. One study that addressed the issue of the specific antibiotic choice was a retrospective evaluation of the differences in outcomes of patients with AECOPD who received first-line (amoxicillin, trimethoprim-sulfamethoxazole, erythromycin, or tetracycline)

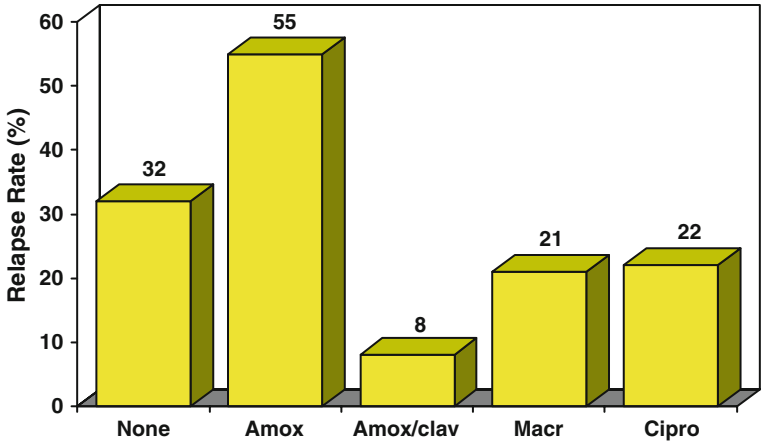


Fig. 11.3. Acute exacerbations of chronic obstructive pulmonary disease: 14-day relapse rates reference after treatment with or without antibiotics [38]. (Amox = amoxicillin, Amox/clav = amoxicillin/ clavulanate, Macr = macrolide, Cipro = ciprofloxacin)

versus third-line (amoxicillin-clavulanate, azithromycin, or ciprofloxacin) antibiotics [62]. In summary, patients who received the third-line antibiotics had significantly better outcomes including lower failure rates (7% vs 20%), prolonged disease-free interval (34 vs 17 weeks from initial exacerbation to the next AECOPD episode), and lower overall cost ($542 vs $942) compared with patients treated with one of the first-line antibiotics. Another retrospective study that addressed issues regarding the choice of antibiotic in the management of AECOPD demonstrated that overall patients who received antibiotics had lower relapse rates (19%) compared with those who did not receive antibiotics (32%), $p < 0.001$ [38]. However, patients who received amoxicillin had even higher relapse rates (54%) than those who did not receive any antibiotics (32%), $p = 0.006$ (Fig. 11.3). Other investigators have shown that the type of antibiotic the patients received during an exacerbation may impact outcome. Miravitlles and colleagues showed that the type of antibiotic used to treat AECOPD was associated with failure rates and late recovery. Patients who received moxifloxacin had a significantly lower rate of failure compared with those taking macrolides (odds ratio [OR] = 0.41; 95% confidence interval [CI] = 0.31–0.55) and amoxicillin/clavulanic acid OR = 0.35 (95% CI = 0.26–0. 45) [55]. It is important to point out that Wilson and colleagues found that differences observed in outcomes of antibiotic treatment could be confounded by factors related to medical history, severity of disease, and use of concomitant medications such as bronchodilators [56]. These studies demonstrated that the use of antibiotics was associated with a low therapy failure rate. In addition, appropriate antibiotic selection is important, based on the results of these studies as well as the widespread reports of increasing antimicrobial resistance to the common pathogens isolated in patients with AECOPD.

Clinical Parameters to Stratify Patients into Risk Groups

Because relapse after initial treatment for acute exacerbation may lead to prolonged disability, a new course of antibiotics, an emergency visit, or even hospital admission, it is crucial to identify patients most at risk for relapse. Identification of risk factors for

failure may permit the implementation of more aggressive broad spectrum treatment and close follow-up. In a further step, risk factors associated with relapse should be incorporated into management guidelines to aid in identifying at-risk patients. There are many approaches to managing patients with AECOPD, but it is important to note that the available recommendations are largely based on expert opinion and have not been prospectively evaluated in clinical trials [2, 45, 46, 63]. Having said this, an important first step in the management of AECOPD is to identify patients who should be hospitalized for their treatment. The ATS/ERS guidelines recommend that patients with the following criteria should be hospitalized: (1) the presence of high-risk comorbid conditions, including pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal or liver failure, (2) inadequate response of symptoms to outpatient management, (3) marked increase in dyspnoea, (4) inability to eat or sleep due to symptoms, (5) worsening hypoxemia, (6) worsening hypercapnia, (7) changes in mental status, (8) inability of the patient to care for her/himself (lack of home support), (9) uncertain diagnosis, or (10) inadequate home care [2].

Among the risk factors for relapse, severity of the underlying disease is one of the most important. Although impairment of respiratory function does not in itself make patients susceptible to infection, it does influence the outcome of a lower respiratory tract infection [56, 64]. Severe airflow obstruction, hypoxemia, and the presence of hypercapnia are all risk factors leading to poor outcome. Kessler et al. observed that carbon dioxide retention ($Paco_2$ higher than 44 mmHg) and pulmonary hypertension (mean pulmonary artery pressure at rest higher than 20 mmHg) were the best predictors of hospitalization [54]. Niewoehner and colleagues demonstrated that predictors of hospitalization from AECOPD included lower lung function, older age, unscheduled/emergency center visits in the prior year, cardiovascular comorbidity, and prednisone use at baseline [65]. In a retrospective study of 1001 COPD patients recruited in primary care, severity of FEV_1 impairment was independently associated with increasing risk of suffering two or more acute exacerbations of COPD per year; furthermore, FEV_1 impairment was associated with increasing risk of hospital admission during the same period [61]. Grossman et al. found that patients with severe airflow obstruction were more than four times more likely to be admitted to the hospital than were patients with mild to moderate disease, and the risk was similar for patients with disease for more than 10 years [66].

Frequent past exacerbations is also a factor that is strongly associated with recurrent exacerbations and risk of relapse [15, 37, 61]. A large study in the community found that the risk of failure increased by 7.6% for every extra visit to the primary care physician during the year previous to the study [55]. In a case-control study, García–Aymerich and colleagues observed that a low FEV_1, underprescription of long-term oxygen therapy in hypoxemic patients, and having been admitted more than three times the previous year were all significantly and independently associated with a high probability of admission in the future [42].

Significant cardiopulmonary comorbidity has been shown to be a risk factor for treatment failure, hospitalization, and mortality for AECOPD [16, 31, 38, 40, 41, 61]. The presence of ischemic heart disease or cardiac insufficiency correlated strongly with an increased risk of hospital admission for decompensated COPD with an odds ratio of 1.97 (CI 95% = 1.24–3.14) [61]. However, in a hospital-based population of severe COPD patients (29% with an FEV_1 <35% and 27% with oxygen therapy), no association between comorbidity and outcome was found [38]. These results suggest that cardiac comorbidity is a risk factor of poor outcome, particularly in patients with mild to moderate COPD; however, when the lung disease is severe, impairment in

Table 11.2 Summary of risk factors for relapse after ambulatory treatment of acute exacerbation of COPD.

- Coexisting cardiopulmonary disease
- Increasing number of previous visits to the general practitioner for respiratory problems
- Increasing number of previous exacerbations
- Increasing baseline dyspnoea
- Severity of FEV_1 impairment
- Use of home oxygen

pulmonary function prevails over cardiac disease. Additionally, comorbidity appears to be a risk factor for severe life-threatening exacerbations that may result in hospital admission and even be a cause of death, particularly in older patients [67]. Other risk factors for poor outcome include increasing age and the presence of chronic mucous hypersecretion (CMH), both of which are facilitating factors for exacerbations [41, 61]. Table 11.2 shows a summary of risk factors for relapse after ambulatory treatment of acute exacerbation of COPD [37, 38, 40–42].

One reasonable approach to the management of patients with AECOPD is based on utilizing certain clinical criteria to risk stratify patients (Table 11.3) [45, 46, 63]. *Group 1* includes previously healthy patients without significant underlying lung disease (near-normal FEV_1) who present with acute respiratory symptoms. These patients most likely have a post-viral tracheobronchitis and usually do not require treatment with any antibiotics. One study in this type of patients (Group 1) evaluated azithromycin versus Vitamin C and was prematurely stopped by the data safety monitoring committee because the interim analysis did NOT demonstrate any differences in outcomes (time to return to normal activities, health-related quality of life, etc.) [69]. Therefore, antibiotics are not indicated in patients stratified to Group 1 [45, 46, 63]. Patients in *Group 2* account for the majority of patients seen by primary care providers (>70% of patients who present with AECOPD) and include those with fewer than four episodes of AECOPD within the previous year, no significant cardiovascular co-morbidities, and an FEV_1 ≥50% predicted. These patients most likely have one of the "core" organisms and may be treated with one of the newer macrolides (azithromycin or clarithromycin), a newer cephalosporin, or doxycycline [45, 46, 63]. Patients in *Groups 3 and 4* include patients (usually <15% of the total population with AECOPD) with age over 65 years, 4 or more exacerbations within the previous year, FEV_1 <50% predicted, or the presence of one of the significant cardiac co-morbidities (CHF or IHD). These patients are at higher risk for relapse and therefore, treatment with either amoxicillin-clavulanate or a fluoroquinolone may be considered [45, 46, 63]. Controversy remains regarding length of treatment with antibiotics; however, some data suggest that short courses of antibiotics may be as effective as longer courses of antibiotics [70, 71].

Prevention

The two most important preventative measures are smoking cessation and active immunizations, including influenza and pneumococcal vaccinations. Active smoking cessation should be included in the therapy for all COPD patients. Influenza is an important cause of lower respiratory tract infections including AECOPD and pneumonia. Influenza A and B often reach epidemic proportions during the winter months. Epidemiological studies demonstrate that influenza vaccination markedly

Table 11.3 Potential antimicrobial options for an AECOPD based on host and pathogen factors (Based on data from [68]).

Category	Likely pathogens	Antimicrobial treatment
Uncomplicated AECOPD Age <65 years FEV_1 >50% predicted <4 exacerbations/year No comorbid conditions	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *H. parainfluenzae* Viral *M. pneumoniae* *C. pneumoniae*	Macrolide[a] Ketolides[b] Doxycycline Second or third generation cephalosporin Respiratory quinolone[b]
Complicated AECOPD Age >65 years FEV_1 < 50% predicted ≥4 exacerbations/year Comorbid conditions	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *H. parainfluenzae* Viral *M. pneumoniae* *C. pneumoniae* Gram negative enteric bacilli	Respiratory quinolone[b] Amoxicillin/clavulanate
Complicated AECOPD at risk for *Pseudomonas aeruginosa* infection FEV_1 <35% predicted Recurrent courses of antibiotics or steroids Bronchiectasis	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *H. parainfluenzae* Viral *M. pneumoniae* *C. pneumoniae* Gram negative enteric bacilli *Pseudomonas aeruginosa*	Fluoroquinolone with anti-pseudomonal activity[c]

[a]In active smokers *H. influenzae* infection more prevalent – azithromycin and clarithromycin demonstrate improved in vitro activity

[b]Levofloxacin, moxifloxacin, gatifloxacin, gemifloxacin, and telithromycin have activity against penicillin-resistant *S. pneumoniae*

[c]Ciprofloxacin and levofloxacin have enhanced antipseudomonal activity

reduces the frequency, morbidity, and mortality of lower respiratory infections [72]. In order to define the effects and benefits of the influenza vaccination in elderly persons with chronic lung disease, Nichol et al. conducted a retrospective, multi-season cohort study in a large managed care organization. The outcomes in vaccinated and unvaccinated individuals were compared after adjusting for baseline demographics and health characteristics [73]. Overall, the vaccination rates were greater than 70%. Hospitalization rates in unvaccinated patients for pneumonia and influenza were twice as high in the influenza season compared with the non-influenza periods (Fig. 11.4). Vaccinated patients had fewer outpatient visits, hospitalizations, and deaths. Therefore, the influenza vaccine should be given to all patients with COPD.

The polyvalent pneumococcal vaccine has been shown to be effective in preventing pneumococcal bacteremia and pneumonia [74]. The available 23-serotype pneumococcal capsule vaccine has been shown to have an aggregate efficacy of more than 60%, but tends to decline with age and reduced immune status [75]. This vaccine is also recommended in patients with COPD. There are no contraindications for use of either the pneumococcal or influenza vaccine immediately after an episode of pneumonia

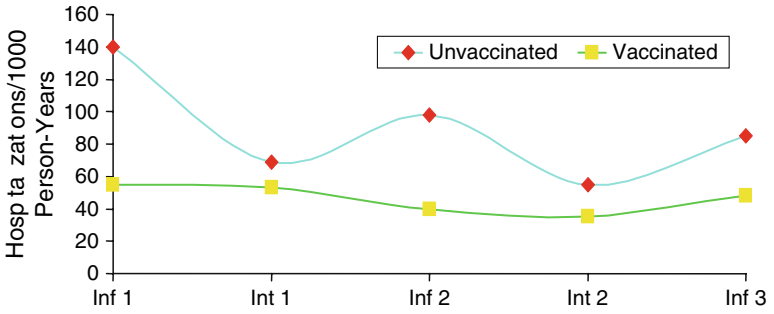


Fig. 11.4. Observed annualized rates of hospitalization for pneumonia and influenza among vaccinated and unvaccinated persons for each study period (Reprinted from [73]. With permission)

or AECOPD. Vaccines can be given simultaneously without affecting their potency. There are currently no other vaccines available in adults to prevent lower respiratory tract infections; however, vaccines intended to prevent infections due to non-typable *Haemophilus* species or *Pseudomonas* species are being developed but are not yet available.

In addition to the preventative measure mentioned in the previous paragraphs, clinical studies demonstrated that chronic maintenance therapy in patients with COPD can significantly decrease the frequency of exacerbations. A recent meta-analysis of nine placebo-controlled RCTs involving 4,198 patients with moderate to severe COPD demonstrated a 21% (95% confidence interval [CI], 10–31%) reduction in episodes of AECOPD in patients receiving a long-acting beta-2 agonist (LABA) [76]. The majority of the trials were of short duration (12–16 weeks), leaving the question of the benefit of long-term administration on AECOPD open. One long-term trial (52 weeks) showed a trend in the same direction. Pooled results from five published clinical trials (3,574 patients with moderate to severe COPD) of a long-acting anticholinergic agent (tiotropium) demonstrated a reduction in AECOPD rates compared with either placebo (Relative Risk [RR] 0.74; 95% CI, 0.62–0.89) or with ipratropium bromide (RR 0.78; 95% CI, 0.63–0.95), while Niewoehner and colleagues demonstrated a 23% reduction in episodes of AECOPD in the tiotropium-treated group of veterans compared with placebo [76, 77]. Inhaled corticosteroids (ICS) have also been shown in six placebo-controlled trials (1,741 patients) to reduce AECOPD rates by 24% (95% CI, 20–28%); although patients with more severe lung dysfunction (as measured by Forced Expiratory Volume in 1 s – FEV_1) had the most benefit from these agents [76]. Five clinical trials evaluated the effect of ICS on mortality. Pooled results of these five trials demonstrate a trend toward lower mortality rates (RR 0.78 with a 95% CI, 0.58–1.06) [76]. Two clinical trials (2,277 patients) demonstrated that the combination of agents (ICS plus LABA) is associated with lower exacerbation rates compared with monotherapy with LABA (RR 0.80; 95% CI, 0.71–0.90) or with placebo (RR 0.70; 95% CI, 0.62–0.78) [76]. A trend was observed toward decreased AECOPD compared with monotherapy with inhaled corticosteroids, but it did not reach statistical significance. More recently, an RCT demonstrated treatment with fluticasone propionate/salmeterol 250/50 significantly reduced the annual rate of moderate to severe exacerbations by 30.5% compared with salmeterol (1.06 and 1.53 per subject per year, respectively, $p < 0.001$) and the annual rate of exacerbations requiring oral corticosteroids by 40% ($p < 0.001$) [78]. Currently two agents (fluticasone propionate/salmeterol 250/50 and tiotropium bromide 18micrograms) are approved by the FDA to reduce AECOPD

[78, 79]. At the present time, the FDA has not approved any inhaled corticosteroid alone for use in any patients with COPD; but fluticasone propionate/salmeterol and budesonide/formoterol are approved and indicated for improving FEV_1 in patients with COPD and formoterol, salmeterol, arformoterol, and tiotropium are all approved for bronchodilation in all patients with COPD.

Summary

Exacerbations represent important events in the natural history of COPD and are associated with significant cost, morbidity, and mortality. Patients with frequent exacerbations often experience impaired quality of life and faster decline of lung function over time. In addition, exacerbations, particularly those requiring hospitalization, are responsible for largest proportion of direct costs expended for the management of COPD. Despite making substantial progress in understanding the etiology of COPD exacerbations, much still needs to be learned. The complexity of the host-pathogen interaction that determines the onset and course of exacerbations needs further exploration, including examining (1) host cellular and molecular mechanisms, (2) the determinants of pathogen virulence, and (3) their interaction with airway epithelial cells and macrophages. Novel methods of treatment and prevention would undoubtedly emerge from insight into the mechanisms and pathophysiology of exacerbations.

References

1. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA (1987) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 106:196–204
2. Celli BR, MacNee W (2004) ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23:932–946
3. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC (2002) Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. MMWR Surveill Summ 51:1–16
4. Anzueto A, Sethi S, Martinez FJ (2007) Exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 4:554–564
5. Global Initiative for Chronic Obstructive Lung Disease (GLOBAL) (2008) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: workshop. Updated ed. 2008. Available from: http://www.goldcopd.com/goldwr2008clean.pdf
6. O'Donnell DE, Aaron S, Bourbeau J et al (2007) Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. [Review] [366 refs]. Can Respir J 14(Suppl B):5B–32B
7. Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R (1999) Treatment cost of acute exacerbations of chronic bronchitis. Clin Ther 21:576–591
8. Miravitlles M, Murio C, Guerrero T, Gisbert R (2002) Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD*. Chest 121:1449–1455
9. Miravitlles M, Anzueto A, Legnani D, Forstmeier L, Fargel M (2007) Patient's perception of exacerbations of COPD – the PERCEIVE study. Respir Med 101:453–460
10. Kanner RE, Anthonisen NR, Connett JE, The Lung Health Study Research Group (2001) Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. Am J Respir Crit Care Med 164:358–364
11. Connors AF Jr, Dawson NV, Thomas C et al (1996) Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand

Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 154:959–967
12. Spencer S, Calverley PM, Sherwood Burge P, Jones PW, ISOLDE (Inhaled Steroids in Obstructive Lung Disease) Study Group (2001) Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:122–128
13. Juniper EF, Guyatt GH, Willan A, Griffith LE (1994) Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol 47:81–87
14. Seemungal TAR, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA (2000) Time Course and Recovery of Exacerbations in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 161:1608–1613
15. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA (1998) Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1418–1422
16. Miravitlles M, Ferrer M, Pont A et al (2004) Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 59:387–395
17. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA (1995) Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 274:1852–1857
18. Roberts CM, Lowe D, Bucknall CE, Ryland I, Kelly Y, Pearson MG (2002) Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. Thorax 57:137–141
19. Esteban A, Anzueto A, Frutos F et al (2002) Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 287:345–355
20. Petty TL, Lakshminarayan S, Sahn SA, Zwillich CW, Nett LM (1975) Intensive respiratory care unit. Review of ten years' experience. JAMA 233:34–37
21. Almagro P, Calbo E, OchoadeEchaguen A et al (2002) Mortality after hospitalization for COPD. Chest 121:1441–1448
22. Groenewegen KH, Schols AM, Wouters EF (2003) Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 124:459–467
23. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R (2005) Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 60:925–931
24. Bach PB, Brown C, Gelfand SE, McCrory DC (2001) Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 134:600–620
25. Snow V, Lascher S, Mottur-Pilson C (2001) Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 134:595–599
26. Girou E, Brun-Buisson C, Taille S, Lemaire F, Brochard L (2003) Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. JAMA 290:2985–2991
27. Aaron SD, Vandemheen KL, Hebert P et al (2003) Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 348:2618–2625
28. Niewoehner DE, Erbland ML, Deupree RH et al (1999) Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group.[see comment]. N Engl J Med 340:1941–1947
29. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 163:1256–1276
30. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK (2000) Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. [see comment]. BMJ 320:1297–1303

31. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J (1998) Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet 351:773–780
32. Greenberg SB, Allen M, Wilson J, Atmar RL (2000) Respiratory viral infections in adults with and without chronic obstructive pulmonary disease. Am J Respir Crit Care Med 162:167–173
33. Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA (2002) Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57:847–852
34. Miravitlles M, Mayordomo C, Artes M, Sanchez-Agudo L, Nicolau F, Segu JL (1999) Treatment of chronic obstructive pulmonary disease and its exacerbations in general practice. EOLO Group. Estudio Observacional de la Limitacion Obstructiva al Flujo aEreo. Respir Med 93:173–179
35. Gompertz S, Bayley DL, Hill SL, Stockley RA (2001) Relationship between airway inflammation and the frequency of exacerbations in patients with smoking related COPD. Thorax 56:36–41
36. Miravitlles M, Murio C, Guerrero T (2001) Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. DAFNE Study Group. Eur Respir J 17:928–933
37. Dewan NA, Rafique S, Kanwar B et al (2000) Acute exacerbation of COPD: factors associated with poor treatment outcome. Chest 117:662–671
38. Adams SG, Melo J, Luther M, Anzueto A (2000) Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 117:1345–1352
39. Murata GH, Gorby MS, Chick TW, Halperin AK (1989) Use of emergency medical services by patients with decompensated obstructive lung disease. Ann Emerg Med 18:501–506
40. Murata GH, Gorby MS, Kapsner CO, Chick TW, Halperin AK (1992) A multivariate model for predicting hospital admissions for patients with decompensated chronic obstructive pulmonary disease. Arch Intern Med 152:82–86
41. Antonelli Incalzi R, Fuso L, De Rosa M et al (1997) Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Respir J 10:2794–2800
42. Garcia-Aymerich J, Monso E, Marrades RM et al (2001) Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. Am J Respir Crit Care Med 164:1002–1007
43. Murphy TF, Sethi S (1992) Bacterial infection in chronic obstructive pulmonary disease. Am Rev Respir Dis 146:1067–1083
44. Saint S, Bent S, Vittinghoff E, Grady D (1995) Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. [see comment]. JAMA 273:957–960
45. Balter MS, Hyland RH, Low DE et al (1994) Recommendations on the management of chronic bronchitis: a practical guide for Canadian physicians. Can Med Assoc J 151(Suppl 10):5–23
46. Balter MS, La Forge J, Low DE et al (2003) Canadian guidelines for the management of acute exacerbations of chronic bronchitis: executive summary. Can Respir J 10:248–258
47. Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H (1998) Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. Chest 113:1542–1548
48. Miravitlles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, Gallego M (1999) Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. Chest 116:40–46
49. Monso E, Ruiz J, Rosell A et al (1995) Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med 152:1316–1320
50. Cabello H, Torres A, Celis R et al (1997) Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. Eur Respir J 10:1137–1144

51. Martinez JA, Rodriguez E, Bastida T, Buges J, Torres M (1994) Quantitative study of the bronchial bacterial flora in acute exacerbations of chronic bronchitis. Chest 105:976
52. Fagon JY, Chastre J, Trouillet JL et al (1990) Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Use of the protected specimen brush technique in 54 mechanically ventilated patients. Am Rev Respir Dis 142:1004–1008
53. Soler N, Torres A, Ewig S et al (1998) Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 157:1498–1505
54. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E (1999) Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:158–164
55. Miravitlles M, Llor C, Naberan K, Cots JM, Molina J, the EFEMAP study group (2005) Variables associated with recovery from acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease. Respir Med 99:955–965
56. Wilson R, Jones P, Schaberg T et al (2006) Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. Thorax 61:337–342
57. Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F (2001) Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. [see comment]. Lancet 358:2020–2025
58. Murata GH, Gorby MS, Kapsner CO, Chick TW, Halperin AK (1992) A multivariate model for the prediction of relapse after outpatient treatment of decompensated chronic obstructive pulmonary disease. Arch Intern Med 152:73–77
59. Ball P, Harris JM, Lowson D, Tillotson G, Wilson R (1995) Acute infective exacerbations of chronic bronchitis. QJM 88:61–68
60. Murata GH, Gorby MS, Chick TW, Halperin AK (1991) Treatment of decompensated chronic obstructive pulmonary disease in the emergency department – correlation between clinical features and prognosis. Ann Emerg Med 20:125–129
61. Miravitlles M, Guerrero T, Mayordomo C, Sanchez-Agudo L, Nicolau F, Segu JL (2000) Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. [comment]. Respiration 67:495–501
62. Destache CJ, Dewan N, O'Donohue WJ, Campbell JC, Angelillo VA (1999) Clinical and economic considerations in the treatment of acute exacerbations of chronic bronchitis. [see comment]. J Antimicrob Chemother 43(Suppl A):107–113
63. Balter MS, La Forge J, Low DE et al (2003) Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can Respir J 10(Suppl B):3B–32B
64. Papi A, Bellettato CM, Braccioni F et al (2006) Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 173:1114–1121
65. Niewoehner DE, Lokhnygina Y, Rice K et al (2007) Risk indexes for exacerbations and hospitalizations due to COPD. Chest 131:20–28
66. Grossman R, Mukherjee J, Vaughan D et al (1998) A 1-year community-based health economic study of ciprofloxacin vs usual antibiotic treatment in acute exacerbations of chronic bronchitis: the Canadian Ciprofloxacin Health Economic Study Group. Chest 113:131–141
67. Vilkman S, Keistinen T, Tuuponen T, Kivela SL (1997) Survival and cause of death among elderly chronic obstructive pulmonary disease patients after first admission to hospital. Respiration 64:281–284
68. Martinez FJ, Han MK, Flaherty K, Curtis J (2006) Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. Expert Rev Anti-Infect Ther 4:101–124
69. Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y (2002) Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. [see comment]. Lancet 359:1648–1654

70. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM (2008) Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. Thorax 63:415–422
71. Falagas ME, Avgeri SG, Matthaiou DK, Dimopoulos G, Siempos II (2008) Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother 62:442–450
72. Centers for Disease Control and Prevention (1995) Prevention and control of influenza: recommendations for the Advisory Committee on Immunization practices. MMWR Morb Mortal Wkly Rep 44:1–22
73. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T (1994) The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. [see comment]. N Engl J Med 331:778–784
74. Centers for Disease Control and Prevention (1991) Update on adult immunization: recommendations of the Immunization Advisory Committee Pneumococcal Disease. MMWR Morb Mortal Wkly Rep 40:42–44
75. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR (1993) Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. JAMA 270:1826–1831
76. Sin DD, McAlister FA, Man SF, Anthonisen NR (2003) Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA 290:2301–2312
77. Niewoehner D, Rice K, Cote C et al (2004) Reduced COPD exacerbations and associated health care utilization with once-daily tiotropium (TIO) in the VA Medical System. Am J Respir Crit Care Med 169:A207
78. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C (2008) Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med 102:1099–1108
79. Tashkin DP, et al. N Engl J Med. 2008; 359:1543–1554.

12

Home Management Issues

Claudio F. Donner

Key Points:

- Home care reduces the time spent in hospital by COPD patients, in particular for re-admissions
- Home care facilitates the hospital discharge for severe COPD patients, in particular those on long term oxygen therapy (LTOT) or ventilatory support
- Home care is an indispensable pre-requisite for home placement of patients on chronic ventilatory support
- Home care is a valid means to assure better compliance to pulmonary rehabilitation
- Home care is costly, and therefore should be used with discretion, i.e. only where justified by the cost/benefit ratio

Keywords COPD • home care • long-term oxygen therapy • noninvasive mechanical ventilation • rehabilitation • ventilatory support

Introduction

Home care services offer a great advantage for patients with respiratory disorders, especially infant or elderly patients, reducing the amount of time needed to be spent in hospital during an acute event, or removing altogether the need for hospitalisation [1]. Evidence would suggest that home care does not have negative effects on patients and, in the case of supported early discharge, home care may well reduce the risk of admission to long-term care or hospital readmission. It is thus an option that should be carefully considered by nurse specialists, clinicians and pulmonary specialists in programming the mix of community-based interventions that can best help patients cope with their respiratory disorder in daily life and maintain their independence.

However, it is necessary to understand which patients can best benefit from home care services. It is fundamental to establish the need for referral for home care, including identification of those patients with respiratory disorders who have received appropriate hospital care and can be discharged from the acute care setting to release beds (and save money). It is particularly important for the pulmonary specialist to understand the role of each member of the home care team and liaise adequately (passing on the necessary information and guidance, as appropriate) with the primary care clinician and others on the team [2].

Home care for respiratory patients includes a complex array of services delivered in an uncontrolled setting in which patients and families are integral members of the health

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_12,

care team. New models for the treatment of a variety of medical and surgical problems, including acute chronic obstructive pulmonary disease (COPD) exacerbation, are being implemented in Europe [3, 4]. For instance, in *supported discharge* or *hospital-at-home* models, patients are assessed for early hospital discharge with follow-up by respiratory specialist nurses through frequent telephone contact and home visits as needed [5]. Another model under investigation is the *acute respiratory assessment service*, in which COPD patients with acute exacerbation are assessed to see whether they are suitable candidates for managing the exacerbation at home with support from a home care team [6–10]. Chest physicians or nurses determine their eligibility for home management on the basis of assessment protocols in the emergency room, with follow-up as in supported discharge models. A third model, a *community-based care management service,* consists of respiratory specialist nurses and physical therapists who make regular, although infrequent, visits to COPD patients who have had more than three hospital admissions in the previous year. In this chronic care management service, patients receive education and support, and can call on help from the service during regular business hours if they need advice or help.

Chest physicians, general practitioners and nurse specialists providing home care need to have specific clinical knowledge and expertise, a patient-centred approach, and a thorough understanding of the cost and reimbursement structures for home care services. Complexity, lack of provider control, and the chronic nature of patient health problems all contribute to the difficulty in demonstrating improved patient outcomes resulting from home care. Future efforts at identifying effectiveness of respiratory home care will be more successful if they take these factors into account [11, 12].

Home health agencies, nurses, chest physicians and other providers, and their advocates, can play an important role in changing the general attitude towards home care as a solution that is both desirable and viable for the individual, and not just a cost-savings exercise. Future goals may include enhancing patient and family satisfaction, reducing the complications consequent upon hospitalisation, maintaining an acceptable quality of life for the patient, and enabling a comfortable and dignified death. Cost reduction should become a collateral benefit, instead of a primary goal for home health care. Figure 12.1 shows the services and personnel available in home care programmes [12–23].

Long Term Oxygen Therapy

LTOT reverses hypoxaemia and prevents hypoxia, and has been shown to improve life expectancy in patients with chronic lung disease [24, 25].

The mechanism for improved survival has yet to be completely delineated, but pulmonary hemodynamics appear to play a role [26–29]. A modest yearly decline in pulmonary artery pressure in association with oxygen therapy has been documented [26]. Pulmonary vascular resistance may be decreased in acute response to oxygen if the patient is nonoedematous, but not in patients with oedema [29].

Continuous oxygen therapy reverses secondary polycythemia, improves cardiac function during rest and exercise [30], reduces the oxygen cost of ventilation, and improves exercise tolerance [31, 32] and quality of life [33]. Hypoxaemic patients ($Pa,O_2 < 50$ mmHg) may experience neuropsychiatric deficits in abstract thinking, motor skills and perceptual motor abilities [34, 35].

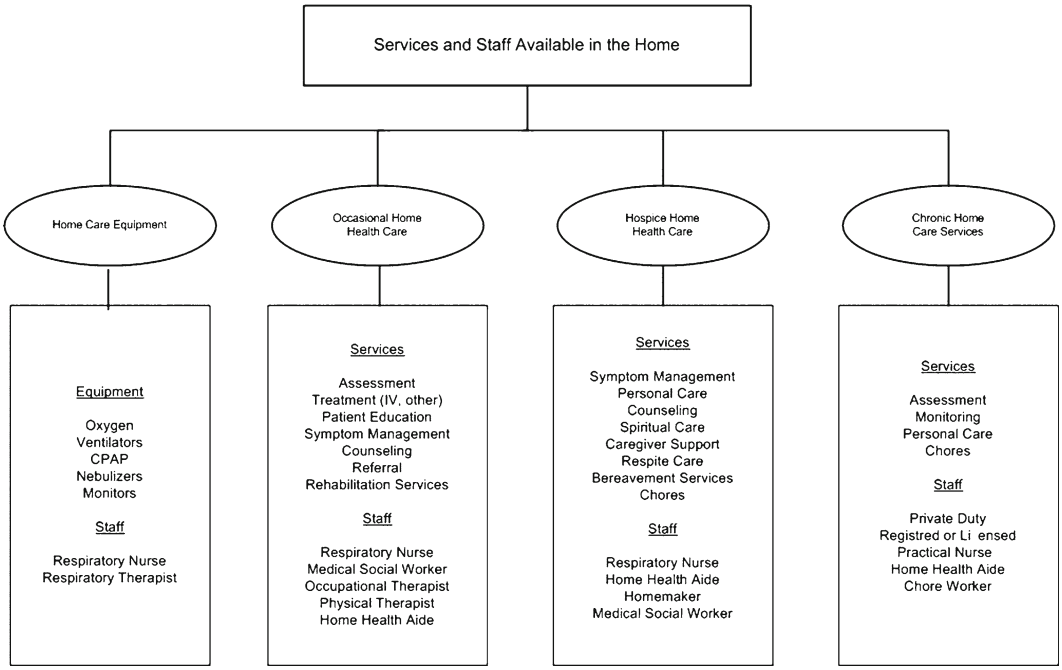


Fig. 12.1. Categories of home services for respiratory-related conditions (Modified from [1])

Hypoxaemic COPD patients candidate for LTOT are importantly symptomatic with poor health-related quality of life (HRQoL) but the effect of LTOT on the HRQoL remains uncertain. In a recent longitudinal study [36] HRQoL was measured in two groups of severe COPD – 43 patients starting LTOT and 25 patients not fulfilling criteria for LTOT and maintained on standard care. HRQoL was measured at baseline and at 2 and 6 months. At baseline the LTOT group showed significantly worse HRQoL as defined by the Chronic Respiratory Questionnaire (CRQ), total generic Dartmouth Primary Care Cooperative Information Project (COOP) Charts, and anxiety domain of the Hospital Anxiety and Depression Scale (HADS). Significant improvements in HRQoL were noted at 2 and 6 months in the LTOT group, whereas the non LTOT group showed a progressive decline in HRQoL. Using validated criteria for a minimal clinically significant improvement in CRQ, there were 28 (68%) and 26 (67%) patients with significant improvement at 2 and 6 months, respectively, in the LTOT group.

Oxygen Sources

Oxygen comes packaged in three types of systems: compressed gas, and liquid or oxygen concentrators. The trade-offs include size and weight of the device, storage capacity, cost and transfillability. The features of the systems are compared in Table 12.1.

Oxygen Delivery Devices

Continuous flow dual-prong nasal cannula is the standard means of oxygen delivery for the stable hypoxaemic patient. It is simple, reliable and generally well tolerated [37, 38]. The nasal cannula delivers a low flow of pure oxygen entrained in a much larger volume of atmospheric air (20.9% oxygen). Each litre per minute of oxygen flow adds about

Table 12.1 Comparison between gas, liquid and concentrator oxygen systems (Modified from [3]).

Features	Concentrator	Compressed gas	Liquid
Availability	Common	Common	Limited
Reliability	Good with regular service	Good but gauges may become inaccurate	Generally good but connector may freeze
Cost	Low but cost of electricity borne by patient	Moderate	High
Power: wall current	Necessary	Not necessary	Not necessary
Transfilling	Good only on special units that allow transfilling	Limited	Excellent
Ambulatory use	Good with gas transfill systems with conserver[a]	Good with conserver	Good alone and with conserver
Stationary weight	~15–25 kg	H cylinder ~100 kg	Reservoir ~50 kg
Use time at 2 L·min^{-1}	Continuous	2.5 days	8.9 days, special system >30 days
Portable weight	Portable units are not presently available	E cylinder ~10 kg with cart	~3 kg with no conserver
Use time at 2 L·min^{-1}	Unlimited	5 h	4 h
Portable weight with conserver	See portable gas transfill with conserver[a]	M6 cylinder ~2 kg	~1.5 kg with conserver
Use time at 2 L·min^{-1}	See portable gas transfill with conserver[a]	12 h	10 h

[a]Oxygen conserving device: some oxygen delivery devices and systems are available that combine the benefits of conserving devices with either gas or liquid systems. For example, the smallest liquid system weighs only ~1.5 kg and provides 10 h of oxygen. The smallest gas system weighs ~2 kg, refills from an oxygen concentrator and provides 12 h of oxygen. Availability of these systems varies by locality [3].

3–4% to the FI,O_2. A rough approximation is that 1 L·min^{-1} increases the FI,O_2 to 24%, 2 L·min^{-1} to 28%, and 3 L·min^{-1} to 32%. However, these small increases are usually sufficient to increase the arterial oxygen content to acceptable clinical levels.

The actual FI,O_2 for any particular patient is variable, depending on the anatomy and patency of the nares and moment-to-moment variation in respiratory rate and pattern, as well as the underlying pathophysiological process. The FI,O_2 is inversely related to the inspiratory rate, i.e. a more rapid inspiratory rate dilutes the oxygen flowing into the nares with more room air, thereby reducing the FI,O_2.

Some studies indicate that mouth breathing impairs oxygen delivery, while others show no such reduction [37, 38]. Most mouth breathers have some nasal airflow as well. Since only a small nasal inspiratory flow is necessary, and some oxygen is stored in the nasal and sinus passages, nasal oxygen delivery is still beneficial to these patients.

Oxygen-Conserving Devices

Oxygen-conserving devices function by targeting oxygen delivery to early inhalation. These devices were developed in an effort to improve the portability of oxygen therapy by reducing the litre flow and thereby enabling patients to use a smaller and lighter ambulatory system, or a standard system for longer time periods. Other advantages include a reduction of overall costs of LTOT and the ability to treat refractory hypoxaemia

Table 12.2 Comparison of oxygen-conserving devices (Modified from [3]).

Conserving device	Reservoir cannula	Demand pulse delivery	Transtracheal catheter
Conserving method	Store during exhalation	Early inspiration delivery	Store at end exhalation; bypass upper airway dead space
Efficiency gain (savings)	2:1–4:1	2:1–7:1	2:1–3:1
Reliability	Good	Less (possibility of mechanical problems)	Less (possibility of complications, e.g. mucus plugs)
Comfort	Adequate – good	Adequate – good	Good
Cosmetics	Obtrusive	Adequate	Good
Cost	Low	Higher	Higher
Unique advantages	Inexpensive Easy initiation Reliable Effective with exercise	Most efficient Alarms programmable	Cosmetics No nasal/ear irritation Good compliance Reduces minute ventilation
Disadvantages	Bulky on face	Mechanically complex Failure is possible	Special care + training required Possibility of surgical complications and mucus plugs

more effectively. There are three distinct devices: reservoir cannulae, demand pulsing oxygen delivery devices and transtracheal oxygen. Their characteristics are summarised in Table 12.2.

Prescribing Home Oxygen Therapy

Patient Education and Compliance

Patient education and monitoring of compliance are essential to assure the success of LTOT. Many patients harbour fears regarding the therapy. Some patients associate a need for LTOT with profound deterioration rather than prolongation of life and enhancement of quality of life. Some may experience anger or denial and therefore avoid using LTOT. Some patients avoid using oxygen in public, because they fear the reaction of others. Some may regard oxygen as an addictive substance and may therefore avoid its use as much as possible. These and other concerns need to be explored and discussed with the patient and family to provide the appropriate rationale for, and reassurance of the benefits of, LTOT (see Fig. 12.2).

Ventilatory Support

The introduction of long term ventilatory support has been one of the most important advances in the management of patients at home with chronic respiratory failure. Home ventilation is a growth area: rapid expansion during the 1990s was stimulated by the development of noninvasive ventilation (NIMV) via a mask and the recognition that an increased number of patient groups can benefit [39]. The benefit obtained from the therapy depends, however, on the underlying cause of the respiratory failure.

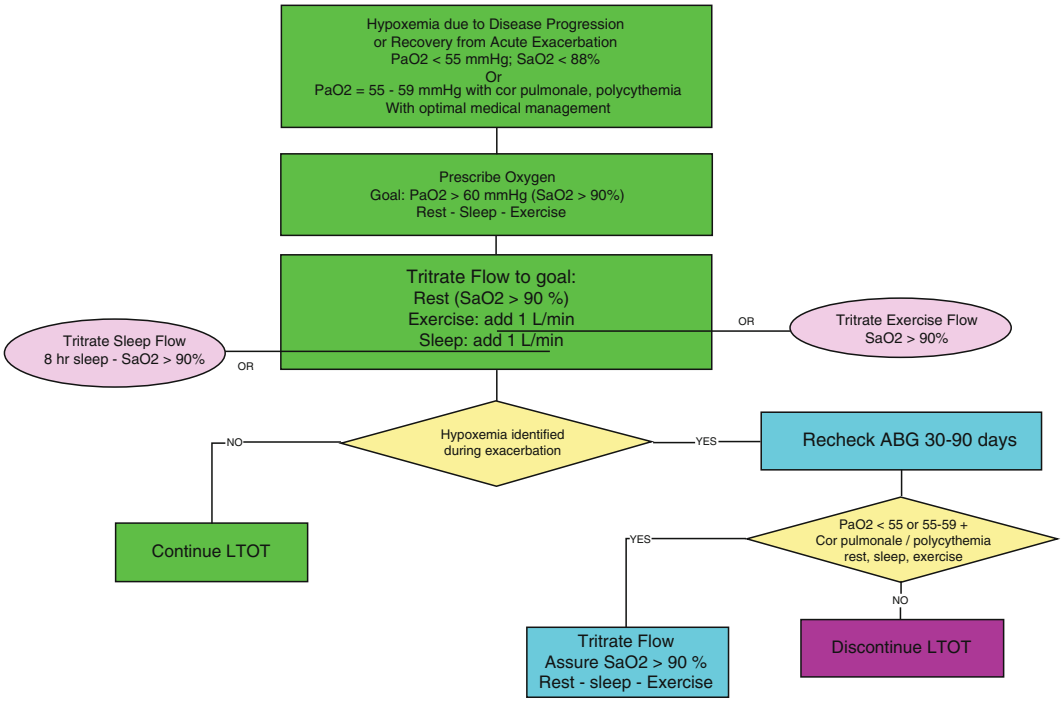


Fig. 12.2. Algorithm for long term oxygen therapy (Modified from [3])

Patients with chest wall disease and post-poliomyelitis show the best improvements in survival and quality of life. But even patients with progressive neuromuscular disease such as Duchenne muscular dystrophy and amyotrophic lateral sclerosis can also derive prolongation of life, palliation of symptoms and an improvement in quality of life. The longer-term effects of home mechanical ventilation in hypercapnic COPD are not so clear, and further large, well-designed controlled studies are required to evaluate the effects of non-invasive mechanical ventilation (NIMV) not only on survival, but also on quality of life and disease exacerbation [40, 41]. If the initial experience with NIMV in COPD is confirmed in larger trials, then this important therapy will be available for an even larger group of patients worldwide. At present chronic ventilatory support in COPD is reserved for patients who are unweanable after an episode of acute respiratory failure or unable to maintain an acceptable $PaCO_2$ value in time without partial ventilatory support (usually night-time).

Although patients receiving NIMV in the home outnumber those receiving invasive ventilation via tracheostomy [42], there is substantial variation in practice between European countries.

As stated before, home ventilation in COPD patients remains controversial, notwithstanding the presence of studies of undoubted interest that underline its efficacy and important role in the management of end-stage COPD [43–48]. Multi-centre randomised controlled trials on LTOT versus NIMV + LTOT in COPD have produced mixed results [40, 41], although certain subgroups, e.g. those with recurrent infective exacerbations requiring short-term NIV, patients aged >65 years, and those with uncontrolled hypercapnia on LTOT or symptomatic nocturnal hypoventilation, may benefit. At the other end of the age spectrum, children as young as a few months can be

successfully treated with non-invasive ventilation [43]. Most work on paediatric home ventilation centres has been carried out on children with congenital neuromuscular disease. Pressure preset bilevel ventilators are now the dominant form of ventilator in adults and children. Discharge planning is vital for the home ventilator patient and a sensible risk management strategy needs to be already in place. Long term ventilatory support is not realisable without a structured organisation including the hospital team and the home team in close cooperation. In particular, the home is responsible for providing home equipment and specialised nursing staff who will attend at home, evaluating and reinforcing correct health care habits and delivering community-based physician coverage.

The provision of home care to patients on ventilatory support is complex and challenging. The following aspects can contribute to a successful home placement:

1. An interdisciplinary approach assures that all aspects of care are included in the clinical plan
2. Clinical care pathways, algorithms, and standard protocols based on physician, caregiver, and clinical nurse collaboration are successful management strategies
3. Formal discharge planning meetings with participation of patients, families, caregivers, and social workers provide a forum for discharge planning and an avenue to address ethical issues such as advance directives, resuscitation status, and patient self-determination decisions
4. Full participation by nurses in all aspects of the unit's activities is a cost-effective strategy for maximising positive outcomes for patients and their families. Patients on chronic ventilatory support and their families are in great need of emotional support. Although a cost-benefit analysis is an effective way to evaluate the home ventilatory support programme, the human element must not be forgotten. This is a daily challenge for the staff and other health professionals engaged in the home care of the patient

Our goal should be to increase understanding of the challenges and opportunities present in the care of these patients and their families from the nursing perspective. Aspects of this model are adaptable to other health systems, and can be modified as appropriate. For example, in environments without caregivers, trained respiratory nurses can collaborate with dedicated physicians to coordinate the care of patients.

Methods

Artificial ventilation is achieved by delivering positive pressure to the airway (either invasively via an endotracheal tube (ET) or tracheostomy, or noninvasively via nasal/oral interface) or applying negative pressure to the chest wall.

Mechanical ventilation can be proposed, in the absence of exacerbations, as a long-term treatment for two principal reasons: to ensure patient survival in the case of permanently insufficient spontaneous breathing and to prevent episodes of acute respiratory failure (ARF).

1. In the first case, use of the ventilator is restricted to *patients who*, following intubation, *cannot be weaned* and thus are tracheostomised and prescribed home mechanical ventilation. Such patients, completely dependent on the ventilator, must be assisted totally by the ventilator in the case of apnea. Only volume-cycled ventilators are at present able to ensure support ventilation.

2. *Long-term preventive ventilation*, on the other hand, can be used in stable patients to diminish episodes of acute respiratory failure and, as a consequence, improve survival. Two possibilities exist:
   (a) *Invasive ventilation via tracheostomy*. The data reported in the literature come from retrospective studies or are based on historical controls: in one study there was no difference in the 5-year survival of such patients compared to groups treated only with traditional medical therapy [43]. Since a large proportion of these patients had been tracheostomised in the presence of satisfactory blood gas levels, this therapeutic approach is thus not recommendable at least in these stages of the disease.
   (b) *Non-invasive ventilation, using positive pressure ventilators with face or nasal mask or intermittent negative-pressure devices*. Non-invasive mechanical ventilation, whether by positive pressure [44–49] or negative pressure [50], has proved particularly effective as a treatment of acute or chronic respiratory failure, but its efficacy as a long-term preventive measure has still to be established. American authors showed that nocturnal ventilation for 3 months is poorly tolerated and fails to produce significant physiological effects apart from those concerning the neuropsychological state [47]. But more recently, British authors reported that non-invasive pressure support ventilation associated with oxygen therapy can improve the level of capnia, exercise tolerance and quality of sleep compared to oxygen alone [44, 48]. The discordance between the two studies can be explained by the fact that, in the first study, patients were recruited with a low level of capnia and were on controlled ventilation, whereas in the second the patients were generally more severe and were on total-assist ventilation.

LTOT remains the treatment of choice in respiratory failure due to COPD. However, it has been argued that non-invasive positive pressure ventilation (NIPPV) may offer advantages by controlling hypercapnia and reducing the work of breathing by resting the respiratory muscles in patients with severe airflow obstruction. At present the value of NIPPV in COPD is controversial. The **a**dvantages of mask ventilation are as follows:

- Intermittent delivery of ventilation
- No need for endotracheal intubation
- Use of different modalities of ventilation
- Normal swallowing, feeding, speech
- Physiological air warming and humidification
- Physiological cough
- Easier weaning
- Unchanged possibilities of endotracheal intubation

The predominant mode is now NIPPV, which has superseded tracheostomy-intermittent positive pressure ventilation (T-IPPV) in most cases where bulbar reflexes are intact and ventilatory dependence is not complete.

At present there are no precise indications concerning which is the better mode of ventilation since no studies on the subject exist in patients affected by COPD. However the following guidelines may be useful:

1. Positive-pressure devices are preferable to intermittent negative-pressure devices because they are easier to handle and less noisy
2. Nasal masks are better tolerated than face masks

3. Pressure-cycled ventilators seem better adapted to the needs of the patient since they are theoretically able to determine the patient's breathing pattern (flow volume and timing), whereas with volume-cycled ventilators the breathing pattern is "dictated" by the operator.

Indications

As mentioned previously the indication for NPPV in patients with COPD is the presence of hypercapnia. However, the "critical threshold" of $PaCO_2$ to implement this method is still controversial. It is important also to take into account the natural history of the underlying condition, in order to anticipate future needs such as, for example, the extension from nocturnal to diurnal ventilatory support and the associated co-morbidities, and the level of impairment that might determine the success of maintaining the individual at home.

Taking all of this into account, it would seem advisable to restrict home care to carefully selected patients who have: severe hypercapnia ($PaCO_2 \geq 55$ mmHg), a good stable ventilator response, good compliance to mechanical ventilation, valid caregiver support, and in whom the use of chronic ventilation is the only medical procedure suitable for obtaining a satisfactory arterial blood gas equilibrium.

Home Follow Up

Periodic assistance should be provided by a multidisciplinary team including nurses, respiratory therapist, psychologist, and physician. The ideal follow-up system should include one visit weekly by the respiratory therapist and one domiciliary check up by the physician [51]. Once a year, one short-term hospitalisation is recommended in order to check the efficacy of ventilatory therapy.

The education of patients and all the individuals involved in the home care constitutes a crucial aspect that is fundamental for the success of the home care itself. The education process should start as soon as possible during the patient's hospital stay. The most suitable method is bedside teaching in small groups for sessions of 30–60 min [52], including a description of the disease, the principles of assisted ventilation and the goals of long term ventilatory support. The training procedure should include routine and emergency management of all respiratory equipment as well as the administration of drugs and any other care, when needed. Before the discharge of patients from hospital to the home, all the care givers involved should be well prepared and confident in their ability to cope: a short trial of home care is strongly recommended before discharge.

Prior to discharge, the home environment needs to be checked to make sure that there is adequate space for the patient, family and other care givers, and adequate storage facilities [53–57]. There should be no fire, health or safety hazards present in the home. Electrical, heating, air-conditioning and ventilation systems need to be of an adequate standard. Finally, caregivers must have assured access to the medical team through a hotline or 24-h/day telephone service, for any advice or if the need arises for patient readmission.

Long term ventilatory support requires medical, nursing and technical resources. Medical support is best assured through an ongoing collaboration between the general practitioner and pulmonologist, in order to ensure clinical stability and manage co-morbidities and acute exacerbation of the disease. Usually, a regular monitoring of daytime and overnight gas exchange is recommended every 6 months or at least at

annual intervals. Nurses or respiratory therapists with experience in home mechanical ventilation represent the reference figure for home monitoring, providing an essential support for the many issues that usually challenge the family caregivers. Technical support includes the regular maintenance of all devices, with periodic checks. Advances in telematic communication systems have opened up new possibilities for home monitoring, making it possible to have continuous data on the clinical monitoring and also on the correct functioning of the devices. This aspect is particularly important for patients living in outlying areas [51].

With a careful selection of patients and a carefully designed programme, the home care of patients on chronic ventilatory support can improve not only the quality of life of these patients but also (despite its high costs) reduce the health care costs through a drastic cut in the costs of hospitalisation and through a reduction in the number of admissions to ICU for acute exacerbation.

Quality control of the equipment used in home mechanical ventilation is necessary in order to ensure that patients safely and accurately receive the prescribed ventilatory support. The aim of a 2005 European Survey [58] was to collect data on the quality-control procedures in different centres and countries. The survey was carried out in the context of a European Commission Concerted Action covering 16 European countries. The study was extensive and detailed, involving 326 centres, which provided home ventilation to >20,000 patients. The survey showed that (1) ventilator servicing was mainly carried out by external companies (62% of centres), with a servicing frequency ranging from 3 to 12 months; (2) interaction between servicing companies and prescribers was limited (only 61% of centres were always informed of major incidents); (3) participation of centres in equipment quality control was poor (only 56% of centres assessed that patients/caregivers correctly cleaned/maintained the ventilator); and (4) centres were insufficiently aware of vigilance systems (only 23% of centres). Moreover, the data showed considerable inter- and intra-country differences. The size of the centre was an important determinant of many of these quality-control aspects. This survey provides information that will enable the European Commission Concerted Action to formulate recommendations on procedures for home-ventilator quality control [58].

Home Rehabilitation

Rehabilitation is an ongoing therapeutic approach that lasts for the whole of the patient's life and for which it is very important to ensure the best possible compliance to treatment. Home care can play an important role in ensuring a good adherence to treatment in patients on pulmonary rehabilitation. For example, there are very positive results in the community-based programmes of rehabilitation, which have a very positive impact on quality of life and exercise tolerance [59]. Strijbos described a case series of patients, randomised to either a hospital outpatient pulmonary rehabilitation programme or a home-based programme lasting 12 months, with supervision twice a week. Similar improvements in both groups were observed at 3 and 6 months, but only the patients who underwent the home-based programme showed a sustained improvement at 18 months [60].

Although there is good evidence that rehabilitation improves HRQoL and functional exercise capacity, these improvements diminish with time almost certainly because of reduced patient compliance [61]. Pulmonary rehabilitation involves a coordinated multidisciplinary treatment plan that focuses on all aspects of the disease over time and

is indeed a component of integrated care of the COPD patient [62]. Home rehabilitation should play a major role in assuring sufficient adherence to treatment in COPD patients. However, given the high costs of actuating a good home care program, a cost-benefit analysis should be carried out, and home care should be reserved to severe patients and those who have frequent exacerbation of the disease and especially to patients who, after a trial period, have demonstrated a good compliance to the home management programme.

Summary

Home care services offer a great advantage for patients with respiratory disorders, especially for infant or elderly patients, reducing the amount of time needed to be spent in hospital during an acute event, or removing altogether the need for hospitalisation. Home care facilitates the hospital discharge for severe COPD patients, in particular for those on LTOT or ventilatory support, representing an indispensable pre-requisite for home placement of patients on chronic mechanical ventilation. The education of patients and all the individuals involved in the home care constitutes a crucial aspect that is fundamental for the success of the home care itself, and the education process should start as soon as possible during the patient's hospital stay.

Home rehabilitation should play a major role in assuring sufficient adherence to treatment in COPD patients. However, given the high costs of actuating a good home care programme, a cost-benefit analysis needs to be carried out, and home care should be reserved for severe patients and those who have frequent exacerbation of the disease, and especially for patients who, after a trial period, have shown a good compliance.

References

1. Statement on home care for patients with respiratory disorders. Am J Respir Crit Care Med 171:1443–1464 (2005)
2. Nici L, Donner CF, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltais F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T, on behalf of the ATS/ERS Pulmonary Rehabilitation Writing Committee (2006) American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173:1390–1413
3. Celli BR, MacNee W, and committee members (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23:932–946
4. Davies L, Wilkinson M, Bonner S, Calverley PMA, Angus RM (2000) "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomized controlled trial. BMJ 321:1265–1268
5. Richards SH, Coast J, Gunnell DJ, Peters TJ, Pounsford J, Darlow M-A (1998) Randomised controlled trial comparing effectiveness and acceptability of an early discharge, hospital at home scheme with hospital care. BMJ 316:1796–1801
6. Sala E, Alegre L, Carrera M, Ibars M, Orriols FJ, Blanco ML, Carceles F, Bertran S, Matta F, Font I et al (2001) Supported discharge shortens hospital stay in patients hospitalized because of an exacerbation of COPD. Eur Respir J 17:1138–1142
7. Gravil JH, Al-Rawas OA, Cotton MM, Flanigan U, Irwin A, Stevenson RD (1998) Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service. Lancet 351:1853–1855

8. Hernandez C, Casas A, Escarrabill J, Alonso J, Puig-Junoy J, Farrero E, Vilagut G, Collvinent B, Rodriguez-Roisin R, Roca J, partners of CHRONIC Project (2003) Home hospitalization of exacerbated chronic obstructive pulmonary disease patients. Eur Respir J 21:58–67
9. Skwarska E, Cohen G, Skwarski KM, Lamb C, Bushell D, Parker S, MacNee W (2000) Randomized controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease. Thorax 55:907–912
10. Cotton MM, Bucknall CE, Dagg KD, Johnson MK, MacGregor G, Stewart C, Stevenson RD (2000) Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Thorax 55:902–906
11. Shepperd S, Harwood D, Jenkinson C, Gray A, Vessey M, Morgan P (1998) Randomized controlled trial comparing hospital at home care with inpatient hospital care. I. Three month follow up of health outcomes. BMJ 316:1786–1791
12. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, Renzi P, Nault D, Borychi E, Schwartzman K et al (2003) Reduction of hospital utilization in patients with chronic obstructive pulmonary disease. Arch Intern Med 163:585–591
13. Neff DF, Madigan E, Narsavage G (2003) APN-directed transitional home care model: achieving positive outcomes for patients with COPD. Home Healthc Nurse 21:543–549
14. Naylor MD, Brooten D, Campbell R, Jacobsen BS, Mezey MD, Pauly MV, Schwartz JS (1999) Comprehensive discharge planning and home follow-up of hospitalized elders. JAMA 281:613–620
15. Spratt G, Petty TL (2001) Partnering for optimal respiratory home care: physicians working with respiratory therapists to optimally meet respiratory home care needs. Respir Care 46:475–488
16. Hernandez MTE, Rubio M, Ruiz FO, Riera HS, Gil RS, Gomez JC (2000) Results of a home-based training program for patients with COPD. Chest 118:106–114
17. Oh E-G (2003) The effects of home-based pulmonary rehabilitation in patients with chronic lung disease. Int J Nurs Stud 40:873–879
18. Strijbos JH, Postma DS, van Altena R, Gimeno F, Koëter GH (1996) Feasibility and effects of a home-care rehabilitation program in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 16:386–393
19. Puente-Maestu L, Sanz ML, Cubillo JM, Mayol J, Casaburi R (2000) Comparison of effects of supervised *versus* self-monitored training programmes with chronic obstructive pulmonary disease. Eur Respir J 15:517–525
20. Strijbos JH, Postma DS, van Altena R, Gimeno F, Koëter GH (1996) A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD: a follow-up of 18 months. Chest 109:366–372
21. Wijkstra PJ, van der Mark TW, Kraan J, van Altena R, Koëter GH, Postma DS (1996) Long-term effects of home rehabilitation on physical performance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153:1234–1241
22. Hughes SL, Weaver FM, Giobbie-Hurder A, Manheim L, Henderson W, Kubal JD, Ulasevich A, Cummings J (2000) Effectiveness of team-managed home-based primary care: a randomized multicentre trial. JAMA 284:2877–2885
23. Hermiz O, Comino E, Marks G, Daffurn K, Wilson S, Harris M (2002) Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. BMJ 325:938–940
24. Report of the Medical Research Council Working Party (1981) Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1:681–685
25. Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 93:391–398
26. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A (1985) Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 131:493–498

27. Oswald-Mammosser M, Weitzenblum E, Quoix E et al (1995) Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. Chest 107:1193–1198
28. Zielinski J, Tobiasz M, Hawrylkiewicz I, Sliwinksi P, Palasiewicz G (1998) Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. Chest 113:65–70
29. MacNee W, Wathen CG, Flenley DC, Muir AD (1988) The effects of controlled oxygen therapy on ventricular function in patients with stable and decompensated cor pulmonale. Am Rev Respir Dis 137:1289–1295
30. Zielinski J (1999) Effects of long-term oxygen therapy in patients with chronic obstructive pulmonary disease. Curr Opin Pulm Med 5:81–87
31. Dean NC, Brown JK, Himelman RB et al (1992) Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. Am Rev Respir Dis 146:941–945
32. Somfay A, Porszasz J, Lee SM, Casaburi R (2001) Dose-response effect of oxygen on hypertension and exercise endurance in nonhypoxaemic COPD patients. Eur Respir J 18:77–84
33. Eaton T, Garrett JE, Young P et al (2002) Ambulatory oxygen improves quality of life of COPD patients: a randomised controlled study. Eur Respir J 20:306–312
34. Grant I, Heaton RK (1985) Neuropsychiatric abnormalities in advanced COPD. In: Petty TL (ed) Chronic obstructive pulmonary disease. Marcel Dekker, New York, pp 355–373
35. Thakur N, Blanc PD, Julian LJ, Yelin EH, Katz PP, Sidney S, Iribarren C, Eisner MD (2010) COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. Int J Chron Obstruct Pulmon Dis 5:263–9.
36. Eaton T, Lewis C, Young P, Kennedy Y, Garrett JE, Kolbe J (2004) Long-term oxygen therapy improves health-related quality of life. Respir Med 98:285–93
37. Kory RC, Bergmann JC, Sweet RD et al (1962) Comparative evaluation of oxygen therapy techniques. JAMA 179:123–128
38. Gibson RL, Comer PB, Beckman RW et al (1976) Actual tracheal oxygen concentration with commonly used therapy. Anesthesiology 44:71–73
39. Mehta S, Hill NS (2001) Noninvasive ventilation. Am J Respir Crit Care Med 163:540–77
40. Muir JF, Cuvelier A, Tenang B (1997) European task force on mechanical ventilation COPD. Long-term home nasal intermittent positive pressure ventilation (NIPPV) plus oxygen therapy (LTOT) versus LTOT alone in severe hypercapnic COPD. Preliminary results of a European multicentre trial. Am J Respir Crit Care Med 155:A408
41. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N, on the behalf of the Rehabilitation and Chronic Study Group, Italian Association of Hospital Pulmonologists (AIPO) (2002) The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 20(3):529–538
42. Muir JF, Girault C, Cardinaud JP, Polu JM (1994) Survival and long-term follow up of tracheostomized patients with COPD treated by home mechanical ventilation. A multicentre French study in 259 patients. French Cooperative Study group. Chest 106:201–209
43. Fauroux B, Boffa C, Desguerre I, Estournet B, Trang H (2003) Long-term noninvasive mechanical ventilation for children at home: a national survey. Pediatr Pulmonol 35(2):119–25
44. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA (1995) Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 152:538–44
45. Gay PC, Hubmayr RD, Stroetz RW (1996) Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clin Proc 71:533–42
46. Casanova C, Celli BR, Tost L et al (2000) Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 118:1582–90

47. Strumpf DA, Millman RP, Carlisle CC et al (1991) Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis 144:1234–9
48. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA (1991) Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. Eur Respir J 4:1044–1052
49. Nava S, Navalesi P (2001) Domiciliary noninvasive ventilatory support. In: Similowski T, Whitelaw WA, Derenne JP (eds) Clinical management of chronic obstructive pulmonary disease. Marcel Dekker, New York, pp 731–758
50. Corrado A, De Paola E, Gorini M, Messori A, Bruscoli G, Nutini S, Tozzi D, Ginanni R (1996) Intermittent negative pressure ventilation in the treatment of hypoxic hypercapnic coma in chronic respiratory insufficiency. Thorax 51:1077–1082
51. Robert D, Vitacca M (2005) Ventilatory assistance at home. In: Donner CF, Ambrosino N, Goldstein RS (eds) Pulmonary rehabilitation. Hodder Arnold, London, pp 343–352
52. Thompson CL, Richmond M (1990) Teaching home care for ventilator-dependent patients: the patients' perception. Heart Lung 19:79–83
53. Findei A, Larson JL, Gallo A, Shekleton M (1994) Caring for individuals using home ventilators: an appraisal by family caregivers. Rehabil Nurs 19:6–11
54. Make B, Gilmartin M, Brody JS, Snider GL (1984) Rehabilitation of ventilator-dependent subjects with lung diseases. The concept and initial experience. Chest 86:358–365
55. Goldberg AI, Noah Z, Fleming M et al (1987) Qualità of care for life-supported children who require prolonged mechanical ventilation at home. QRB Qual Rev Bull 13:81–88
56. Miller MD, Steele NF, Nadell JM et al (1993) Ventilator-assisted youth: appraisal and nursing care. J Neurosci Nurs 25:287–295
57. Rozell BR, Newman KL (1994) Extending a critical path for patients who are ventilator dependent: nursing case management in the home setting. Home Healthc Nurse 12:21–25
58. Farre R, Lloyd-Owen SJ, Ambrosino N, Donaldson G, Escarrabill J, Fauroux B, Robert D, Schoenhofer B, Simonds A, Wedzicha JA (2005) Quality control of equipment in home mechanical ventilation: a European survey. Eur Respir J 26(1):86–94
59. Wijkstra PJ, Ten Vergert EM, Van Altena RM et al (1995) Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. Thorax 50:824–828
60. Strijbos JH, Postma DS, Van Altena RM et al (1996) A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. Chest 109:366–372
61. Goldstein RS, ZuWallack R (2005) Long term compliance after chronic obstructive pulmonary disease rehabilitation. In: Donner CF, Ambrosino N, Goldstein RS (eds) Pulmonary rehabilitation. Hodder Arnold, London, pp 369–376
62. Nici L, Raskin J, Rochester C, Bourbeau JC, Carlin BW, Casaburi R, Cote C, Crouch RH, Diez-Morales LF, Celli BR, Donner CF, Fahy BF, Garvey C, Goldstein R, Lane-Reticker A, Lareau SC, Make B, Maltais F, McCormick J, Morgan MDL, Ries AL, Troosters T, ZuWallack R (2009) Pulmonary rehabilitation what we know and what we need to know. J Cardiopulm Rehabil Prev 29:141–151

13

Co-Morbidities and Systemic Effects of COPD

Emiel F.M. Wouters and Erica P.A. Rutten

Key Points:

- Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with significant extrapulmonary effects, which may contribute to the disease severity in individual patients.
- An increasing amount of attention has been paid to causal relationships between one disorder and another and to an underlying vulnerability to different disorders.
- A patient-oriented approach to COPD needs to take into account that several coexisting components of the chronic disease can contribute to the experienced symptomatology.

Keywords Cardiovascular disease • Charlson index • extrapulmonary • inflammation • neoplasm • osteoporosis • systemic

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, and the burden of the disorder will continue to increase over the next 20 years. COPD is characterized by airflow limitation and classification or staging systems, which so far have been largely based only on the degree of airflow limitation despite the recognized imperfect relation between the extent of airflow limitation and the presence of symptoms. Especially in the later phase of the disease, COPD is now considered as a multicomponent disease and the use of all-cause mortality as a paramount end-point for the evaluation of novel therapies has focused attention on the role of co-morbidities as part of the natural history of the disease process. Unfortunately, there is no universally accepted definition of co-morbidity. Co-morbidity has been defined as the presence of more than one disease or health condition in an individual at a given time. This association may reflect a causal relationship between one disorder and another or an underlying vulnerability to both disorders or the appearance of the illnesses may be unrelated to any common etiology or vulnerability. Others define co-morbidity more strictly as the presence of a concomitant but unrelated pathological or disease process.

Smoking is still the most important risk factor for COPD. Cigarette smoking is the leading cause of preventable mortality in the developed world and is related to a wide spectrum of smoke-related diseases. The 2004 US Surgeon General's report reviewed

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_13,

Table 13.1 Smoking related disorders.

Cancer of the:	**The presence of:**
Bladder	Abdominal aortic aneurysm
Cervix	Atherosclerosis
Esophagus	Cerebrovascular disease
Kidney	Coronary heart disease
Larynx	Chronic obstructive pulmonary disease
Lung	Pneumonia
Acute myeloid leukemia	Respiratory effects in utero
Oral cavity and pharynx	Respiratory effects in childhood
Pancreas	
Stomach	
Reproductive effects:	**Other effects:**
Fetal death and stillbirths	Cataract
Reduced fertility	Diminished health status
Low birth weight	Hip fractures
Pregnancy complications	Low bone density
	Peptic ulcer disease

available data linking active cigarette smoking to disease and determined that smoking causes various pathologies [1] (Table 13.1). The relation between tobacco smoke and disease is complex and influenced by a number of factors. Presence of these diseases in patients diagnosed with COPD is at least related to a common vulnerability to the toxic and carcinogenic effects of tobacco smoke. Other diseases have probably a more mechanistic link to COPD: some evidence has implicated pulmonary and systemic inflammation as a common link between COPD and certain co-morbid conditions. This process of systemic inflammation may also increase the vulnerability of the patient to other smoke-related conditions. Indeed, COPD is characterized by an abnormal inflammatory response of the lung parenchyma to inhaled irritants and toxins and by the presence of systemic inflammation. By this mechanism, a link has been suggested between COPD and systemic complications such as cachexia or muscle wasting, osteoporosis, and cardiovascular diseases [2].

This chapter reviews current evidence with respect to muscle wasting, cardiovascular morbidity, endocrinological disturbances, disturbances in fluid homeostasis, and osteoporosis.

Prevalence of Co-Morbidities in COPD

A limited number of studies have systematically reviewed co-morbid conditions in COPD. A study conducted by UK General Practices reported that COPD is associated with many co-morbidities, particularly those related to cardiovascular-, bone-, and other smoking-related conditions [3]. Another study revealed that patients with COPD had a higher prevalence of certain co-morbid conditions, including coronary artery disease, congestive heart failure, other cardiovascular disease, local malignant neoplasm, neurological disease other than stroke with hemiplegia, ulcers, and gastritis [4]. Other studies have evaluated co-morbidity as part of the work-up of patients hospitalized for acute exacerbations [5, 6]. Co-morbidity in these studies was checked by the Charlson-index, an automated method to quantify co-morbidity for analytic purposes [7]. These studies showed that the Charlson index is associated with reduced survival. A recent evaluation of the USA National Hospital

discharge survey revealed that hospital diagnosis of COPD was associated with a higher rate of age-adjusted, in-hospital mortality for pneumonia, hypertension, heart failure, ventilatory failure, and thoracic malignancies and was not associated with a greater prevalence of hospitalization or in-hospital mortality for acute and chronic renal failure, HIV, gastro-intestinal hemorrhage, and cerebrovascular disease [8].

Further prospective studies based on adequate definitions of co-morbid conditions and objective criteria of these pathological conditions are urgently needed in order to objectify the problem of co-morbidity in COPD.

Muscle Wasting

Typical symptoms of patients with COPD are shortness of breath, first only during exercise and, at a later stage, also at rest [9, 10], and exercise intolerance. The latter is not only related to the respiratory impairment, but also to systemic features like weight loss and loss of fat-free mass (FFM). FFM gives a reflection of the metabolic active organs in which skeletal muscle is being the largest, and therefore, FFM depletion is associated with muscle weakness, reduced exercise tolerance [11], and impaired health status [12]. Body mass index (BMI) and overall systemic inflammation appeared to be the major determinants for hospitalization and death risk in end-stage respiratory disease [13]. However, Schols et al. [14]. showed that the FFMI (FFM corrected for height squared) was an independent predictor for survival. The authors concluded that FFMI provided information concerning disease prognosis that is beyond that provided by BMI. In line, measurement of the mid-tight cross-sectional area with computed tomography(CT) scan gave a better prediction of survival than did BMI [15]. Another study also reported that FFMI is a significant predictor of mortality, independent of covariates such as sex, smoking, lung function, and even BMI [16]. Since it is shown that the prevalence of muscle wasting in COPD is an independent predictor of mortality, the systemic effects of the disease cannot be overlooked any more. Therefore, objective assessment of FFM in the screening of COPD gained interest. In addition, to develop effective therapies and rehabilitation programs to prevent or treat muscle wasting in COPD, it is important to receive knowledge about the factors and the mechanisms involved in the process of muscle wasting.

Prevalence of Muscle Wasting

Weight loss commonly occurs in patients with COPD. A decreased body weight was reported in 49% of 253 patients with COPD in a pulmonary rehabilitation center [17]. Besides the prevalence of weight loss, the actual prevalence of muscle wasting is probably underestimated when extrapolated from body weight measurements because FFM may be reduced despite preservation of body weight. In a study by Schols et al. [14], a group of 412 COPD patients was divided into four subgroups, depending on their BMI and body composition. The results showed that the survival rate of patients suffering from cachexia (low BMI and low FFMI) or muscle atrophy (normal BMI and low FFMI) did not differ significantly, but was higher than the survival rate of patients suffering from semistarvation (low BMI and normal FFMI). Thus, independent of the BMI and disease severity, FFMI predicted the mortality rate. From a study conducted in a large out-patient group, it was concluded that the prevalence of FFM depletion was about 30% in patients with an FEV1 between 30% and 70% *pred* [18], and was associated with impaired peripheral muscle strength [19]. These data imply, together with recent national and international guidelines [20, 21], a need for a multidimensional index for the

staging for COPD that incorporates, besides the lung function measurements, assessment of the body composition. Indeed, recent national and international guidelines imply a need for a multidimensional index for the staging of COPD that incorporates assessment of the body composition, as well as the lung function measurements. In practical terms, bioelectrical impedance measurement (BIA) is an easy, noninvasive, validated, and convenient method of measuring the fat and fat-free body compartments.

Pathogenesis of Muscle Wasting

Whole body weight loss generally occurs when energy expenditure exceeds energy intake. Increased resting energy expenditure has indeed been reported in patients with COPD [22],which was independent of the severity of COPD but influenced the patients' physical performance [23].However, in numerous patients, daily activity level was decreased [24], so that their total energy expenditure was actually not different compared to healthy controls. Loss of body weight together with an excessive loss of skeletal muscle mass in chronic disease (cachexia) differs from loss of body weight alone by the presence of metabolic modifications related to the underlying disease. Inactivity *per se* contributes to a decrease of skeletal muscle mass via several adaptive changes such as reduced proportion of type I fibers and oxidative enzyme capacity, muscle fiber atrophy, and reduced muscle capillarization [25].However, peripheral skeletal muscle wasting in COPD is due not only to muscle disuse, but also to a form of myopathy that involves a whole cascade of factors that contribute to the development of muscle wasting (Fig. 13.1).

Wasting of skeletal muscle mass is always the result of an imbalance between muscle protein synthesis and muscle protein breakdown. A higher myofibrillar protein breakdown is shown in cachectic COPD patients, although there are no differences in

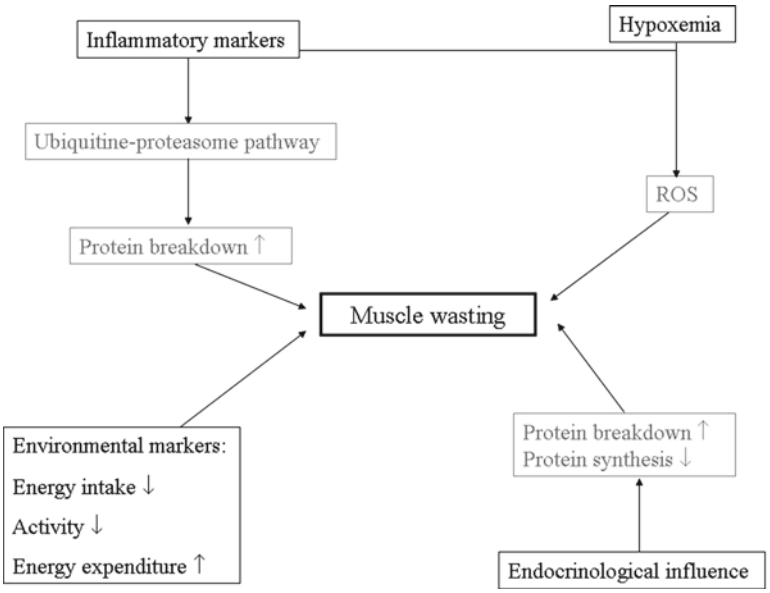


Fig. 13.1. Schematic overview of various factors involved in the development of muscle wasting in patients with COPD

whole body protein breakdown [26]. Various mechanisms are involved in the increased protein breakdown, but the ubiquitine-proteasome pathway is assumed to provide most of the proteolytic activity required for the degradation of myofibrillar protein [27]. The contribution of this pathway to the development of cachexia is a hot topic now, and a number of factors that play a crucial role in the activation of the ubiquitine-proteasome pathway have been detected. Animal studies have shown that the proinflammatory cytokines tumor necrose factor-α (TNF-α) and interleukine-6 (IL-6) stimulate the ubiquitine-proteasome pathway [28], via the activation of nuclear factor-kappa B (NF-κB) that was increased in underweight COPD patients [29]. A direct effect of inflammation on muscle wasting has not been found so far in humans, but many data in the literature strongly support a causal relationship. Like other chronic diseases, COPD is characterized by low-grade systemic inflammation [30, 31], which is associated with an increased production of TNF-α [32] and IL-6 [33]. In addition, it has recently been shown that exercise induces more systemic inflammation in muscle-wasted patients with COPD than in nonmuscle-wasted patients [34]. Besides systemic inflammation, patients with COPD also suffer from local lung inflammation as proved by the increased markers of soluble TNF-α and IL-6 in the sputum of clinically stable patients [35]. However, the results described in this manuscript did not show a direct correlation between local and systemic inflammation. On the other hand, a meta-analysis by Gan et al. [36] concluded that system inflammation is at least partly caused by the lung inflammation, although the mechanism behind it is not clear. In a recent paper, overexpression of pulmonary inflammatory markers in a mouse model showed decreased muscle and body weights, suggesting that local inflammation can extend through the system and cause muscle wasting [37]. Like inflammation, systemic hypoxia is a common finding in COPD and both factors contribute to the generation of reactive oxygen species (ROS) [38]. Oxidative stress occurs during an imbalance between the ROS production and the antioxidant capacity to scavenge these ROS products. In COPD patients, both altered antioxidant status [39, 40] and an increased systemic oxidative stress [41] at rest and after low-intensity exercise [42] have been shown. Moreover, an impairment of the adaptive response to oxidative stress is also reported in COPD patients [39, 43]. The exercise-induced oxidative stress was even more pronounced in muscle-wasted patients with COPD compared to – nonmuscle-wasted patients [34]. Although a relation between systemic oxidative stress and muscle wasting is well described [25], the mechanisms of how oxidative stress contributes to muscle wasting is not completely clear. ROS affect the cellular metabolism by damaging DNA and by affecting the cellular oxidative capacity, resulting in apoptosis. On the other hand, ROS can induce the production of IL-6, assuming that oxidative stress can act as the cause rather than the effect of systemic inflammation [34]. More research has to clarify the exact mechanism of how a disturbed oxidant-antioxidant balance induces muscle in COPD patients.

Besides an increased protein breakdown, a decreased muscle protein synthesis due to a disturbed cell regeneration capacity can also contribute to the muscle-wasting syndrome. Satellite cells are myogenic precursor cells that play an essential role in the regeneration of injured muscle and maintenance of muscle mass. The myogenic regulatory factor MyoD appears to be important in satellite cell differentiation. A number of factors have been implicated in the activation and proliferation of satellite cells. On the other hand, inflammatory markers like NF-κB and TNF-α have been shown to inhibit MyoD expression and can thus contribute to a disturbed regeneration capacity and hence muscle wasting.

Amino acids are the building blocks of muscle proteins and a disturbance in the amino acid metabolism can contribute to skeletal muscle wasting. In this view, plasma leucine concentration is often reduced in patients with COPD and this was associated

with decreased levels of FFM [44]. Moreover, skeletal muscle glutamate concentration is consistently decreased in patients with COPD [30, 44]. Both amino acids are able to induce an insulin response, and leucine increases protein synthesis, while glutamate plays a central role in the amino-transamination reactions. Therefore, disturbances in these amino acids can also contribute to muscle wasting.

Apart from the mechanical alterations in skeletal muscle of patients with COPD due to inflammation or hypoxia, endocrinological differences can also be a factor contributing to the muscle-wasting process in these patients. In this view, a reduced level of anabolic hormones in patients with COPD contributes to an impaired anabolic response needed for maintenance of skeletal muscle mass. In general, anabolic stimuli induce an increase in protein synthesis and a reduction in protein breakdown in order to stimulate muscle growth and development.

Consequences

FFM and FFMI are independent predictors of mortality in COPD [14, 45]. In a cohort of more than 4,000 patients treated with long-term oxygen therapy, it was shown that low body weight is an independent risk factor for mortality and the highest survival rate was reported in overweight patients [46].In addition, in patients with chronic respiratory insufficiency, the nutritional status was closely linked to the prognosis [47]. Furthermore, muscle wasting was associated with muscle weakness and reduced exercise tolerance [11], which was in turn related to less muscle strength [18, 19, 48] and impaired health status [12]. Furthermore, reduced body mass had an independent negative effect on muscle aerobic capacity in COPD patients [49]. The risk of being hospitalized with COPD was significantly increased in patients with low BMI and a limited 6-min walking distance [50].

Management

Even with the knowledge of the multifactorial pathogenesis of muscle wasting in patients with COPD, prevention and management of muscle wasting is complex (Fig. 13.2). Reasonably, nutritional supplementation is often prescribed in patients with low body mass, with or without low FFM, to increase their food intake and thereby help them to gain body weight. However, nutritional supplementation alone is overruled because there is a risk of their gaining only fat mass instead of FFM after restoration of energy balance. Also, normal food intake can be substituted by the supplement with the consequence that the total energy intake remains unchanged. Indeed, a meta-analysis of reported randomized trials of calorie supplementation given for more than 2 weeks found no significant improvements in anthropometry, lung function, or exercise capacity [51]. Physical exercise is often suggested as an anabolic stimulus to increase the protein storage in skeletal muscle instead of gaining fat mass. Whole body exercise training during an 8-week rehabilitation program was indeed able to increase body weight as a result of increased FFM, while body fat mass tended to decrease in normal-weight patients with COPD [52]. Additionally, in depleted patients with COPD who were entering an 8-week rehabilitation program, embedding of nutritional supplementation was effective in improving body composition and muscle function capacity [53]. However, a substantial number of patients failed to respond to nutritional support, as they were able to gain neither FFM nor body weight. These patients were characterized by elevated systemic inflammatory response [31, 54].

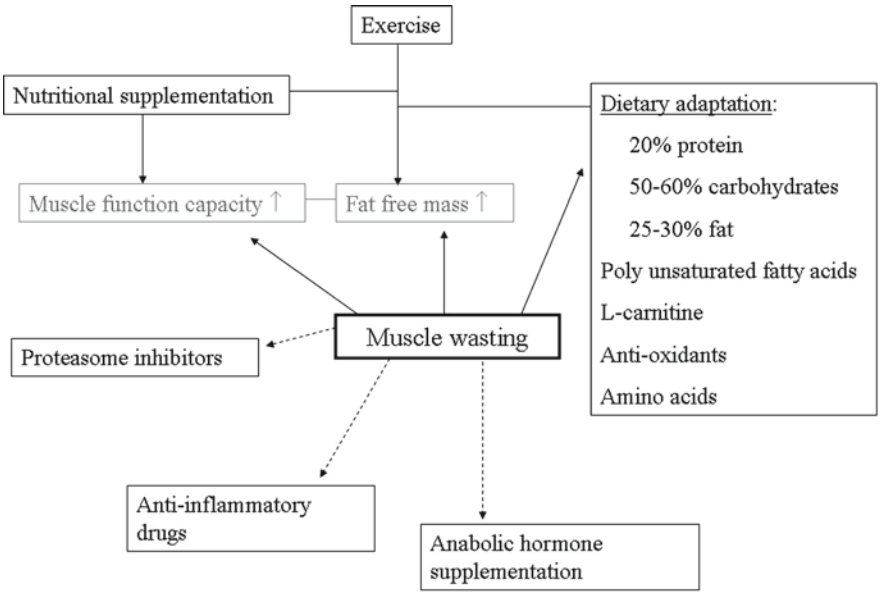


Fig. 13.2. Various options to modulate the muscle wasting process in patients with COPD

Research on hormonal treatment or treatment of their mediators to increase skeletal muscle mass is currently in the spotlights. For example, testosterone supplementation combined with physical resistance training resulted in increased lean body mass and muscle strength in men with severe COPD and low testosterone levels [55]. Ghrelin is another circulating hormone that is implicated in both energy metabolism and inflammation, and which stimulates secretion of growth hormone. Three-week treatment with ghrelin resulted in improved body composition, reduced level of muscle wasting, and increased functional capacity in cachectic patients with COPD [56]. Following the cascade, modulating the ubiquitine proteasome pathway by proteasome inhibitors such as Muscle Ring Finger 1 (MURF1) is shown to protect against muscle wasting [57]. However, although hormonal therapy or other pharmacological treatment may result in an increase in skeletal muscle mass and strength or a prevention of muscle wasting, other drug-related metabolic pathways may be affected as well. Before routine use can be accomplished, caution is warranted until research confirms the safety of their use.

Apart from nutritional or pharmacological therapy, dietary adaptation, possibly combined with an anabolic stimulus, is one of the most obvious modulations to prevent or treat nutritional depletion and muscle wasting in patients with COPD. Concerning macronutrient distribution, protein should correspond for 20% of the total energy intake, whereas the quantity of carbohydrates ranges between 50% and 60% and that of fat between 25% and 30% [58]. Adequate availability of nonprotein calories prevents the ingested protein from being consumed as a source of energy. Besides the macronutrient content, various specific nutrients play a role in the treatment of several underlying mechanisms involved in muscle wasting. Amino acids are the constituents of muscle proteins and a disturbed amino acid metabolism can contribute to the development of muscle wasting. Therefore, supplementation of specific amino acids can be an option to prevent loss of skeletal muscle. Subsequently, branched chain amino acids and particular leucine are suggested to play a pivotal role in the regulation of protein metabolism [59]. In line, the increased whole-body myofibrillar protein

breakdown in cachectic patients with COPD was associated with decreased plasma glutamate concentration [26]. Because glutamate plays a central role in the amino acid metabolism via transamination reactions, its role in the development of muscle wasting should be investigated. However, glutamate supplementation in patients with COPD influenced the intestinal area particularly [60]. Fish oil derived n-3 polyunsaturated fatty acids (PUFA) have been suggested to positively affect the inflammatory response and, hence, skeletal muscle wasting. Inflammatory cells contain high proportions of n-6 PUFA and low proportions of n-3 PUFA. Accordingly, n-3 PUFA supplementation of the diet of healthy volunteers resulted in a decreased production of proinflammatory cytokines [61]. However, an 8-week supplementation of n-3 PUFA capsules resulted in improved exercise capacity without increased FFM in normal weight patients with moderate-to-severe COPD [31]. L-Carnitine is an amine that functions in the energy metabolism in favor of the lipid metabolism, to spare muscle glycogen in muscle fatigue [62]. Normal-weight patients with COPD receiving L-carnitine supplementation during rehabilitation showed higher exercise tolerance and inspiratory muscle strength, but again no effect on nutritional status. The same story goes with antioxidant supplementation in periods of oxidative stress in patients with COPD. Supplementation of *N*-acetyl cysteine [62] or vitamin E or A [63] may result in a better oxidant/antioxidant balance but no data are yet available about the body composition or the prognosis of muscle wasting after long-term food supplementation of these food nutrients. Creatine phosphate is an explosive and anaerobic energy source in skeletal muscle. Creatine supplementation to enhance performance via increasing muscle mass is investigated in many population groups. In normal weight patients with COPD, creatine supplementation for 12 weeks during rehabilitation resulted in increased FFM, peripheral muscle strength, and endurance [64].

Hormonal Disturbances in COPD

Disturbances in the growth hormone/insulin-like growth factor-I (IGF-I) system, in the thyroid hormone system, and in the hypothalamic–pituitary–gonadal axis are discussed as these endocrinological disturbances can contribute to systemic manifestations of COPD as muscle weakness, muscle wasting, and osteoporosis.

Growth Hormone/Insulin-Like Growth Factor-I in COPD

Growth hormone provides stimulation for muscle growth and development. Growth hormone exerts its effects primarily by increasing levels of insulin-like growth factors. Healthy elderly individuals have decreased levels of IGF-I, the major mediator of growth hormone's anabolic action on muscle [65]. In addition to increasing age, systemic corticosteroids (commonly used to treat COPD exacerbations) are known to down-regulate the growth hormone system.

Little information is available regarding circulating growth hormone or IGF levels in COPD. Pituitary growth hormone secretion is pulsatile; circulating levels vary substantially over the course of the day. For this reason, growth hormone level in a single blood sample has limited importance. Most data about the function of the growth hormone axis have been inferred from measurement of IGF-I levels, which are considered to reflect integrated growth hormone secretion. The data that exist suggest that IGF-I levels in stable COPD patients tend to be low [66, 67], consistent with the impression that the growth hormone axis is suppressed by chronic disease. On the other hand, a few

studies suggested increased growth hormone concentrations in COPD and especially in hypoxemic COPD [68]. In COPD, physiological stress such as chronic hypoxia and bronchoconstriction could possibly induce an increase in growth hormone. In growth hormone-deficient adults, administration of growth hormone increases muscle mass and strength, and improves exercise performance [69]. However, while administration of growth hormone to healthy elderly individuals increases muscle mass, improvements in muscle strength and endurance have not generally been detected. Considering studies in patients with COPD, Suchner et al. [69] reported that 1-week treatment with growth hormone in six severely underweight (≥10% weight loss in the previous year) patients with COPD resulted in a positive nitrogen balance, and also in increased fat oxidation and energy expenditure, and decreased glucose oxidation. No changes in body weight, muscle function or lung function were found [70]. In an uncontrolled study design involving seven underweight (<90% of ideal body weight) patients with COPD, 3 weeks of recombinant human growth hormone administration increased weight and improved nitrogen balance and maximal inspiratory pressure, with no adverse effects [71]. A controlled study has examined whether administration of growth hormone enhances the benefits of exercise training in a study of 16 patients with COPD [66]. The group that received growth hormone plus endurance exercise training increased lean body mass, whereas the group that received exercise training alone did not. Despite the increase in muscle mass, no significant change in maximum inspiratory pressure or handgrip strength was observed in either group. There were no significant differences between groups in the improvements after training in peak oxygen uptake in an incremental exercise test; 6-min walk distance decreased in the growth hormone group but not the placebo group [66]. Altogether, it is difficult to find a rationale for the use of growth hormone in COPD at this time.

Thyroid Hormone in COPD

An important function of thyroid hormone is regulation of metabolism and thermogenesis. Abnormalities in thyroid function potentially influence energy balance and body composition. Hypermetabolism is commonly observed in patients with COPD; this has been attributed to increased energy expenditure both at rest [22] and during physical activities [72]. A hypermetabolic state in combination with insufficient dietary intake will result in a negative energy balance and may conceivably contribute to weight loss in COPD [73]. The prevalence of thyroid dysfunction in COPD and its role in pulmonary cachexia has not been extensively studied.

Thyroid hormone levels have been reported in a group of 11 clinically stable normal-weight patients with COPD [74]. Dimopoulou et al. [75] found that, as a group, patients with COPD had normal serum thyroid hormone levels. Serum total thyroxine (TT4), total triiodothyronine (TT3), resin T3 uptake (RT3U), reverse triiodothyronine (rT3), and thyroid-stimulating hormone (TSH) levels were measured. The free thyroxine and free triiodothyronine indexes along with the TT3/TT4 ratio were calculated; the latter was used as a marker of peripheral conversion of thyroxine into triiodothyronine. In patients with forced expiratory volume in one second (FEV_1) ≥ 50% predicted TT3, TT4, and TT3/TT4 ratio did not correlate with age, FEV_1, arterial oxygen tension (Pa,O_2) or inhaled corticosteroid use. In patients with FEV_1 < 50% predicted, however, there was a strong positive correlation between TT3/TT4 ratio and Pa,O_2 [75]. Based on this work, hypoxemia seems to be a determinant of the peripheral metabolism of thyroid hormones. Whether this constitutes an unfavorable adaptation in the metabolism of patients with COPD must be studied further. Another study investigated

neuroendocrine function before and after at least 4 months of long-term oxygen treatment (LTOT) in 12 male, stable, hypoxemic COPD patients [76]. Patients received thyroid-releasing hormone challenge before and after this period. Pretreatment thyroid hormone levels were within normal range. Low FEV_1 was associated with low basal and stimulated TSH levels. No significant hormonal changes were noted following an average of 8 months of LTOT for the entire study group. However, in a subgroup ($n=6$) with an increase in arterial oxygen saturation exceeding 7% points while receiving LTOT, nocturnal excretion of S-free thyroxin was reduced by 20%. Therefore, in patients with chronic hypoxemia, thyroid function is not influenced by LTOT except for a subgroup with severe nocturnal hypoxemia [76]. Taken together, no evidence has been presented so far that thyroid function is substantially altered in COPD, except perhaps in a subgroup of patients with severe hypoxemia.

Testosterone in COPD

In males, testosterone is secreted mainly by the gonads. Secretion is stimulated by luteinizing and follicle-stimulating hormones, which are produced in the pituitary. In females, circulating testosterone levels are much lower; the main sites of secretion are the adrenals and the ovaries. Total testosterone consists of ~30% of testosterone strongly bound to sex hormone binding globulin (SHBG), with the remaining 70% denoting bioavailable testosterone, including testosterone weakly bound to albumin (68%) and free testosterone (2%) [77].

Semple et al. [78] found low testosterone levels in acutely ill, hospitalized COPD patients with hypoxemia (Pa,O_2 ranging from 5 to 10 kPa). The degree of testosterone depression was correlated to the severity of arterial hypoxemia and hypercapnia [78]. Whether hypogonadism is correlated to disease severity in terms of low FEV_1 or impaired diffusing capacity, remains to be determined. Given the clinical impression that patients with COPD may demonstrate signs compatible with hypogonadism, Kamischke et al. [79] investigated the relationship between testosterone deficiency and corticosteroid use. Thirty-six males with COPD of whom 16 were receiving oral glucocorticoid medication (mean ± SD dose 9.4 ± 4.4 mg prednisolone) were cross-sectionally investigated. No differences were seen between the groups, except for a shorter 6-min walking distance in patients receiving glucocorticoids compared to patients without oral steroid therapy. Serum levels of testosterone were below normal (<12 nM) in 15 of 36 patients. Serum levels of free testosterone (free T) were decreased (<200 pM) in 25 of the 36 patients, including all patients receiving glucocorticoid treatment. In the 16 patients taking glucocorticoids, free T was inversely correlated with current glucocorticoid dosage and positively correlated with BMI. Therefore, glucocorticoid treatment appears to aggravate hypogonadism. A study in asthmatic males treated with maintenance systemic glucocorticoids showed reduced total and free testosterone concentrations, which could be restored by 12 months' therapy with intramuscular testosterone [80]. Additional factors besides hypoxemia and chronic use of systemic glucocorticoids may be involved in hypogonadism in COPD. There is evidence of an enhanced systemic inflammatory response associated with FFM wasting in COPD [81]. Although little information is yet available on the involvement of the systemic inflammatory response in testosterone metabolism, experimental data in healthy males showed that a single dose of recombinant human TNF induced an increase in luteinizing hormone, followed by a 50% decrease in serum total testosterone [82]. These data suggest that TNF affects the hypothalamopituitary-testicular axis at multiple levels and might be involved in hypogonadism in systemic diseases. Hypogonadism, accompanied by chronic disease

or not, is associated with wasting of body cell mass [83, 84]. In healthy, elderly males, no association was found between functional tests (isometric strength of upper and lower extremities, up-and-go test) and testosterone concentrations. The effects of testosterone supplementation have been studied in health and in certain diseases. Bhasin et al. [85] performed a randomized, double-blind, placebo-controlled study in 43 healthy males with experience in weight-lifting. They were randomized into four groups: placebo-no strength training, placebo-strength training (weight-lifting three times daily), testosterone (600 mg intramuscularly weekly for 10 weeks) – no strength training, and testosterone-strength training. Protein and energy intake were standardized. Of the males in the no-strength training groups, those with testosterone treatment had greater increases in FFM (3.2 kg vs 0.8 kg), in triceps and quadriceps muscle size, and in muscle strength. The males in the testosterone-strength training group had greater increases in FFM (6.1 kg, $p<0.001$), muscle size, and muscle strength than those in the two no-strength training groups. The males in the placebo strength-training group achieved an increase in FFM of 2.1 kg ($p=0.017$). It can be concluded from this well-designed study that supraphysiological doses of testosterone, especially when combined with strength training, increase FFM and muscle size and strength in healthy males. Only a few studies of anabolic steroid supplementation in COPD have been reported. In a study by Schols et al. [86] where a relatively low dose of nandrolone every 2 weeks for 8 weeks was administrated to males and females with COPD, an increase in lean body mass and respiratory muscle strength was observed. Six months of stanozolol administration to males with COPD resulted in increased body weight, lean body mass, but no endurance exercise changes [87]. Forty-nine subjects completed a 4-month uncontrolled observational study of oxandrolone; their body weight increased, but 6-min walk did not [88]. It seems appropriate to conclude that further evidence has to be gathered before testosterone repletion can be routinely recommended for patients with COPD.

Bone Disturbances in COPD

Osteoporosis has been recognized as one of the systemic effects of COPD. Osteoporosis is a systemic skeletal disease characterized by microarchitectural reduction of bone tissue, leading to a low bone mass, increased bone fragility, and thereby, increased fracture risk [89]. The preclinical state of osteoporosis is called osteopenia. Osteoporosis is commonly found in postmenopausal females and elderly subjects, or as a consequence of chronic disease or medical treatment. Different methods of bone mineral density (BMD) measurements can be used. Dual energy X-ray absorptiometry (DXA) is currently the most frequently used and is accurate, reproducible, and involves very low doses of radiation. BMD is expressed in standard deviation of means, the T and Z scores. The T score is a standard deviation compared to a young adult sex-matched control population. The Z score is a standard deviation compared to an age- and sex-matched control population [90]. One standard deviation reduction in the BMD increases the fracture risk by 1.5–3-fold [91]. Large epidemiological studies aimed at assessing the incidence and prevalence of osteoporosis within populations of patients with COPD at various stages of disease severity are lacking. Depending on the study population, as many as 35–72% of patients with COPD have been reported to be osteopenic, and 36–60% of patients with COPD have osteoporosis [92]. In 56% of the COPD patients admitted for pulmonary rehabilitation, there were indications of bone mineral loss, and osteoporosis was present in 36% of these patients [93]. Another study reported osteoporosis in 27.2% and osteopenia in 38.3% at the total

lumbar site; at the total hip site, osteoporosis was present in 19.8% and osteopenia in 51.9% of the patients [94]. Frequency of bone loss at either the hip or lumbar spine was related to the severity of lung disease. Based on the data from participants in the Third National Health and Nutrition Examination Survey in the United States, Sin et al. reported that airflow limitation was associated with increased odds of osteoporosis compared with no obstruction: airflow obstruction, independent of age, BMI, and medications including recent use of corticosteroids, increased the risk of osteoporosis in a severity-dependent fashion [95]. These and other data suggest that osteoporosis is found in a proportion of patients with COPD and confirms the view that long-term epidemiological studies are required in order to identify the patients who have a high risk to develop osteoporosis.

The etiology of osteoporosis in COPD is very complex and various factors may contribute to its pathogenesis. Potential risk factors are extensively reviewed in recent papers [90]. In the context of the current review, BMI and body composition, hypogonadism and endocrinological abnormalities, as well as the potential role of the chronic systemic inflammation, are important aspects to be discussed.

Some studies have reported that in underweight elderly patients, the bone mineral content is reduced compared to that in age-matched subjects with normal BMI [96, 97]. Others have reported positive relationships between the BMI and bone mass in patients with COPD [98, 99]. The possible relationship between weight loss and particularly loss of FFM and BMD in COPD is further explored in the study of Bolton et al. [94]. These authors reported that loss of FFM and loss of BMD were related, occurred commonly, and could be subclinical in patients with COPD. Furthermore, they demonstrated increased excretion of cellular and bone collagen protein breakdown products in those patients with low FFM and low BMD, indicating a protein catabolic state in these patients.

Hypogonadism and the reduced availability of sex hormones contribute to the development of osteoporosis. In addition to sex hormones, the insulin-like growth factors play a potential role in the development of osteoporosis. Insulin growth factor 1 (IGF-1) may influence bone mass directly or through its role in the preservation of the skeletal muscle mass. Further studies are needed to analyze the potential link between IGF-1 activity on the bone and skeletal muscles, and the pathogenesis of osteoporosis [90].

Systemic inflammation may have an association with loss of bone, with similar relationships reported in other chronic diseases [90, 100, 101]. In vitro, both IL-6 and TNFalpha stimulate osteoclasts and increase bone resorption [102–106]. Further research is required to evaluate the possible relationships between systemic inflammation and bone loss in COPD.

Systemic inflammation is particularly linked to activation of the osteoclastogenesis by the OPG/RANK/RANKL system. Differentiation, activation, and survival of osteoclasts are regulated by the balance between RANKL (RANK ligand) and osteoprotegerin (OPG). OPG is also known as osteoclast inhibitory factor and is a TNF receptor family member, which functions as a decoy receptor. RANKL is also a TNF family member. RANKL exhibits its activity thorough RANK (receptor activator of NF-κB), another membrane-bound member of the TNF receptor family [107–109]. RANKL is produced in bone marrow by osteoblasts, and both osteoblastic and fibroblastic stromal cells. Known inducers of bone resorption and hypercalaemia, such as IL-1, TNFa, parathyroid hormone (PTH), PTH-related peptide (PTHrp), Vitamin D, and others act indirectly through production of RANKL, so OPG can be considered as a natural RANKL antagonist of osteoclast activity independent of inducing cytokine [110] (Fig. 13.3). In this way, OPG may provide a pharmacological tool for osteoporotic and erosive bone disorders [111].

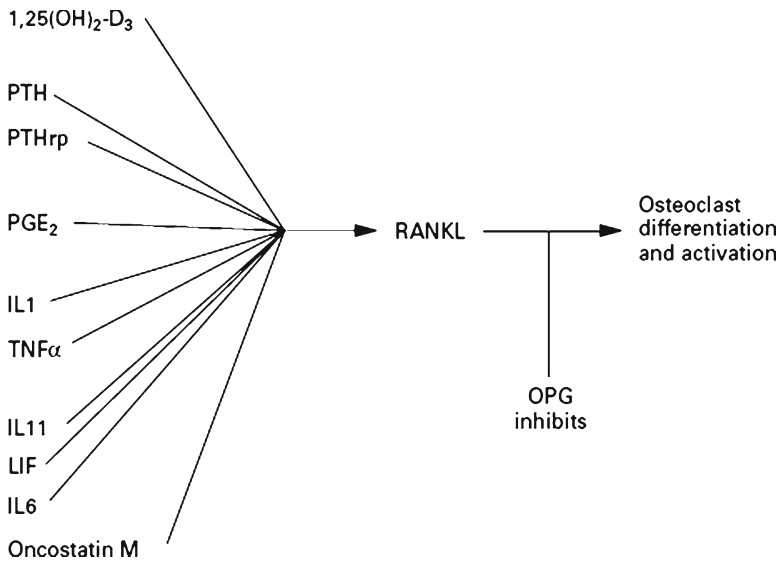


Fig. 13.3. The balance of RANKL and osteoprotegerin (*OPG*) controls osteoclast activity. Most (all?) known inducers of bone resorption and hypercalcaemia act indirectly through production of RANKL, hence OPG can be used pharmacologically to control osteoclast activity independent of the inducing cytokine

Disturbances in Fluid Homeostasis

COPD commonly leads to massive oedema and the development of cor pulmonale. The mechanisms by which patients with COPD retain salt and water are not completely understood. Little information is available on changes in body fluid volumes in patients with COPD, and the few available data are conflicting [112–116]. Although there is certainly volume excess at advanced stages when gross oedema is present, the extent to which expansion of the extracellular volume occurs at earlier stages is not clear. Both hypoxemia and hypercapnia can affect renal sodium excretion in severe COPD. Clinically stable hypercapnic patients commonly show impaired excretion of sodium and water, and correlations have been found between the degree of hypercapnia and the impairment in sodium excretion. Renin and aldosterone concentrations are inversely correlated with total sodium loss, both in patients with severe but stable COPD and those with acute respiratory failure [117–120]. Hypoxemia causes a significant fall in urinary sodium output, with no changes in water excretion, probably related to a decline in glomerular filtration rate [121]. Correction of hypoxemia results in increased natriuresis [122]. Patients with COPD probably have impaired ability to excrete sodium and their kidneys are likely to be in a sodium-retaining state, particularly evident when hypoxemia and hypercapnia develop. Renal blood flow is also severely depressed in patients with acute exacerbations and extensive oedema. Cardiac output is generally normal even in patients with severe COPD; therefore, the renal fraction – that part of the cardiac output flowing through the kidneys – must be reduced [116]. Severe hypoxemia is associated with reduced renal flow [123–126]. In the presence of hypercapnia, renal perfusion also progressively falls, and this vasoconstrictor mechanism withstands vasodilatory stimuli [124, 127, 128]. Several neurohumoral systems have been investigated in patients with COPD. The findings show that both

antinatriuretic and natriuretic systems are activated in COPD [76, 116, 119–121, 129–135]. De Leeuw and Dees [136] have formulated a vascular theory to explain disturbed fluid homeostasis in COPD. They postulate that underfilling is the driving force behind the continuous expansion of the extracellular volume; carbon dioxide acts as a potent vasodilator and an increased carbon dioxide tension will substantially lower peripheral vascular resistance and increase arterial capacity. Furthermore, owing to the reduction in precapillary tone, the point of filtration equilibrium in the capillaries will move distally, resulting in increased extravasation and loss of plasma volume. Consequently, the effective circulating volume will be reduced and the reduction will stimulate the sympathetic nervous system, renin, and arginine vasopressin. The kidney will respond with vasoconstriction and sodium retention to restore intravascular volume and tissue perfusion. Because the whole volume cannot be kept within the vascular system, oedema develops. As long as hypercapnia is maintained or worsens, there will be continuing vasodilation, retention of sodium and water, and expansion of oedema. The use of diuretics will even aggravate this vicious circle by further stimulating sodium loss and compensatory renin activation.

Cardiovascular Morbidity and Mortality

Cardiovascular diseases form one of the most important co-morbidities related to COPD. In a cohort of mild COPD patients, the Lung Health Study showed that lung cancer and cardiovascular complications accounted for nearly two-thirds of all deaths during follow-up. The main causes of death in mild or moderate COPD are lung cancer and cardiovascular diseases, while in more advanced COPD respiratory failure becomes the most important cause of death [137]. Other studies confirmed these findings. A 3-year follow-up study of 4,284 patients who received hospital treatment for coronary heart disease reported mortality rates of 21% for patients diagnosed with COPD versus 9% for those without COPD [138]. A cohort study including 11,943 COPD patients reported an approximately two to fourfold increased risk of death at 3-year follow-up due to cardiovascular diseases compared with an age- and sex-matched control group without COPD. Cardiovascular diseases accounted for 42% of first hospitalizations and 44% of second hospitalizations of patients with mild COPD, followed up in the Lung Health Study [137]. The rate of hospitalizations for lower respiratory tract infection was only one-third of that for cardiovascular illnesses. For every 10% decrease in FEV_1, cardiovascular mortality increased by 28%, and nonfatal cardiovascular events increased by almost 20%, after adjustments for relevant confounders such as age, sex, smoking status, and treatment assignment [139].

Strong epidemiological evidence points to reduced FEV_1 as a marker of cardiovascular mortality. A longitudinal population-based study reported that patients with poor lung function had the highest risk of cardiovascular mortality. The risk of death from ischemic heart disease was more than fivefold higher for the lowest vs. the highest lung function quintiles [140]. An increased mortality with decreased lung function is confirmed by many other studies [141–144]. A systematic review and meta-analysis that included >80.000 patients identified an almost twofold risk of cardiovascular mortality in patients with the lowest vs. the highest lung function quintiles [140]. Another study assessed the role of lung function on cardiovascular mortality and reported that FEV_1 is a predictor of all-cause mortality, after controlling for physical fitness and smoking status [145]. Others found that poor lung function accounted for approximately

one-quarter of the attributable mortality risk related to ischemic heart disease [146]. Therefore, it can be concluded that COPD is an important risk factor for atherosclerosis, ischemic heart disease, stroke, and sudden cardiac death.

The underlying mechanisms contributing to this increased risk for atherosclerosis in COPD are poorly understood. The pathogenesis of atherosclerosis is complex and multifactorial. Persistent low-grade systemic inflammation is believed to be one of the centerpiece events leading to plaque formation, and there are compelling epidemiological data linking systemic inflammation to atherosclerosis, ischemic heart disease, strokes, and coronary deaths [147]. COPD is characterized by systemic inflammation [148]. Interestingly, systemic inflammation is not solely associated with severe COPD but may also be present in those with mild and moderate COPD. Most of these data are obtained in cross-sectional study; the persistence of this systemic inflammation is yet poorly documented. Most studies in COPD have been conducted by evaluation of a limited number of molecules involved in the promotion or amplification of atherosclerosis. The most studied of these molecules in COPD is C-reactive protein (CRP).

Indeed, accumulating evidence suggests that circulating CRP represents one of the strongest independent predictors of vascular death. CRP influences vascular vulnerability directly by a variety of mechanisms [149]. In one study, an important interplay is suggested between systemic inflammation measured by CRP levels and airflow limitation in the development of cardiovascular morbidity by application of a cardiac infarction injury score based on a ECG scoring scheme [150]. Recently, increased arterial stiffness related to the severity of airflow limitation was reported in COPD patients. This arterial stiffening was related to the level of systemic inflammation [151]. Besides CRP, fibrinogen has been evaluated in a limited number of studies, demonstrating increased fibrinogen levels in COPD patients.

Besides CRP and fibrinogen, many other factors can induce and promote inflammation or atherogenesis [147]. Low-density lipoprotein (LDL) is one of the principal risk factors for atherosclerosis. Indeed, LDL is a major cause of injury to the endothelium and underlying smooth muscle. When LDL particles become trapped in an artery, they can undergo progressive oxidation and be internalized by macrophages by means of the scavenger receptors on the surfaces of these cells. The internalization leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, resulting in the formation of foam cells. Homocysteine is another factor contributing to atherogenesis as it is toxic to the endothelium and is prothrombic and it increases collagen production and decreases the availability of nitric oxide. Limited data in COPD are yet available demonstrating elevated plasma homocysteine levels in COPD. An immunoregulatory molecule, CD40 ligand, can be expressed by macrophages, T cells, endothelium and smooth muscle and its receptor, CD40 is expressed on the same cells. Both are upregulated in lesions of atherosclerosis providing evidence of the role of immune activation in the process of atherosclerosis. Ligation of CD40 mediates an array of proinflammatory effects, including the expression of cytokines, chemokines, adhesion molecules, matrix metalloproteinases, and growth factors. These activities are crucial to the process of atherogenesis and promote plaque instability. No data are yet available about upregulation of the CD40 system in COPD [149].

At present, adipose tissue is no longer considered as an inert tissue mainly devoted to energy storage but is emerging as an active participant in regulating physiologic and pathologic processes, including inflammation. Adipose tissue in the current view is that of an active secretory organ, sending out and responding to signals that modulate a variety of biological processes. Adipokines are proteins produced by adipocytes: leptin

and adiponectin are primarily produced by these cells and can therefore be properly classified as adipokines [152, 153].

Leptin, a 167-amino acid peptide hormone produced by white adipose tissue, is primarily involved in the regulation of food intake and energy expenditure. Leptin receptors are expressed in many tissues including the cardiovascular system. Plasma leptin concentration is proportional to body adiposity and is markedly increased in obese individuals. Recent studies suggest that hyperleptinaemia may play a role in cardiovascular diseases including atherosclerosis [154]. Leptin exerts many potentially atherogenic effects such as induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation, migration, hypertrophy, and proliferation of vascular smooth muscle cells. Leptin-deficient and leptin-receptor-deficient mice are protected from arterial thrombosis and neointimal hyperplasia in response to arterial wall injury. Several clinical studies have demonstrated that high leptin level predicts acute cardiovascular events, restenosis after coronary angioplasty, and cerebral stroke independently of traditional risk factors. In addition, plasma leptin correlates with markers of subclinical atherosclerosis such as carotid artery intima thickness and coronary artery calcifications.

Adiponectin, the protein that is almost exclusively secreted from adipocytes, is a potent modulator of glucose and lipid metabolism and an indicator of metabolic disorders. Low-plasma adiponectin levels are negatively associated with insulin resistance; they are predictive of type 2 diabetes onset and are related to increased risk for the development of cardiovascular disease. The underlying mechanisms include the direct effects of adiponectin on fat oxidation and vasculature [155]. Fat tissue is also involved in the systemic inflammatory process by production of other cytokines and acute phase response proteins such as Interleukin-6 and plasminogen activator inhibitor-1 (PAI-1). PAI-1 is an important factor in the maintenance of vascular hemostasis, inhibiting the activation of plasminogen, the precursor of plasmin, which is involved in the breakdown of fibrin. In order to understand the underlying mechanisms of cardiovascular changes in COPD, it would be important to understand the interplay and relative contribution of the multifactorial factors involved [152].

Conclusions

Nowadays COPD is defined as a preventable and treatable disease with significant extrapulmonary effects, which may contribute to the disease severity in individual patients. Some of these extrapulmonary effects are at present considered as co-morbid conditions. There is growing attention on causal relationships between one disorder and another or for an underlying vulnerability to different disorders. Better understanding of the role and consequences of systemic inflammation in certain phenotypes of COPD as well as understanding the chronicity of underlying inflammatory processes will broaden our current approach to COPD as a single disease. A patient-oriented approach of COPD needs to take into account that several co-existing components of the chronic disease can contribute to the experienced symptomatology of the patient. Respiratory specialists need to extend their expertise to broader diagnostic and treatment approaches to optimally manage the patient suffering from COPD. This approach certainly will result in a better treatable disease condition and more health for the patient.

References

1. The health consequences of smoking: a report of the surgeon general. Atlanta: US Department of health and human services. Centers for Disease and Control, 2004
2. Wouters EF (2002) Chronic obstructive pulmonary disease. 5: Systemic effects of COPD. Thorax 57:1067–1070
3. Soriano JB, Visick GT, Muellerova H et al (2005) Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 128:2099–2107
4. Mapel DW, Hurley JS, Frost FJ et al (2000) Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med 160:2653–2658
5. Groenewegen KH, Schols AM, Wouters EF (2003) Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 124:459–467
6. Almagro P, Calbo E, Ochoa de Echaguen A et al (2002) Mortality after hospitalization for COPD. Chest 121:1441–1448
7. Charlson ME, Pompei P, Ales KL et al (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
8. Holguin F, Folch E, Redd SC et al (2005) Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest 128:2005–2011
9. Feenstra TL, van Genugten ML, Hoogenveen RT et al (2001) The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 164:590–596
10. American Thoracic Society (1995) Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:S77–S121
11. Baarends EM, Schols AM, Mostert R et al (1997) Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. Eur Respir J 10:2807–2813
12. Mostert R, Goris A, Weling-Scheepers C et al (2000) Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 94:859–867
13. Cano NJ, Pichard C, Roth H et al (2004) C-reactive protein and body mass index predict outcome in end-stage respiratory failure. Chest 126:540–546
14. Schols AM, Broekhuizen R, Weling-Scheepers CA et al (2005) Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 82:53–59
15. Marquis K, Debigare R, Lacasse Y et al (2002) Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:809–813
16. Vestbo J (2006) Clinical assessment, staging, and epidemiology of chronic obstructive pulmonary disease exacerbations. Proc Am Thorac Soc 3:252–256
17. Schols AM, Slangen J, Volovics L et al (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797
18. Vermeeren MA, Creutzberg EC, Schols AM et al (2006) Prevalence of nutritional depletion in a large out-patient population of patients with COPD. Respir Med 100:1349–1355
19. Gosker HR, Lencer NH, Franssen FM et al (2003) Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. Chest 123:1416–1424
20. Wouters EF (2006) Muscle wasting in chronic obstructive pulmonary disease: to bother and to measure! Am J Respir Crit Care Med 173:4–5
21. Halpin DM (2006) Assessing the severity of COPD. Prim Care Respir J 15:78–80
22. Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FC et al (1998) Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. Eur J Clin Nutr 52:396–401
23. Sergi G, Coin A, Marin S et al (2006) Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease. Respir Med 100:1918–1924

24. Baarends EM, Schols AM, Westerterp KR et al (1997) Total daily energy expenditure relative to resting energy expenditure in clinically stable patients with COPD. Thorax 52:780–785
25. Couillard A, Prefaut C (2005) From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. Eur Respir J 26:703–719
26. Rutten EP, Franssen FM, Engelen MP et al (2006) Greater whole-body myofibrillar protein breakdown in cachectic patients with chronic obstructive pulmonary disease. Am J Clin Nutr 83:829–834
27. Hasselgren PO, Fischer JE (2001) Muscle cachexia: current concepts of intracellular mechanisms and molecular regulation. Ann Surg 233:9–17
28. Langen RC, Schols AM, Kelders MC et al (2001) Inflammatory cytokines inhibit myogenic differentiation through activation of nuclear factor-kappaB. FASEB J 15:1169–1180
29. Agusti A, Morla M, Sauleda J et al (2004) NF-kappaB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. Thorax 59:483–487
30. Pouw EM, Schols AM, Deutz NE et al (1998) Plasma and muscle amino acid levels in relation to resting energy expenditure and inflammation in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:797–801
31. Broekhuizen R, Wouters EF, Creutzberg EC et al (2005) Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. Thorax 60:376–382
32. Takabatake N, Nakamura H, Abe S et al (2000) The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alpha system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:1179–1184
33. Bolton CE, Broekhuizen R, Ionescu AA et al (2007) Cellular protein breakdown and systemic inflammation are unaffected by pulmonary rehabilitation in COPD. Thorax 62:109–114
34. Van Helvoort HA, Heijdra YF, Thijs HM et al (2006) Exercise-induced systemic effects in muscle-wasted patients with COPD. Med Sci Sports Exerc 38:1543–1552
35. Vernooy JH, Kucukaycan M, Jacobs JA et al (2002) Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. Am J Respir Crit Care Med 166:1218–1224
36. Gan WQ, Man SF, Senthilselvan A et al (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59:574–580
37. Langen RC, Schols AM, Kelders MC et al (2006) Muscle wasting and impaired muscle regeneration in a murine model of chronic pulmonary inflammation. Am J Respir Cell Mol Biol 35:689–696
38. Langen RC, Korn SH, Wouters EF (2003) ROS in the local and systemic pathogenesis of COPD. Free Radic Biol Med 35:226–235
39. Engelen MP, Schols AM, Does JD et al (2000) Altered glutamate metabolism is associated with reduced muscle glutathione levels in patients with emphysema. Am J Respir Crit Care Med 161:98–103
40. Gosker HR, Bast A, Haenen GR et al (2005) Altered antioxidant status in peripheral skeletal muscle of patients with COPD. Respir Med 99:118–125
41. Mercken EM, Hageman GJ, Schols AM et al (2005) Rehabilitation decreases exercise-induced oxidative stress in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 172:994–1001
42. Heunks LM, Vina J, van Herwaarden CL et al (1999) Xanthine oxidase is involved in exercise-induced oxidative stress in chronic obstructive pulmonary disease. Am J Physiol 277:R1697–R1704
43. Rabinovich RA, Ardite E, Troosters T et al (2001) Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:1114–1118
44. Engelen MP, Wouters EF, Deutz NE et al (2000) Factors contributing to alterations in skeletal muscle and plasma amino acid profiles in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 72:1480–1487

45. Vestbo J, Prescott E, Almdal T et al (2006) Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med 173:79–83
46. Chailleux E, Laaban JP, Veale D (2003) Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. Chest 123:1460–1466
47. Toth S, Tkacova R, Matula P et al (2004) Nutritional depletion in relation to mortality in patients with chronic respiratory insufficiency treated with long-term oxygen therapy. Wien Klin Wochenschr 116:617–621
48. Engelen MP, Schols AM, Does JD et al (2000) Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 71:733–738
49. Palange P, Forte S, Onorati P et al (1998) Effect of reduced body weight on muscle aerobic capacity in patients with COPD. Chest 114:12–18
50. Kessler R, Faller M, Fourgaut G et al (Jan 1999) Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:158–164
51. Ferreira IM, Brooks D, Lacasse Y et al (2000) Nutritional support for individuals with COPD: a meta-analysis. Chest 117:672–678
52. Franssen FM, Broekhuizen R, Janssen PP et al (2004) Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. Chest 125:2021–2028
53. Creutzberg EC, Wouters EF, Mostert R et al (2003) Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. Nutrition 19:120–127
54. Creutzberg EC, Schols AM, Weling-Scheepers CA et al (2000) Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:745–752
55. Casaburi R, Bhasin S, Cosentino L et al (2004) Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170:870–878
56. Nagaya N, Itoh T, Murakami S et al (2005) Treatment of cachexia with ghrelin in patients with COPD. Chest 128:1187–1193
57. Bodine SC, Stitt TN, Gonzalez M et al (2001) Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol 3:1014–1019
58. Fernandes AC, Bezerra OM (2006) Nutrition therapy for chronic obstructive pulmonary disease and related nutritional complications. J Bras Pneumol 32:461–471
59. Engelen MP, Rutten EP, De Castro CL et al (2007) Supplementation of soy protein with branched-chain amino acids alters protein metabolism in healthy elderly and even more in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 85:431–439
60. Rutten EP, Engelen MP, Wouters EF et al (2006) Metabolic effects of glutamine and glutamate ingestion in healthy subjects and in persons with chronic obstructive pulmonary disease. Am J Clin Nutr 83:115–123
61. Schols A (2003) Nutritional modulation as part of the integrated management of chronic obstructive pulmonary disease. Proc Nutr Soc 62:783–791
62. Borghi-Silva A, Baldissera V, Sampaio LM et al (2006) L-carnitine as an ergogenic aid for patients with chronic obstructive pulmonary disease submitted to whole-body and respiratory muscle training programs. Braz J Med Biol Res 39:465–474
63. Tug T, Karatas F, Terzi SM (2004) Antioxidant vitamins (A, C and E) and malondialdehyde levels in acute exacerbation and stable periods of patients with chronic obstructive pulmonary disease. Clin Invest Med 27:123–128
64. Fuld JP, Kilduff LP, Neder JA et al (2005) Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax 60:531–537

65. Casaburi R (2001) Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Med Sci Sports Exerc 33:S662–S670
66. Scalvini S, Volterrani M, Vitacca M et al (1996) Plasma hormone levels and haemodynamics in patients with chronic obstructive lung disease. Monaldi Arch Chest Dis 51:380–386
67. Hjalmarsen A, Aasebo U, Birkeland K et al (1996) Impaired glucose tolerance in patients with chronic hypoxic pulmonary disease. Diabetes Metab 22:37–42
68. Mador MJ, Bozkanat E (2001) Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Respir Res 2:216–224
69. Suchner U, Rothkopf MM, Stanislaus G et al (1990) Growth hormone and pulmonary disease. Metabolic effects in patients receiving parenteral nutrition. Arch Intern Med 150:1225–1230
70. Pape GS, Friedman M, Underwood LE et al (1991) The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. Chest 99:1495–1500
71. Burdet L, de Muralt B, Schutz Y et al (1997) Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. Am J Respir Crit Care Med 156:1800–1806
72. Baarends EM, Schols AM, Pannemans DL et al (1997) Total free living energy expenditure in patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:549–554
73. Schols AM, Soeters PB, Mostert R et al (1991) Energy balance in chronic obstructive pulmonary disease. Am Rev Respir Dis 143:1248–1252
74. Hugli O, Frascarolo P, Schutz Y et al (1993) Diet-induced thermogenesis in chronic obstructive pulmonary disease. Am Rev Respir Dis 148:1479–1483
75. Dimopoulou I, Ilias I, Mastorakos G et al (2001) Effects of severity of chronic obstructive pulmonary disease on thyroid function. Metabolism 50:1397–1401
76. Bratel T, Wennlund A, Carlstrom K (2000) Impact of hypoxaemia on neuroendocrine function and catecholamine secretion in chronic obstructive pulmonary disease (COPD). Effects of long-term oxygen treatment. Respir Med 94:1221–1228
77. Tremblay RR, Gagne JM (2005) Can we get away from serum total testosterone in the diagnosis of andropause? Aging Male 8:147–150
78. Semple PD, Beastall GH, Watson WS et al (1980) Serum testosterone depression associated with hypoxia in respiratory failure. Clin Sci (Lond) 58:105–106
79. Kamischke A, Kemper DE, Castel MA et al (1998) Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur Respir J 11:41–45
80. Reid IR, Wattie DJ, Evans MC et al (1996) Testosterone therapy in glucocorticoid-treated men. Arch Intern Med 156:1173–1177
81. Schols AM, Buurman WA, van den Staal Brekel AJ et al (1996) Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 51:819–824
82. van der Poll T, Romijn JA, Endert E et al (1993) Effects of tumor necrosis factor on the hypothalamic-pituitary-testicular axis in healthy men. Metabolism 42:303–307
83. Bhasin S, Storer TW, Berman N et al (1997) Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 82:407–413
84. Bhasin S, Storer TW, Asbel-Sethi N et al (1998) Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. J Clin Endocrinol Metab 83:3155–3162
85. Bhasin S, Storer TW, Berman N et al (1996) The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1–7
86. Schols AM, Soeters PB, Mostert R et al (1995) Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med 152:1268–1274
87. Ferreira IM, Verreschi IT, Nery LE et al (1998) The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 114:19–28

88. Yeh SS, DeGuzman B, Kramer T (2002) Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. Chest 122:421–428
89. Johnston C, Slemenda C (1993) Risk assessment: theoretical considerations. Am J Med 95:2S–5S
90. Ionescu AA, Schoon E (2003) Osteoporosis in chronic obstructive pulmonary disease. Eur Respir J Suppl 46:64s–75s
91. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259
92. Biskobing DM (2002) COPD and osteoporosis. Chest 121:609–620
93. Engelen MP, Schols AM, Heidendal GA et al (1998) Dual-energy X-ray absorptiometry in the clinical evaluation of body composition and bone mineral density in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 68:1298–1303
94. Bolton CE, Ionescu AA, Shiels KM et al (2004) Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170:1286–1293
95. Sin DD, Man JP, Man SF (2003) The risk of osteoporosis in Caucasian men and women with obstructive airways disease. Am J Med 114:10–14
96. Aloia JF, Vaswani A, Ma R et al (1995) To what extent is bone mass determined by fat-free or fat mass? Am J Clin Nutr 61:1110–1114
97. Coin A, Sergi G, Beninca P et al (2000) Bone mineral density and body composition in underweight and normal elderly subjects. Osteoporos Int 11:1043–1050
98. Iqbal F, Michaelson J, Thaler L et al (1999) Declining bone mass in men with chronic pulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. Chest 116:1616–1624
99. Nishimura Y, Nakata H, Tsutsumi M et al (1997) Relationship between changes of bone mineral content and twelve-minute walking distance in men with chronic obstructive pulmonary disease: a longitudinal study. Intern Med 36:450–453
100. Anker SD, Clark AL, Teixeira MM et al (1999) Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 83:612–615, A610
101. Espat NJ, Moldawer LL, Copeland EM 3rd (1995) Cytokine-mediated alterations in host metabolism prevent nutritional repletion in cachectic cancer patients. J Surg Oncol 58:77–82
102. Bertolini DR, Nedwin GE, Bringman TS et al (1986) Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. Nature 319: 516–518
103. Gowen M, Mundy GR (1986) Actions of recombinant interleukin 1, interleukin 2, and interferon-gamma on bone resorption in vitro. J Immunol 136:2478–2482
104. Raisz LG (1988) Local and systemic factors in the pathogenesis of osteoporosis. N Engl J Med 318:818–828
105. Manolagas SC, Jilka RL (1995) Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. N Engl J Med 332:305–311
106. Neale SD, Schulze E, Smith R et al (2002) The influence of serum cytokines and growth factors on osteoclast formation in Paget's disease. QJM 95:233–240
107. Simonet WS, Lacey DL, Dunstan CR et al (1997) Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 89:309–319
108. Morinaga T, Nakagawa N, Yasuda H et al (1998) Cloning and characterization of the gene encoding human osteoprotegerin/osteoclastogenesis-inhibitory factor. Eur J Biochem 254:685–691
109. Anderson DM, Maraskovsky E, Billingsley WL et al (1997) A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. Nature 390:175–179
110. Feige U (2001) Osteoprotegerin. Ann Rheum Dis 60(Suppl 3):iii81–iii84
111. Bekker PJ, Holloway D, Nakanishi A et al (2001) The effect of a single dose of osteoprotegerin in postmenopausal women. J Bone Miner Res 16:348–360
112. Campbell RH, Brand HL, Cox JR et al (1975) Body weight and body water in chronic cor pulmonale. Clin Sci Mol Med 49:323–335

113. Baum GL, Dick MM, Blum A et al (1959) Total body exchangeable potassium and sodium and extracellular fluid in chronic pulmonary insufficiency. Am Heart J 58:53–58
114. Bauer FK, Telfer N, Herbst HH et al (1965) Hyponatremia and increased exchangeable sodium in chronic obstructive lung disease. Am J Med Sci 250:245–253
115. Anand IS, Chandrashekhar Y, Ferrari R et al (1992) Pathogenesis of congestive state in chronic obstructive pulmonary disease. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. Circulation 86:12–21
116. Farber MO, Bright TP, Strawbridge RA et al (1975) Impaired water handling in chronic obstructive lung disease. J Lab Clin Med 85:41–49
117. Farber MO, Kiblawi SS, Strawbridge RA et al (1977) Studies on plasma vasopressin and the renin-angiotensin-aldosterone system in chronic obstructive lung disease. J Lab Clin Med 90:373–380
118. Farber MO, Roberts LR, Weinberger MH et al (1982) Abnormalities of sodium and H2O handling in chronic obstructive lung disease. Arch Intern Med 142:1326–1330
119. Farber MO, Weinberger MH, Robertson GL et al (1984) Hormonal abnormalities affecting sodium and water balance in acute respiratory failure due to chronic obstructive lung disease. Chest 85:49–54
120. Stewart AG, Bardsley PA, Baudouin SV et al (1991) Changes in atrial natriuretic peptide concentrations during intravenous saline infusion in hypoxic cor pulmonale. Thorax 46:829–834
121. Mannix ET, Dowdeswell I, Carlone S et al (1990) The effect of oxygen on sodium excretion in hypoxemic patients with chronic obstructive lung disease. Chest 97:840–844
122. De Angelis C, Perrone A, Ferri C et al (1993) Oxygen administration increases plasma digoxin-like substance and renal sodium excretion in chronic hypoxic patients. Am J Nephrol 13:173–177
123. Palange P (1998) Renal and hormonal abnormalities in chronic obstructive pulmonary disease (COPD). Thorax 53:989–991
124. Baudouin SV, Bott J, Ward A et al (1992) Short term effect of oxygen on renal haemodynamics in patients with hypoxaemic chronic obstructive airways disease. Thorax 47:550–554
125. Sharkey RA, Mulloy EM, O'Neill SJ (1999) The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. Chest 115:1588–1592
126. Howes TQ, Keilty SE, Maskrey VL et al (1996) Effect of L-arginine on renal blood flow in normal subjects and patients with hypoxic chronic obstructive pulmonary disease. Thorax 51:516–519
127. Sharkey RA, Mulloy EM, Kilgallen IA et al (1997) Renal functional reserve in patients with severe chronic obstructive pulmonary disease. Thorax 52:411–415
128. Schalekamp MA, Krauss XH, Schalekamp-Kuyken MP et al (1971) Studies on the mechanism of hypernatriuresis in essential hypertension in relation to measurements of plasma renin concentration, body fluid compartments and renal function. Clin Sci 41:219–231
129. Fishman AP, Maxwell MH, Crowder CH et al (1951) Kidney function in cor pulmonale; particular consideration of changes in renal hemodynamics and sodium excretion during variation in level of oxygenation. Circulation 3:703–721
130. Carlone S, Palange P, Mannix ET et al (1989) Atrial natriuretic peptide, renin and aldosterone in obstructive lung disease and heart failure. Am J Med Sci 298:243–248
131. Adnot S, Andrivet P, Chabrier PE et al (1990) Plasma levels of atrial natriuretic factor, renin activity, and aldosterone in patients with chronic obstructive pulmonary disease. Response to O_2 removal and to hyperoxia. Am Rev Respir Dis 141:1178–1184
132. de Leeuw PW, Kho TL, Falke HE et al (1978) Haemodynamic and endocrinological profile of essential hypertension. Acta Med Scand Suppl 622:5–86
133. Baudouin SV (1997) Oedema and cor pulmonale revisited. Thorax 52:401–402
134. Winter RJ, Davidson AC, Treacher D et al (1989) Atrial natriuretic peptide concentrations in hypoxic secondary pulmonary hypertension: relation to haemodynamic and blood gas variables and response to supplemental oxygen. Thorax 44:58–62

135. MacNee W (1994) Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One Am J Respir Crit Care Med 150:833–852
136. de Leeuw PW, Dees A (2003) Fluid homeostasis in chronic obstructive lung disease. Eur Respir J Suppl 46:33s–40s
137. Anthonisen NR, Connett JE, Kiley JP et al (1994) Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study [see comments]. JAMA 272:1497–1505
138. Berger JS, Sanborn TA, Sherman W et al (2004) Effect of chronic obstructive pulmonary disease on survival of patients with coronary heart disease having percutaneous coronary intervention. Am J Cardiol 94:649–651
139. Anthonisen NR, Connett JE, Enright PL et al (2002) Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 166:333–339
140. Sin DD, Wu L, Man SF (2005) The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. Chest 127:1952–1959
141. Sorlie PD, Kannel WB, O'Connor G (1989) Mortality associated with respiratory function and symptoms in advanced age. The Framingham Study. Am Rev Respir Dis 140:379–384
142. Ebi-Kryston KL, Hawthorne VM, Rose G et al (1989) Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United States. Int J Epidemiol 18:84–88
143. Persson C, Bengtsson C, Lapidus L et al (1986) Peak expiratory flow and risk of cardiovascular disease and death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Am J Epidemiol 124:942–948
144. Truelsen T, Prescott E, Lange P et al (2001) Lung function and risk of fatal and non-fatal stroke. The Copenhagen City Heart Study. Int J Epidemiol 30:145–151
145. Stavem K, Aaser E, Sandvik L et al (2005) Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. Eur Respir J 25:618–625
146. Hole DJ, Watt GC, Davey-Smith G et al (1996) Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 313:711–715, discussion 715–716
147. Epstein SE, Stabile E, Kinnaird T et al (2004) Janus phenomenon: the interrelated tradeoffs inherent in therapies designed to enhance collateral formation and those designed to inhibit atherogenesis. Circulation 109:2826–2831
148. Lopez AD, Shibuya K, Rao C et al (2006) Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 27:397–412
149. Szmitko PE, Wang CH, Weisel RD et al (2003) New markers of inflammation and endothelial cell activation: Part I. Circulation 108:1917–1923
150. Sin DD, Man SF (2003) Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 107:1514–1519
151. Sabit R, Bolton CE, Edwards PH et al (2007) Arterial Stiffness and Osteoporosis in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 175:1259–1265
152. Fantuzzi G (2005) Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 115:911–919, quiz 920
153. Trayhurn P (2004) Of genes and genomes – and dark matter. Br J Nutr 91:1–2
154. Beltowski J (2006) Leptin and atherosclerosis. Atherosclerosis 189:47–60
155. Kantartzis K, Rittig K, Balletshofer B et al (2006) The relationships of plasma adiponectin with a favorable lipid profile, decreased inflammation, and less ectopic fat accumulation depend on adiposity. Clin Chem 52:1934–1942

14

Non-Pharmacological and Surgical Management of COPD

Kevin M. Chan, Fernando J. Martinez, and Andrew C. Chang

Key Points:

- Surgical intervention including bullectomy, lung volume reduction surgery (LVRS) and lung transplantation can be considered in a select group of chronic obstructive pulmonary disease (COPD) patients.
- Bullectomy may result in improvement of some of the indices of respiratory function and dyspnoea with a gradual worsening over the years.
- Surgical LVRS results in improvement of various lung function parameters and exercise capacity. In addition, LVRS offers survival benefit in patients with upper lobe dominant disease and low exercise tolerance at base line. In contrast, patients with diffuse very advanced disease have higher mortality with LVRS.
- Lung transplantation may be complicated by chronic allograft rejection and infection. Careful preoperative selection and preparation is essential for a successful outcome.

Keywords Lung volume reduction surgery • transplant • bullectomy

History of Nonpharmacological Therapy for Emphysema

Detailed discussions of the surgical history of emphysema management have been published [4]. These approaches reflected the state of knowledge of their era. Early investigators attempted to improve thoracic mobility, with procedures including costochondrectomy and transverse sternotomy, with upredictable results [5]. Subsequently, techniques were developed to decrease the size of the thoracic cage, to improve diaphragmatic architecture and function, or support the membranous trachea using various prosthetic devices [5]. Practical considerations limited widespread use of these techniques [5].

Brantigan and colleagues attempted to reduce hyperinflation by surgically reducing lung volume [6, 7]. Although symptomatic improvement was reported, significant operative mortality [6] limited widespread application. Over the subsequent 40 years, various groups applied similar principles in small case series using various surgical techniques [8]. The current era of surgical lung volume reduction was ushered by Cooper and colleagues who reported dramatic improvement following bilateral LVRS performed via median sternotomy (MS) [9]. Subsequently, multiple investigators reported more limited improvement [10]. The results of the National Emphysema

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_14,

Treatment Trial (NETT) [11, 12] and other randomized trials [13–15] have provided much more definitive recommendations regarding the role of LVRS in patients with advanced emphysema.

Lung transplantation dates back to the early 1960s albeit with uniformly poor initial results [16]. Patterson et al. reported successful double lung transplantation (DLT) in COPD patients [17], while Mal et al. reported successful single lung transplantation (SLT) in COPD patients [18]. SLT became the predominant surgical therapy for advanced COPD [4] until 2006 when over 50% of annual lung transplants for COPD reported to the International Society of Heart and Lung Transplantation (ISHLT) Registry were double lung procedures [19]. COPD remains the main indication for lung transplantation (36%)[19].

Techniques

As exhaustive descriptions of the surgical techniques are outside the scope of this article, only important concepts will be briefly reviewed.

Bullectomy

Multiple techniques have been utilized to achieve resection of localized bullae, including standard lateral thoracotomy, bilateral resection via MS and video assisted thoracoscopy (VATS) with stapling or endoloop ligation.

LVRS Without Giant Bullae

The approaches to LVRS have included MS [20], standard thoracotomy and VATS [21]. Laser ablation has fallen out of favor due to its higher complication rates [22]. In general, comparative studies have suggested greater improvement with bilateral procedures. NETT investigators prospectively confirmed similar morbidity and mortality with bilateral VATS or MS although the overall length of stay was longer for MS and more MS patients were living independently by 30 days after surgery [12].

Bronchoscopic Lung Volume Reduction

Despite the success of surgical LVRS, surgical morbidity and mortality is still significant[11, 12]. Safer alternatives incorporating an endobronchial approach to lung volume reduction are under investigation [23, 24]. The most studied technique involves endoscopically placed one-way valves that prevent air from entering isolated segments while allowing gases and secretions to escape [25, 26]. An alternative method involves the creation of broncho-parenchymal passages. This has been postulated to increase expiratory flow in diffusely emphysematous lungs [27]. Multicenter trials evaluating these techniques are ongoing.

Placement of one-way valves in selected airways is guided by flexible bronchoscopy while the patient is under conscious sedation or general anesthesia [23, 28a, 29]. Device deployment requires guidewire placement with direct bronchoscopic visualization. Revised versions of these devices can be deployed by using a catheter passed through the working channel of the bronchoscope [23]. One to ten valves are inserted in unilateral [28a] or

bilateral upper lobes [29]. The creation of communications between segmental bronchi and emphysematous lung parenchyma has been investigated using a catheter to create the "bypass" channels followed by the placement of a drug-eluting stent [27]. In a recently completed randomized trial evaluating unilateral endobronchial valve therapy with standard medical care, improvements were observed in lung function, exercise tolerance and symptom relief. Subjects treated with endobronchial valve therapy also had higher rates of COPD exacerbation, pneumonia and post-implantation hemoptysis [28b]. While these results are promising, further clinical trials will be necessary to identify suitable populations for this therapy.

Lung Transplantation

Controversy continues to revolve around the optimal transplant procedure in patients with COPD [30], although recent data suggest improved long-term outcomes in COPD patients treated with DLT versus SLT [31, 32]. For example, data from the Registry of the ISHLT reveals significantly better survival after DLT for COPD even when stratified by age [19, 32] (Fig. 14.4). Unfortunately, the lack of prospective data collection and adjustment for influencing variables limits definitive conclusions.

What Are the Results of Nonpharmacological Therapies?

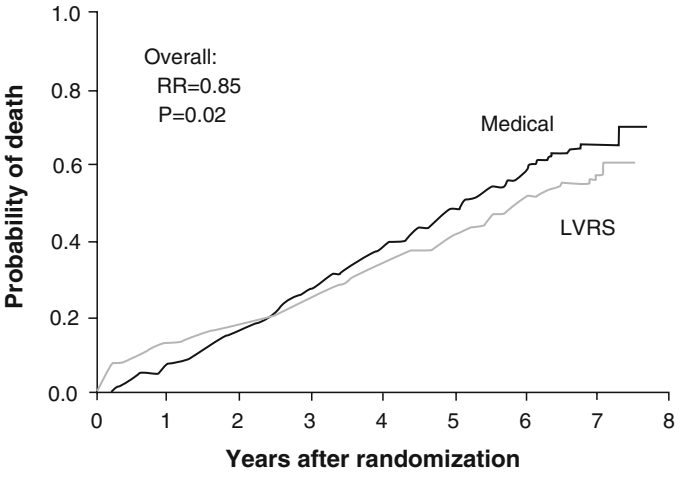
Bullectomy

Bullectomy appears to be of short-term benefit in highly selected patients [33]. None of the 22 studies reviewed included a control group and most were retrospective in nature. Improvements in hypoxemia and hypercapnea were most frequently reported, while improvement in airflow was more heterogeneous. When measured, total lung capacity, residual volume and trapped gas generally decreased. In highly selected patients, cor pulmonale reversed if hypoxemia and hypercapnea were present. Most authors described improvement in dyspnoea. Little long-term follow-up data have been reported. In general, maintenance of improvement was generally noted although in many of the patients a gradual worsening was seen over the years [34–38].

LVRS Without Giant Bullae

Since the early report of Cooper and colleagues in 1995 [9] numerous reports of outcomes following LVRS have appeared in the literature [10, 39]. Although several of these studies likely reported duplicate patient data, several methodological problems were noted consistently in these studies. The results of several randomized, controlled trials have clarified results of LVRS [13–15, 40–43]. The NETT was a large prospective, randomized, multicenter study comparing optimum medical therapy with optimum therapy plus LVRS [11]. Of 3,777 patients considered for entry, 1,218 were randomized to treatment. Importantly, LVRS was associated with an improvement in long-term mortality compared to medically treated patients in an intention-to-treat analysis (Fig. 14.1).

In comparison to initial reports, the majority of case series have confirmed significant mean improvements in spirometry although to a lesser extent than initially suggested [39]. Reported changes in pulmonary function clearly indicated a short-term improvement in spirometry favoring surgery over medical therapy. This was exemplified by the results of two randomized trials (Fig. 14.2a, b). In general, bilateral LVRS has resulted in greater short-term improvement. One multicenter prospective study comparing unilateral VATS LVRS with bilateral VATS LVRS noted that pulmonary



No.at risk								
LVRS	608	526	496	454	352	227	122	29
Medical	610	564	507	441	335	210	99	29
Probability of death								
LVRS		0.13	0.18	0.25	0.34	0.42	0.52	0.57
Medical		0.08	0.17	0.28	0.38	0.49	0.58	0.65
Ratio		1.79	1.09	0.91	0.89	0.86	0.89	0.88
P		0.001	0.48	0.35	0.15	0.02	0.05	0.86

Fig. 14.1. Kaplan-Meier estimates of the cumulative probability of death as a function of years after randomization to lung volume reduction surgery (*LVRS*, *gray line*) or medical treatment (*black line*) in the National Emphysema Treatment Trial. The *p* value is for the Fisher exact test for the difference in the proportions of patients who died during the 4.3 years (median) follow-up in all patients randomized (From Naunheim et al. [44]. With permission)

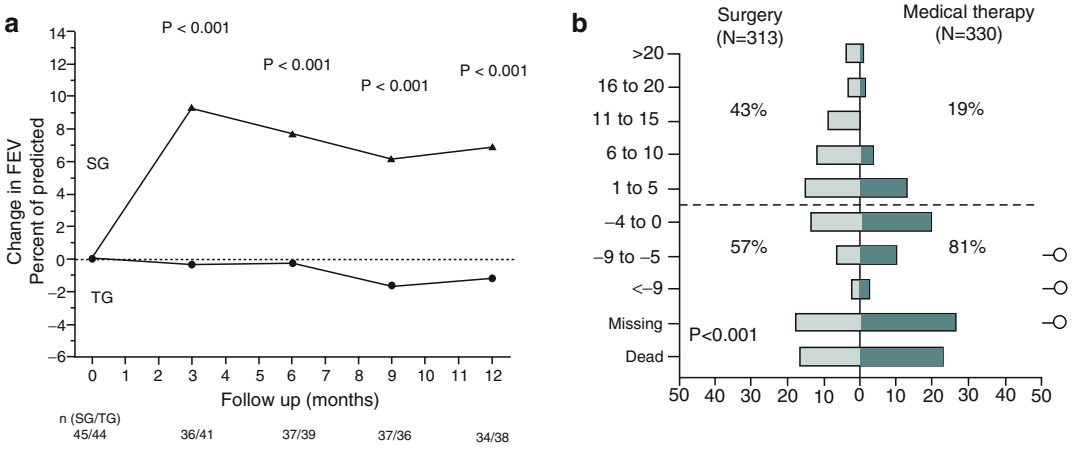


Fig. 14.2. (**a**) Absolute change in FEV1% predicted in patients treated with surgery (*SG*) compared to those treated with continued training (*TG*). (**b**) Histograms of changes from base line in FEV_1 after 24 months of follow-up. Base-line measurements were performed after pulmonary rehabilitation. Patients previously identified as high-risk were excluded. Patients who were too ill to complete the procedure or who declined to complete the procedure but did not explain why were included in the "missing" category. *p* values were determined by the Wilcoxon rank-sum test. The degree to which the bars are shifted to the upper left of the chart indicates the degree of relative benefit of lung-volume–reduction surgery over medical treatment. The percentage shown in each quadrant is the percentage of patients in the specified treatment group with a change in the outcome falling into that quadrant. This was an intention-to-treat analysis (**a**: From [43]; **b**: From [11]. With permission)

function improvement favored the bilateral approach [45]. The results of laser procedures appeared to be worse than stapling techniques [21, 46]. Modest differences are noted when comparing bilateral LVRS performed by VATS or MS. Prospectively collected data from the NETT confirmed similar functional benefits between bilateral LVRS performed using MS or VATS [12].

Variability in improved FEV_1 has been well described. Figure 14.2b illustrates the heterogeneous spirometric response for the NETT 24 months after randomization to surgery or medical therapy. A significant proportion of patients experienced little improvement in FEV_1, even in the short term. Although data are limited, lung volumes have generally decreased during short-term follow-up while changes in DL_{CO} have been modest [39]. Changes in resting arterial blood gases have ranged from significant improvements in paO_2 and decreases in $paCO_2$ to little change [39, 47]. Data regarding long-term functional follow-up are limited. Brenner et al. reported the rate of FEV_1 change greater than 6 months after LVRS [48]. They noted a greater decrease in FEV_1 (0.255 ± 0.057 l/year) in those patients experiencing the greatest improvement in the initial 6 months after surgery. The lowest rate of drop in FEV_1 appeared in those with the least initial improvement. One group presented a median of 4 years of follow-up in 200 patients treated with bilateral LVRS [49]. Although data collection was not complete, a majority of patients still exhibited spirometric improvement 3 and 5 years after surgery.

Most available data have described consistent improvements in simple measures of exercise capacity such as timed measures of walk distance [11, 39]. Several groups have reported consistent, short-term increases in maximal work load, $\dot{V}O_2$ and $\dot{V}_E$ [39]. The NETT investigators confirmed an increase in maximal achieved wattage during oxygen supplemented cycle ergometry in surgical patients; less improvement was noted in patients that continued aggressive medical management [11]. Dolmage and colleagues [50] reported improved peak $\dot{V}O_2$ and power with a greater minute ventilation and tidal volume. Importantly, this study confirmed an improvement in operational lung volumes among patients undergoing operation. Limited data are available regarding long-term maintenance of improvements in exercise capacity. Compared to preoperative values, a higher 6-min walk distance has been seen in surgically treated patients [51, 52]. NETT investigators noted that surgical patients, in contrast to medically treated patients, were more likely to maintain improved maximal wattage during oxygen supplemented cardiopulmonary exercise testing during long-term follow-up [44].

Dyspnoea improvement has been reported by several groups using the Medical Research Council dyspnoea scores or the transitional dyspnoea index (TDI) [39]. NETT investigators have presented detailed assessment of breathlessness using the University of California Shortness of Breath Questionnaire (UCSD SOB) (Fig. 14.3); a heterogenous response was noted, although a clear benefit is seen in the surgically treated group compared to medically managed patients. Results of formal health status measurement have been presented [53]. Short-term improvement in health status using the Medical Outcomes Survey-Short Form 36 (SF-36), the Nottingham Health Profile, and other disease specific instruments have been published [39]. The Canadian controlled trial reported clear improvement in health status measured with the Chronic Respiratory Questionnaire (CRQ) in patients treated surgically compared to a matched group randomized to medical therapy [14], while NETT investigators noted significant improvement in the St. George's Respiratory Questionnaire (SGRQ) of surgically treated patients compared to medically treated patients [11]. Long-term SGRQ follow-up from this sentinel group has been reported, which supports a beneficial response favoring surgically treated patients [44].

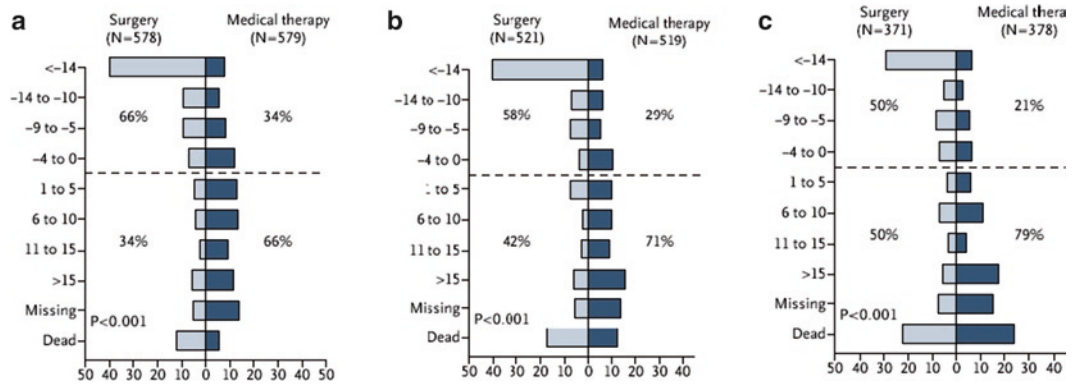


Fig. 14.3. Histograms of changes from base line in the UCSD SOBQ after 6, 12, and 24 months of follow-up. Base-line measurements were performed after pulmonary rehabilitation. Patients previously identified as high-risk were excluded. Patients who were too ill to complete the procedure or who declined to complete the procedure but did not explain why were included in the "missing" category. *p* values were determined by the Wilcoxon rank-sum test. The degree to which the bars are shifted to the upper left of the chart indicates the degree of relative benefit of lung-volume–reduction surgery over medical treatment. The percentage shown in each quadrant is the percentage of patients in the specified treatment group with a change in the outcome falling into that quadrant. This was an intention-to-treat analysis (From [11]. With permission)

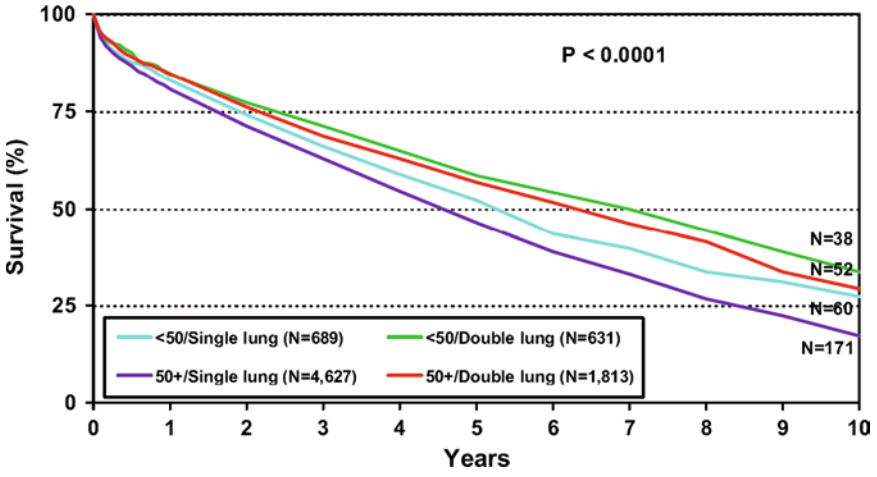


Fig. 14.4. Kaplan-Meier survival after lung transplantation for recipients with COPD for transplantations performed between January 1990 and June 2004, stratified by age range and procedure type (From [19])

Lung Transplantation

Long-term results of lung transplantation have been limited by significant complications which impair survival. Data from the Registry of the ISHLT suggests 82% 1-year, 50% 5-year, and 22% 10-year survival for emphysema patients [19] (Fig. 14.4). While emphysema patients enjoy the greatest survival advantage in the first year after lung transplantation compared to other diagnostic groups, they have the lowest survival rate at 10 years [19].

Consistent spirometric improvement after both SLT and DLT has been reported with less improvement generally seen in SLT compared to DLT [54, 55]. Documentation of long-term results of pulmonary function is scarce. In general, early reports noted that some patients demonstrated stability in FEV_1 improvement while others experienced a decline in pulmonary function after several months [54, 56]. The importance of obliterative bronchiolitis (OB) on this loss of lung function has been recently reviewed [57, 58]. In fact, bronchiolitis obliterans syndrome (BOS) has been defined physiologically as a persistent 20% or greater drop in postoperative FEV_1, in the absence of other acute conditions (airway complications, infection, congestive heart failure, reversible airway reactivity, and systemic disease) [59]. Furthermore, BOS can be staged according to the drop in FEV_1 from the peak, posttransplant value. A decrease in pulmonary function with BOS is particularly likely in SLT compared to DLT recipients [60].

Numerous investigators have reported improved 6-min walk distance after both SLT and DLT [55, 56]. Exercise after SLT or DLT appears to be limited by aerobic capacity and not by ventilatory restriction. Most reports support peripheral muscle dysfunction as the predominant cause of exercise limitation after lung transplantation [61–63]. The cause of this peripheral muscle dysfunction posttransplantation remains unclear, although chronic disease, drug therapy, disuse, and poor nutrition have all been invoked [64–66]. Reports of long-term exercise data after lung transplantation are few. Improvement in 6-min walk distance after transplantation for COPD has been reported to be maintained up to 4 years after transplantation [67]. The same group has recently published a 13-year experience with lung transplantation in COPD [68]. These authors noted a mild decrease in 6-min walk distance 5 years after transplantation although continued stability up to 7 years after surgery in DLT recipients has been described [69]. A significant limitation to exercise remains for patients after lung transplantation, although the effect of long-term aerobic training has not been described in this patient population.

Limited data are available detailing changes in health status after lung transplantation. In general, improvement in health status has been reported [70–72]. Pretransplant anxiety and psychopathology predict posttransplant adjustment with greater anxiety predicting worse posttransplant quality of life [73]. Importantly, recipients with BOS experience decrements in health status, particularly in physical and social functioning and bodily pain [71, 74, 75]. Long-term data reporting improved health related quality of life (HRQL) after transplantation have been reported [69, 76]. After a mean follow up of 2 years, significant improvement in 7 of 8 subscales of the SF-36 were noted but remained below that of the general population in one study [76]. Three to 5-year posttransplant survivors reported more frequent affective, neurocognitive, and physical appearance issues. Headaches and depression were also more common when compared to patients earlier in their transplant course [76]. These symptoms had a greater influence on women resulting in a lower percentage gain in quality of life than men [77].

Which Patients Should and Which Should not Be Considered for Nonpharmacological Therapy?

Increasingly health care providers need to decide which surgical approach is optimal for an individual patient.

Table 14.1 Potential indications and contraindications for classical bullectomy (Adapted from www.thoracic.org/copd).

Parameter	Indications	Contraindications
Clinical	Young age (<50 years) Rapid progressive dyspnoea despite maximal medical therapy Ex smoker	Age > 50 years Comorbid illness Cardiac disease Pulmonary hypertension >10% weight loss Frequent respiratory infections – chronic bronchitis Ongoing tobacco use
Physiologic	Normal or slightly ↓ FVC FEV_1 > 40% pred Little bronchoreversibility "High" trapped lung volume Normal or near normal DL_{CO} Normal PaO_2 and $PaCO_2$	FEV_1 < 35% pred "Low" trapped gas volume Decreased DL_{CO}
Imaging	*CXR* – Bulla > 1/3 hemithorax *CT* – large and localized bulla with vascular crowding and normal, compressed pulmonary parenchyma around bulla *Angiography* – Vascular crowding with preserved distal vascular branching *Isotope scan* – well-localized matching defect with normal uptake & washout for underlying lung	*CXR* – Vanishing lungsyndrome Poorly defined bullae *CT* – Multiple ill-defined bullae in underlying lung *Angiography* – Vague bullae; disrupted vasculature elsewhere *Isotope scan* – Absence of target zones, poor washout in remaining lung

Bullectomy

Most investigators have attempted to identify optimal surgical candidates using pulmonary function tests and radiographic studies to identify compressed normal lung that is most likely to respond to bullectomy [78]. These are summarized in Table 14.1. In general, ideal candidates experience persistent exertional limitation despite optimal medical therapy including pulmonary rehabilitation. Some series have suggested worse surgical result in older patients [34, 79]. Some have suggested higher morbidity and worse long-term results in the presence of superimposed chronic bronchitis [34, 79]. As such, a history of chronic sputum production and recurrent respiratory infections may provide a suggestion of such primary airway disease [1]. Similarly, most authors have reported poorest long-term outcome in those individuals with greater degrees of emphysema in the remaining lung.

Patients with a "restrictive" picture by spirometry with simultaneous elevation of FRC and TLC [80] tend to experience more favorable results, while those with severe obstruction, particularly when associated with smaller bullae, have been suggested to experience worse long-term results [80, 81]. Significant bronchoreversibility has been proposed as an additional, relative contraindication (Table 14.1) [78]. Elevation of the trapped gas volume has been seen in patient groups demonstrating better responses to classic bullectomy [34, 80]. The DL_{CO} has been suggested as a marker of greater underlying emphysema with a better response in those patients with higher DL_{CO} and lack of exertional desaturation [81, 82]. Multiple authors have reported inferior results in patients with bullae occupying < 1/3 of the hemithorax, particularly for the long-term maintenance of long-term functional improvement [34, 79, 83, 84]. In the past 15 years, computed tomography (CT) has become the imaging study of choice in the assessment of bullous structure and size [78].

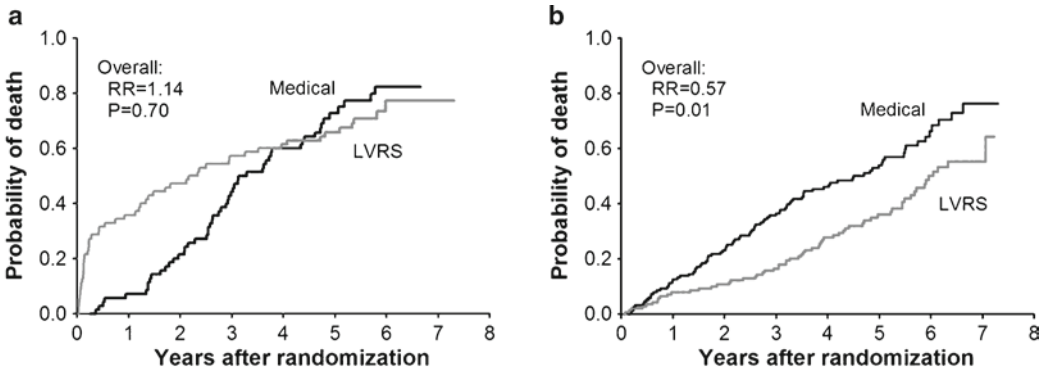
Lung Volume Reduction Without Giant Bullae

The clinical evaluation should be used to identify patients with predominant emphysema [78]. The presence of frequent respiratory infections and chronic, copious sputum production may be useful in identifying patients with primary airway disease [85]. Clinical assessment should attempt to identify patient features predicting a higher mortality or likelihood of a poor functional result (Table 14.2). Coronary artery disease, although frequently seen in this patient group [86], should not be considered an absolute contraindication to surgery [87, 88]. Similarly, pulmonary hypertension has been described as a relative contraindication for LVRS [89], although prohibitive pulmonary hypertension is infrequent in this patient population. The effect of milder pulmonary vascular abnormality has not been prospectively studied [90]. Less favorable outcomes have been reported in the presence of α-1 antitrypsin deficiency [20, 91–94]. NETT investigators reported inferior clinical outcomes in a small number of α-1 antitrypsin deficient individuals undergoing bilateral LVRS [92]. An impaired nutritional status as measured by a lower body mass index (BMI) or by decreased percentage of ideal body weight or fat-free mass index has been associated with increased perioperative complications [95, 96].

Pulmonary function testing has proven instrumental in identifying optimal candidates for surgery (Table 14.2) [78]. A lower limit of FEV_1 that identifies individuals at prohibitive risk has not been agreed upon, although the NETT investigators suggested that a lower FEV_1 was independently predictive of greater postoperative pulmonary

Table 14.2 Potential indications and contraindications for LVRS (Adapted from www.thoracic.org/copd).

Parameter	Indications	Contraindications
Clinical	Age < 75 years	Age > 75–80 years
	Clinical picture consistent with emphysema	Comorbid illness that increases surgical mortality
	Dyspnoea despite maximal medical treatment pulmonary rehabilitation	Clinically significant coronary artery disease
	Ex smoker (> 6 months)	Pulmonary Hypertension (PA systolic > 45 mmHg, PA mean > 35 mmHg)
	Requiring < 20 mg prednisone/day	Surgical constraints: Previous thoracic procedure Pleuradesis Chest wall deformity
Physiologic	FEV_1 after bronchodilator < 45% pred	$FEV_1 \leq 20\%$ predicted and DLCO ≤ 20% pred
	Hyperinflation TLC > 100% pred RV > 150%	↑ inspiratory resistance
	$PaO_2 > 45$ mmHg	
	$PaCO_2 < 60$ mmHg	
	Postrehabilitation 6 min walk distance > 140 m	
	Low postrehabilitation maximal achieved cycle ergometry watts	
Imaging	*CXR* – Hyperinflation	Homogeneous emphysema and $FEV_1 \leq 20\%$ predicted
	CT – High resolution CT confirming severe emphysema, ideally with upper lobe predominance	Non-upper lobe predominant emphysema and high post-rehabilitation cycle ergometry maximal achieved wattage



No. at risk								
LVRS	70	44	36	29	26	20	5	2
Medical	70	64	54	38	27	12	5	0
Probability of death								
LVRS		0.37	0.49	0.59	0.63	0.67	0.77	0.77
Medical		0.09	0.23	0.46	0.61	0.73	0.82	--
Ratio		4.33	2.12	1.28	1.02	0.93	0.94	--
P		<0.001	0.001	0.12	0.86	0.50	0.53	--

No. at risk								
LVRS	139	127	123	115	88	57	32	6
Medical	151	131	115	95	70	47	16	4
Probability of death								
LVRS		0.09	0.12	0.17	0.28	0.36	0.52	0.55
Medical		0.13	0.24	0.37	0.47	0.54	0.66	0.76
Ratio		0.65	0.48	0.47	0.59	0.67	0.78	0.72
P		0.20	0.01	<0.001	0.001	0.003	0.04	0.006

Fig. 14.5. Kaplan–Meier Estimates of the probability of death as a function of the number of months after randomization in the National Emphysema Treatment Trial (*NETT*). *p* values were derived by Fisher's exact test for the comparison between groups over a median follow-up period of 4.3 years. High-risk patients were defined as those with a forced expiratory volume in 1 s that was 20% or less of the predicted value and either homogeneous emphysema or a carbon monoxide diffusing capacity that was 20% or less of the predicted value. A low baseline exercise capacity was defined as a maximal workload at or below the sex-specific 40th percentile (25 W for women and 40 W for men); a high exercise capacity was defined as a workload above this threshold. This was an intention-to-treat analysis. (**a**) Mortality in high risk patients, (**b**) Mortality in patients with upper lobe predominant emphysema and low, post-rehabilitation exercise capacity(From [44]. With permission)

morbidity [97]. Patients with airflow obstruction from emphysema appear to be the ones who benefit most from LVRS [98, 99]. The RV and RV/TLC ratio may be better predictors of response [100], although the NETT did not identify lung volume as a predictor of mortality or functional improvement after bilateral LVRS [11]. Similarly, NETT investigators identified two subgroups of patients at particularly high risk of surgical mortality after bilateral LVRS (Fig. 14.5) [11, 97]; patients with a -postbronchodilator $FEV_1 \leq 20\%$ predicted and a $DL_{CO} \leq 20\%$ exhibited a much higher mortality with LVRS than with medical management. This same group has confirmed that a lower DL_{CO} was independently associated with postoperative pulmonary morbidity [97]. Arterial blood gas abnormalities have been suggested as predictive of a bad outcome. The most definitive data come from the NETT where baseline $paCO_2$ was not associated with impaired outcome despite over 30% of randomized patients exhibiting baseline hypercapnea [11]. Preoperative exercise capacity has been documented to be a predictor of outcome. The most compelling data comes from the NETT, where one of the primary endpoints was maximal achieved work load achieved on a cycle ergometer while breathing 30% supplemental oxygen [11]. A threshold of 40% of the baseline workload demonstrated a clear breakpoint in mortality for the overall study group; this corresponded to a work load of 25 watts for females and 40 watts for male patients [11]. These thresholds, in conjunction with CT data, allowed a clear separation of nonhigh risk patients into four distinct categories (Fig. 14.6 and Table 14.3).

Thoracic imaging is crucially important in the evaluation of patients for LVRS [102], CT has proven particularly useful in identifying topographic heterogeneity [103, 104]. Several groups have suggested that the severity and heterogeneity of emphysema on CT is associated with outcome of LVRS [105–107]. The most compel-

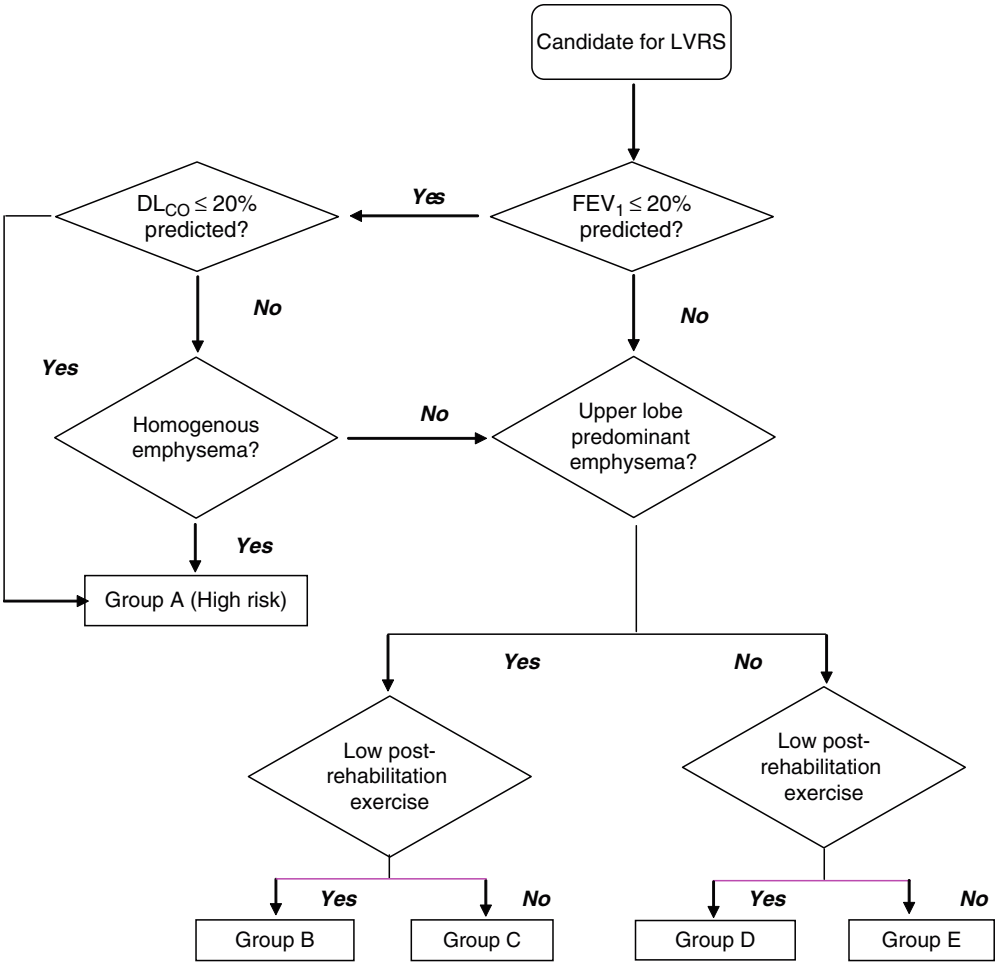


Fig. 14.6. Diagnostic algorithm for patients being considered for LVRS based on data from the National Emphysema Treatment Trial (*NETT*) [11] (From [101]. With permission)

ling data supporting the value of visual grading of emphysema distribution have been provided by NETT investigators [11]. Radiologists at participating clinical centers classified HRCT scans as predominantly exhibiting upper lobe or non-upper lobe emphysema based on visual scoring of disproportionate disease between nonanatomic thirds divided equally from apex to the base [108]. Using this method, in conjunction with the maximal achieved workload during oxygen supplemented maximal cycle ergometry, NETT investigators published several sentinel observations clarifying the role of CT imaging in the evaluation of patients for LVRS. An increased risk of surgical mortality was observed in patients with severe airflow obstruction ($FEV_1 \leq 20\%$ predicted) and either diffuse emphysema on HRCT or a $DL_{CO} \leq 20\%$ predicted (RR 3.9, 95% CI 1.9, 9.0) [11]. Patients with upperlobe predominant emphysema and a low postrehabilitation exercise tolerance exhibited a decreased risk of mortality during long-term follow-up (RR 0.57, $p = 0.01$) after LVRS (Fig. 14.5b) [44]. Patients with non-upper lobe predominant emphysema and a high postrehabilitation exercise capacity experienced an increased risk of death during long-term follow-up after LVRS, which was not statistically significant (RR 1.10, $p = 0.79$). Patients with

Table 14.3 Results of bilateral LVRS compared to medical therapy in patients with severe emphysema. Values in parentheses indicates percentage. Groups A-E refer to the patients as defined in Fig. 14.6 (Adapted from [11, 101]).

	90-day mortality			Total mortality			
Patients	**LVRS**	**Medical therapy**	**p-value**	**LVRS**	**Medical therapy**	**Risk ratio[a]**	**p value**
Group A	20/70 (28.6)	0/70 (0)	<0.001	42/70	30/70	1.82	0.06
Group B	4/139 (2.9)	5/151 (3.3)	1.00	26/139	51/151	0.47	0.005
Group C	6/206 (2.9)	2/213 (0.9)	0.17	34/206	39/213	0.98	0.70
Group D	7/84 (8.3)	0/65 (0)	0.02	28/84	26/65	0.81	0.49
Group E	11/109 (10.1)	1/111 (0.9)	0.003	27/109	14/111	2.06	0.02

	Improvement in exercise capacity[b]				Improvement in health-related quality of life[c]			
Patients	**LVRS**	**Medical therapy**	**Odds ratio**	**p value**	**LVRS**	**Medical therapy**	**Odds ratio**	**p value**
Group A	4/58 (7)	1/48 (2)	3.48	0.37	6/58 (10)	0/48 (0)	–	0.03
Group B	25/84 (30)	0/92 (0)	–	<0.001	40/84 (48)	9/92 (10)	8.38	<0.001
Group C	17/115 (15)	4/138 (3)	5.81	0.001	47/115 (41)	15/138 (11)	5.67	<0.001
Group D	6/49 (12)	3/41 (7)	1.77	0.50	18/49 (37)	3/41 (7)	7.35	0.001
Group E	2/65 (3)	2/59 (3)	0.90	1.00	10/65 (15)	7/59 (12)	1.35	0.61

[a]Risk ratio for total mortality in surgically versus medically treated patients during a mean follow-up of 29.2 months

[b]Increase in the maximal workload of more than 10 W from the patient's postrehabilitation base-line value (24 months after randomization)

[c]Improvement in the health-related quality of life was defined as a decrease in the score on the St. George's Respiratory Questionnaire of more than 8 points (on a 100-point scale) from the patient's postrehabilitation base-line score (24 months after randomization)

upper lobe predominant emphysema and a high postrehabilitation exercise capacity or patients with non-upper lobe predominant emphysema and a low postrehabilitation exercise capacity did not experience a survival advantage or disadvantage [11, 44]. However, regarding this latter group of patients, homogeneous emphysema alone was found to confer increased odds of 90-day mortality, regardless of postrehabilitation exercise capacity (OR 2.99, $p = 0.009$) [97]. Finally, patients with upper lobe predominant emphysema treated surgically were more likely to improve their exercise capacity compared to medically treated patients (Table 14.3). Figure 14.6 and Table 14.3 illustrate an approach to the evaluation of patients based on NETT data.

Lung Transplantation

Given the high morbidity and mortality associated with lung transplantation, careful patient selection is crucial [109]. Furthermore, controversy exists regarding whether a survival benefit is noted after lung transplantation for COPD [110–116]. A summary of potential selection criteria is presented in Table 14.4.

Candidates for lung transplantation should have end-stage pulmonary disease that is nonresponsive to maximal medical management, no other serious major organ system dysfunction or active systemic disease, no active extrapulmonary infection, have the ability to ambulate and participate in pulmonary rehabilitation, have strong social support systems, no evidence of malignancy for at least 2–5 years, no substance addiction (including tobacco use) for at least 6 months, and no untreatable psychiatric condition that would compromise compliance or the ability to "cope" with high stress

Table 14.4 General and disease specific selection guidelines for candidate selection for lung transplantation in COPD patients (Adapted from [109]).

General selection guidelines	COPD disease specific criteria
Relative contraindications	***Referral***
Age older than 65 years	BODE > 5
Critical or unstable clinical condition	***Listing***
Severely limited functional status	BODE > 7–10 or at least one of the following:
Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria	History of hospitalizations for exacerbations associated with acute hypercapnia
Severe obesity (BMI > 31 kg/m^2)	Pulmonary hypertension despite oxygen therapy
Severe or symptomatic osteoporosis	FEV_1 < 20% pred and either DL_{CO} < 20% pred or homogenous distribution of emphysema
Mechanical ventilation	
Other medical conditions that have not resulted in end-stage organ damage should be optimally treated	
Absolute contraindications	
Malignancy in the last 2 years, with the exception of cutaneous (basal and squamous cell) tumors.	
Untreatable advanced dysfunction of another organ system	
Non-curable chronic extrapulmonary infection including chronic active hepatitis B, hepatitis C and HIV	
Significant chest wall/spinal deformity	
Documented nonadherence or inability to follow through with medical therapy or office follow-up	
Untreatable psychiatric or psychologic condition	
Absence of consistent or reliable social support system	
Substance addiction that is either active or within the previous 6 months	

situations [109]. These criteria are usually designated as "absolute" contraindications. Numerous other "relative" contraindications have been suggested and are generally center-dependent (Table 14.4).

Older recipients have a significantly worse survival [19]. The most recent update of the Pulmonary Scientific Council of the ISHLT suggests a potential upper limit for recipient age of greater than 65 years [109]. A BMI of < 17 kg/m2 or > 30 kg//m2 has been associated with greater 90-day mortality [117–119]. Severe osteoporosis should also be considered prior to transplant listing as accelerated bone loss as well as atraumatic fractures are associated with lung transplantation [120–122]. Mechanical ventilation, colonization with antibiotic-resistant bacteria, fungi or atypical mycobacteria; other medical conditions including previous coronary artery bypass grafting, severe gastroesophogeal reflux disease or diabetes mellitus, are additional relative contraindications for lung transplant listing [109]. Therefore, these criteria may be considered contraindications for transplantation.

Physiologic testing has been the most frequently used modality to assess prognosis in patients with COPD [123]. As such, numerous investigators have documented that the FEV_1 after bronchodilator administration is an important predictor of mortality

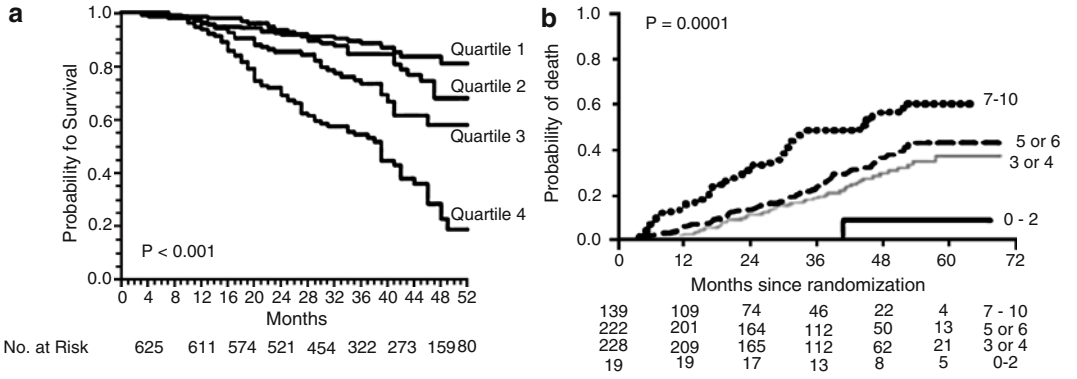


Fig. 14.7. (**a**) Kaplan-Meier survival curves for four quartiles of the body mass index, degree of airflow obstruction, dyspnoea, and exercise capacity index (*BODE*) for a cohort of 625 COPD patients. Quartile 1 is a score of 0–2, quartile 2 is a score of 3–4, quartile 3 is a score of 5–6, while quartile 4 is a score of 7–10. (**b**) Kaplan-Meier estimates of the probability of death as a function of the number of years after randomized patients for medically treated patients in the NETT segregated by modified BODE index. The *p* value was derived from the log rank test for the comparison between subgroups over a median follow-up period of 3.9 years. The curve labels reflect the ranges of BODE scores (**a**: From [132]; **b**: From [133]. With permission)

in COPD [123]. Other predictors of mortality include weight loss [124, 125], dyspnoea [126], and exercise capacity [127]. An acute exacerbation of COPD requiring hospitalization can be predictive of a poor outcome [128, 129]. Multivariate analysis of factors predicting death of patients on the United Network for Organ Sharing (UNOS) lung transplant waiting list confirmed these findings [130].

Recent data have suggested that multidimensional approaches to stratifying disease severity is a better approach to prognostication in COPD [131]. An index incorporating FEV_1, 6-min walk distance, measurement of dyspnoea and BMI, the BODE score, predicts survival better in COPD than spirometry alone [132]. Figure 14.7a illustrates how an increasing quartile of BODE score is associated with a worse prognosis in a large cohort of COPD patients. Similarly, in the NETT medically treated cohort, a group that in many ways resembles COPD patients eligible for transplantation, increasing BODE score is associated with impaired prognosis [133] (Fig. 14.7b). Although comparisons must be made with great caution, one can contrast these estimates of survival with the most recent data presented from the ISHLT (Fig. 14.4). It is evident that one can suggest that only COPD patients with greater BODE scores are likely to experience any survival benefit from transplantation (Table 14.4). Additional data are required to better refine these concepts.

Imaging techniques have a less-defined role in the preoperative evaluation for lung transplantation. The recent report of the NETT Research Group confirms that increasing emphysema volume and distribution independently impact long-term survival in a large cohort of medically treated patients with emphysema [133]. CT appears to alter the surgical approach to lung transplantation in selected patients. Kazerooni and colleagues noted that baseline CT prompted a change in determining which lung was more severely diseased in 27 of 169 patients transplant candidates [134]. Similarly, pulmonary nodules, suspicious for malignancy, have been identified in pretransplant CTs of lung transplant candidates [135]. Finally, the presence of unsuspected bronchiectasis could alter the decision to perform DLT in contrast to SLT.

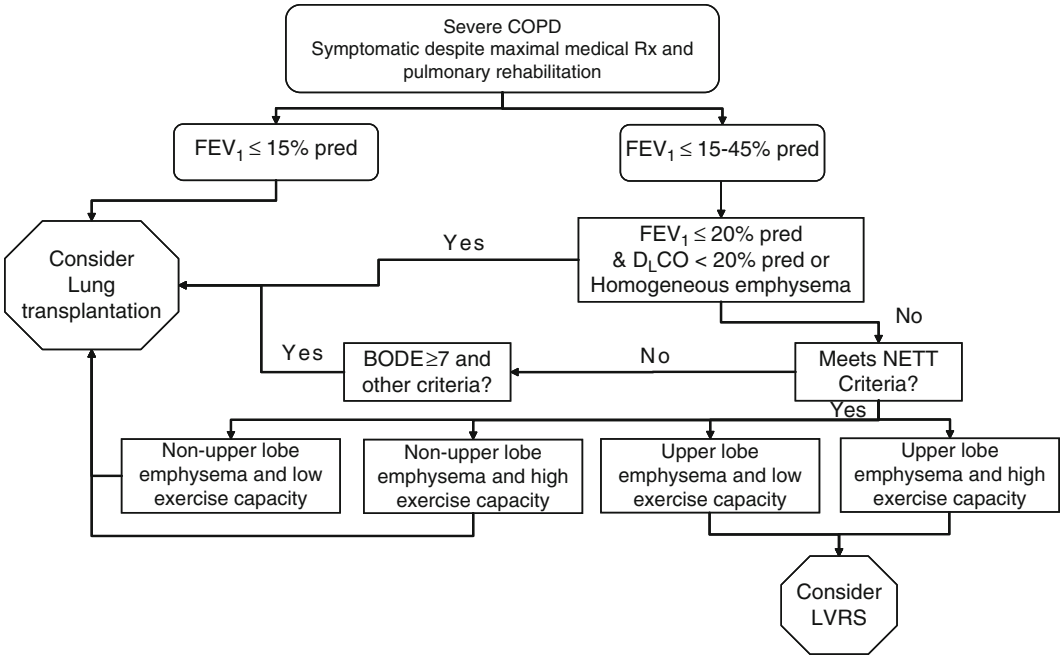


Fig. 14.8. Potential algorithm for the consideration of LVRS and lung transplantation in patients with advanced COPD. NETT criteria include a clinical and radiological scenario consistent with bilateral emphysema, BMI ≤ 31.1 for men and 32.3 for women, prednisone dose ≤ 20 mg daily, FEV1 ≤ 45% predicted, TLC ≥ 100% predicted, RV ≥ 150% predicted, $paCO_2 \leq 60$ mmHg (≤55 mg at altitude), $paO_2 \geq 45$ mmHg (≥ 30 at altitude), stable cardiac status, post-pulmonary rehabilitation 6-min walk distance ≥ 140 m and able to complete 3 min of unloaded pedaling in maximal, oxygen supplemented exercise test [40]. (Modified from [136])

Lung Transplantation Versus LVRS

Given the overlap of selection criteria for lung transplantation and LVRS, it is evident that careful consideration for the optimal surgical procedure needs to take place for individual COPD patients. The data from the NETT are particularly valuable in allowing the proposal of a detailed algorithm (Fig. 14.8). Recommendation for LVRS in patients with non-upper lobe predominant emphysema and low postrehabilitation exercise capacity (Group D, Table 14.3) is tempered by the finding of increased risk for 90-day mortality in this subgroup [97], and consideration of LVRS for this subset of patients should be considered carefully. Additional data are required to confirm the validity of this approach and to refine recommendations.

Conclusions

Extensive literature has been published regarding surgical therapies for advanced COPD, with the most widely accepted directed at surgical relief of hyperinflation. Bullectomy and LVRS are established surgical techniques for a very limited number of patients. The patients with the poorest long-term outcomes appear to be those with the most abnormal respiratory function or greater extent of emphysema on imaging studies. Lung transplantation may serve as a viable therapeutic option for some of these COPD patients.

References

1. Martinez F (1998) Diagnosing chronic obstructive pulmonary disease. The importance of differentiating asthma, emphysema and chronic bronchitis. Postgrad Med 103:112–125
2. Pauwels R, Buist A, Calverley P, Jenkins C, Hurd S, Committee GS (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care 163:1256–1276
3. Celli B, MacNee W, Committee members, ATS/ERS task force (2004) Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J 23(6):932–946
4. Meyers B, Patterson G (2003) Chronic obstructive pulmonary disease. 10: bullectomy, lung volume reduction surgery, and transplantation for patients with chronic obstructive pulmonary disease. Thorax 58:634–638
5. Deslauriers J (1996) History of surgery for emphysema. Semin Thorac Cardiovasc Surg 8:43–51
6. Brantigan O, Kress M, Mueller E (1959) A surgical approach to pulmonary emphysema. Am Rev Respir Dis 39:194–202
7. Brantigan O, Mueller E (1957) Surgical treatment of pulmonary emphysema. Am Surg 23:789–804
8. Wakabayashi A (1995) Thoracoscopic laser pneumoplasty in the treatment of diffuse bullous emphysema. Ann Thorac Surg 60:936–942
9. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, Sundaresan RS, Roper CL (1995) Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 109:106–116
10. Benditt J (2004) Surgical therapies for chronic obstructive pulmonary disease. Respir Care 49:53–61
11. National Emphysema Treatment Trial Research Group (2003) A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073
12. National Emphysema Treatment Trial Research Group (2004) Safety and efficacy of median sternotomy versus video-assisted thoracic surgery for lung volume reduction surgery. J Thorac Cardiovas Surg 127:1350–1360
13. Pompeo E, Marino M, Nofroni I, Matteucci G, Mineo TC (2000) Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. Pulmonary Emphysema Research Group. Ann Thorac Surg 70:948–953, discussion 954
14. Goldstein R, Todd T, Guyatt G, Keshavjee S, Domage T, van Rooy S, Krip B, Maltais F, Leblanc P, Pakhale S et al (2003) Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. Thorax 58:405–410
15. Geddes D, Davies M, Koyama H, Hansell D, Pastorino U, Pepper J, Agent P, Cullinan P, MacNeill S, Goldstraw P (2000) Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 343:239–245
16. Dunitz J, Hertz M (1999) Surgical therapy for COPD: lung transplantation. Semin Respir Crit Care Med 20:365–373
17. Patterson G, Cooper J, Goldman B et al (1988) Technique of successful clinical double lung transplantation. Ann Thorac Surg 45:626–633
18. Mal H, Andreassian B, Pamela F, Duchatelle J, Rondeau E, Dubois F, Baldeyrou P, Kitzis M, Sleiman C, Pariente R (1989) Unilateral lung transplantation in end-stage pulmonary emphysema. Am Rev Respir Dis 140:787–802
19. Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel AO, Taylor DO, Kucheryavaya AY, Hertz MI (2008) Registry of the International Society for Heart and Lung Transplantation: Twenty-fifth official adult lung and heart/lung transplantation report–2008. J Heart Lung Transplant 27:957–969

20. Cooper JD, Patterson GA, Sundaresan RS, Trulock EP, Yusen RD, Pohl MS, Lefrak SS (1996) Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 112:1319–1329
21. Brenner M, Yusen R, McKenna R Jr, Sciurba F, Gelb A, Fischel R, Swain J, Chen J, Kafie F, Lefrak S (1996) Lung volume reduction surgery for emphysema. Chest 110:205–218
22. McKenna R, Brenner M, Gelb A, Mullin M, Singh N, Peters H, Panzera J, Calmese J, Schein M (1996) A randomized, prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. J Thorac Cardiovasc Surg 111:317–322
23. Hopkinson NS (2007) Bronchoscopic lung volume reduction: indications, effects and prospects. Curr Opin Pulm Med 13:125–130
24. Venuta F, Rendina EA, De Giacomo T, Anile M, Diso D, Andreetti C, Pugliese F, Coloni GF (2006) Bronchoscopic procedures for emphysema treatment. Eur J Cardiothorac Surg 29:281–287
25. Snell GI, Holsworth L, Borrill ZL, Thomson KR, Kalff V, Smith JA, Williams TJ (2003) The potential for bronchoscopic lung volume reduction using bronchial prostheses: a pilot study. Chest 124:1073–1080
26. Toma TP, Hopkinson NS, Hillier J, Hansell DM, Morgan C, Goldstraw PG, Polkey MI, Geddes DM (2003) Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 361:931–933
27. Lausberg HF, Chino K, Patterson GA, Meyers BF, Toeniskoetter PD, Cooper JD (2003) Bronchial fenestration improves expiratory flow in emphysematous human lungs. Ann Thorac Surg 75:393–397, discussion 398
28a. Wan IY, Toma TP, Geddes DM, Snell G, Williams T, Venuta F, Yim AP (2006) Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. Chest 129:518–526
28b. Sciurba FC, Ernst A, Hert FJF, Strange C, Criner GJ, Marquette CH, Kovitz KL, Chiacchierini RP, Goldin J, McLennan G (2010) A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 363:1233–1244
29. Wood DE, McKenna RJ Jr, Yusen RD, Sterman DH, Ost DE, Springmeyer SC, Gonzalez HX, Mulligan MS, Gildea T, Houck WV et al (2007) A multicenter trial of an intrabronchial valve for treatment of severe emphysema. J Thorac Cardiovasc Surg 133:65–73
30. Weill D, Keshavjee S (2001) Lung transplantation for emphysema: two lungs or one. J Heart Lung Transplant 20:739–742
31. Hadjiliadis D, Angel LF (2006) Controversies in lung transplantation: are two lungs better than one? Semin Respir Crit Care Med 27:561–566
32. Thabut G, Christie JD, Ravaud P, Castier Y, Brugière O, Fournier M, Mal H, Lesèche G, Porcher R (2008) Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. Lancet 371:744–751
33. Snider GL (1996) Reduction pneumoplasty for giant bullous emphysema. Implications for surgical treatment of nonbullous emphysema. Chest 109:540–548
34. Fitzgerald M, Keelan P, Angell D (1974) Long-term results of surgery for bullous emphysema. Surgery 68:566–582
35. Pearson M, Ogilvie C (1983) Surgical treatment of emphysematous bullae: late outcome. Thorax 38:134–137
36. Schipper P, Meyers B, Battafarano R, Guthrie T, Patterson G, Cooper J (2004) Outcomes after resection of giant emphysematous bullae. Ann Thorac Surg 78:976–982
37. Palla A, Desideri M, Rossi G, Bardi G, Mazzantini D, Mussi A, Giuntini C (2005) Elective surgery for giant bullous emphysema. A 5-year clinical and functional follow-up. Chest 128:2043–2050
38. Neviere R, Catto M, Bautin N, Robin S, Porte H, Desbordes J, Matran R (2006) Longitudinal changes in hyperinflation parameters and exercise capacity after giant bullous emphysema surery. J Thorac Cardiovasc Surg 132:1203–1207
39. Flaherty KR, Martinez FJ (2000) Lung volume reduction surgery for emphysema. Clin Chest Med 21:819–848

40. National Emphysema Treatment Trial Research Group (1999) Rationale and design of the National Emphysema Treatment Trial: a prospective randomized trial of lung volume reduction surgery. Chest 116:1750–1761
41. Lilm E, Ali A, Cartwright N, Sousa I, Chetwynd A, Polkey M, Geddes D, Pepper J, Diggle P, Goldstraw P (2006) Effect and duration of lung volume reduction surgery: mid-term results of the Brompton Trial. Thorac Cardiovasc Surg 54:188–192
42. Miller J, Malthaner R, Goldsmith C, Goeree R, Higgins D, Cox P, Tan L, Road J, the Canadian Lung Volume Reduction Surgery Study (2006) A randomized clinical trial of lung volume reduction surgery versus best medical care for patients with advanced emphysema: a two-year study from Canada. Ann Thorac Surg 81:314–321
43. Hillerdal G, Lofdahl C, Strom K, Skoogh B, Jorfeldt L, Nilsson F, Forslund-Stiby D, Ranstam J, Gyllstedt E, the Swedish VOLREM Group (2005) Comparison of lung volume reduction surgery and physical training on health status and physiologic outcomes. A randomized controlled clinical trial. Chest 128:3489–3499
44. Naunheim K, Wood D, Mohsenifar Z, Sternberg A, Criner G, DeCamp M Jr, Deschamps C, Martinez F, Sciurba F, Tonascia J et al (2006) Long-term follow-up of patients receiving lung-volume reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 82: 431–443
45. Lowdermilk G, Keenan R, Landreneau R, Hazelrigg S, Bavaria J, Kaiser L, Keller C, Naunheim K (2000) Comparison of clinical results for unilateral and bilateral thoracoscopic lung volume reduction. Ann Thorac Surg 69:1670–1674
46. Keenan R, Landrenau R, Sciurba F, Ferson P, Holbert J, Brown M, Fetterman L, Bowers C (1996) Unilateral thoracoscopic surgical approach for diffuse emphysema. J Thorac Cardiovasc Surg 111:308–316
47. Albert R, Benditt J, Hildebrandt J, Wood D, Hlastala M (1998) Lung volume reduction surgery has variable effects on blood gases in patients with emphysema. Am J Respir Crit Care Med 158:71–76
48. Brenner M, McKenna R Jr, Gelb A, Fischel R, Wilson A (1998) Rate of FEV1 change following lung volume reduction surgery. Chest 113:652–659
49. Yusen R, Lefrak S, Gierada D, Davis G, Meyers B, Patterson G, Cooper J (2003) A prospective evaluation of lung volume reduction surgery in 200 consecutive patients. Chest 123:1026–1037
50. Dolmage T, Waddell T, Maltais F, Guyatt G, Todd T, Keshavjee S, van Rooy S, Krip B, LeBlanc P, Goldstein R (2004) The influence of lung volume reduction surgery on exercise in patients with COPD. Eur Respir J 23:269–274
51. Cordova F, O'Brien G, Furukawa S, Kuzma A, Travaline J, Criner G (1997) Stability of improvement in exercise performance and quality of life following bilateral lung volume reduction surgery in severe COPD. Chest 112:907–915
52. Flaherty KR, Kazerooni EA, Curtis JL, Iannettoni M, Lange L, Schork MA, Martinez FJ (2001) Short-term and long-term outcomes after bilateral lung volume reduction surgery: prediction by quantitative CT. Chest 119:1337–1346
53. Yusen R, Morrow L, Brown K (2002) Health-related quality of life after lung volume reduction surgery. Semin Thorac Cardiovasc Surg 14:403–412
54. Levine S, Anzueto A, Peters J, Cronin T, Saki E, Jenkinson S, Bryan C (1994) Medium term functional results of single-lung transplantation for endstage obstructive lung disease. Am J Respir Crit Care Med 150:398–402
55. Gaissert H, Trulock E, Cooper J, Sundaresan R, Patterson G (1996) Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 111:296–307
56. Mal H, Sleiman C, Jebrak G, Messian O, Dubois F, Darne C, Duchatelle J, Mollo J, Fournier M, Kitzis M et al (1994) Functional results of single-lung transplantation for chronic obstructive lung disease. Am J Respir Crit Care Med 149:1476–1481
57. Boehler A, Estenne M (2003) Post-transplant bronchiolitis obliterans. Eur Respir J 22:1007–1018

58. Chan A, Allen R (2004) Bronchiolitis obliterans: an update. Curr Opin Pulm Med 10:133–141
59. Estenne M, Maurer J, Boehler A et al (2002) Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 21:297–310
60. Lama VN, Murray S, Lonigro RJ, Toews GB, Chang A, Lau C, Flint A, Chan KM, Martinez FJ (2007) Course of FEV1 after onset of bronchiolitis obliterans syndrome in lung transplant recipients. Am J Respir Crit Care Med 175(11):1192–1198
61. Kerber A, Szidon P, Kesten S (2000) Skeletal muscle dysfunction in lung transplantation. J Heart Lung Transplant 19:392–400
62. Reinsma GD, ten Hacken NHT, Grevink RG, van der Bij W, Koeter GH, van Weert E (2006) Limiting factors of exercise performance 1 year after lung transplantation. J Heart Lung Transplant 25:1310–1316
63. Williams T, Slater W (2002) Role of cardiopulmonary exercise testing in lung and heart-lung transplantation. In: Weisman I, Zeballos R (eds) Clinical exercise testing prog respir res. Karger, Basel, pp 254–263
64. Hokanson J, Mercier J, Brooks G (1995) Cyclosporine A decreases rat skeletal muscle mitochondiral respiration in vitro. Am J Respir Crit Care Med 151:1848–1851
65. Mercier J, Hokanson J, Brooks G (1995) Effects of cyclosporine A on skeletal muscle mitochondrial respiraton and endurance time in rats. Am J Respir Crit Care Med 151:1532–1536
66. Biring M, Fournier M, Ross D, Lewis M (1998) Cellular adaptations of skeletal muscles to cyclosporin. J Appl Physiol 84:1967–1975
67. Sundaresan R, Shiraishi Y, Trulock E, Manley J, Lynch J, Cooper J, Patterson G (1996) Single or bilateral lung transplantation for emphysema? J Thorac Cardiovasc Surg 112:1485–1495
68. Cassivi S, Meyers B, Battafarano R, Guthrie T, Trulock EP, Lynch DA, Cooper J, Patterson G (2002) Thirteen-year experience in lung transplantation for emphysema. Ann Thorac Surg 74:1663–1669
69. Gerbase MW, Spiliopoulos A, Rochat T, Archinard M, Nicod LP (2005) Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. Chest 128:1371–1378
70. Gross C, Savik K, Bolman R III, Hertz M (1995) Long-term health status and quality of life outcomes of lung transplant recipients. Chest 108:1587–1593
71. TenVergert E, Essink-Bot M, Geertsma A, van Enckevort P, de Boer W, van der Bij W (1998) The effect of lung transplantation on health-related quality of life. A longitudinal study. Chest 113:358–364
72. Vermuelen KM, van der Bij W, Erasmus ME, TenVergert EM (2007) Long-term health-related quality of life after lung transplantation: different predictors for different dimensions. J Heart Lung Transplant 26:188–193
73. Cohen L, Littlefield C, Kelly P, Maurer J, Abbey S (1998) Predictors of quality of life and adjustment after lung transplantation. Chest 113:633–644
74. van Den Berg J, Geertsma A, van der Bij W et al (2000) Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life. Am J Respir Crit Care Med 161:1937–1941
75. Anyanwu A, McGuire A, Rogers C, Murday A (2001) Assessment of quality of life in lung transplantaion using a simple generic tool. Thorax 56:218–222
76. Rodrigue JR, Baz MA, Kanasky JWF, MacNaughton KL (2005) Does lung transplantation improve health-related quality of life? The University of Florida experience. J Heart Lung Transplant 24:755–763
77. Rodrigue JR, Baz MA (2006) Are there sex differences in health-related quality of life after lung transplantation for chronic obstructive pulmonary disease? J Heart Lung Transplant 25:120–125
78. Martinez F, Chang A (2005) Surgical therapy for chronic obstructive pulmonary disease. Semin Respir Crit Care Med 26:167–191
79. Laros CD, Gelissen HJ, Bergstein PG, Van den Bosch JM, Vanderschueren RG, Westermann CJ, Knaepen PJ (1986) Bullectomy for giant bullae in emphysema. J Thorac Cardiovasc Surg 91:63–70

80. Gaensler E, Jederlinic P, FitzGerald M (1986) Patient work-up for bullectomy. J Thorac Imaging 1:75–93
81. Nakahara K, Nakoaka K, Ohno K, Monden Y, Maeda M, Masaoka A, Sawamura K, Kawashima Y (1983) Functional indications for bullectomy of giant bulla. Ann Thorac Surg 35:480–487
82. Hugh-Jones P, Whimster W (1978) The etiology and management of disabling emphysema. Am Rev Respir Dis 117:343–378
83. Nickoladze G (1992) Functional results of surgery for bullous emphysema. Chest 101:119–122
84. Kinnear W, Tatterfield A (1990) Emphysematous bullae: surgery is best for large bullae and moderately impaired lung function. BMJ 300:208–209
85. Flaherty K, Kazerooni E, Martinez F (2000) Differential diagnosis of chronic airflow obstruction. J Asthma 37:201–223
86. Thurnheer R, Muntwyler J, Stammberger U, Bloch K, Zollinger A, Weder W, Russi E (1997) Coronary artery disease in patients undergoing lung volume reduction surgery for emphysema. Chest 112:122–128
87. Whyte R, Bria W, Martinez F, Lewis P, Bolling S (1998) Combined lung volume reduction surgery and mitral valve reconstruction. Ann Thorac Surg 66:1414–1416
88. Schmid R, Stammberger U, Hillinger S, Vogt P, Amman F, Russi E, Weder W (1999) Lung volume reduction surgery combined with cardiac interventions. Eur J Cardiothorac Surg 15:585–591
89. Lefrak S, Yusen R, Trulock E, Pohl M, Patterson A, Cooper J (1997) Recent advances in surgery for emphysema. Annu Rev Med 48:387–398
90. Utz J, Hubmayr R, Deschamps C (1998) Lung volume reduction surgery for emphysema: out on a limb without a nett. Mayo Clin Proc 73:552–556
91. Teschler H, Thompson A, Stamatis G (1999) Short- and long-term functional results after lung volume reduction surgery for severe emphysema. Eur Respir J 13:919–925
92. Stoller J, Gildea T, Ries A, Meli Y, Karafa M, the National Emphysema Treatment Trial Research Group (2007) Lung volume reduction surgery in patients with emphysema and α-1 antitrypsin deficiency. Ann Thorac Surg 83:241–251
93. Cassina P, Teschler H, Konietzko N, Theegarten D, Stamatis G (1998) Two-year results after lung volume reduction surgery in α-1 antitrypsin deficiency *versus* smoker's emphysema. Eur Respir J 12:1028–1032
94. Gelb A, McKenna R, Brenner M, Fischel R, Zamel N (1999) Lung function after bilateral lower lobe lung volume reduction surgery for α1-antitrypsin emphysema. Eur Respir J 14:928–933
95. Mazolewski P, Turner J, Baker M, Kurtz T, Little A (1999) The impact of nutritional status on the outcome of lung volume reduction surgery. A prospective study. Chest 116: 693–696
96. Nezu K, Yoshikawa M, Yoneda T, Kushibe K, Kawaguchi T, Kimura M, Kobayashi A, Takenaka H, Fukuota A, Narita N et al (2001) The effect of nutritional status on morbidity in COPD patients undergoing bilateral lung reduction surgery. Thorac Cardiovasc Surg 49: 216–220
97. Naunheim K, Wood D, Krasna M, DeCamp M Jr, Ginsburg M, McKenna R, Criner G, Hoffman E, Sternberg A, Deschamps C et al (2006) Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial. J Thorac Cardiovasc Surg 131:43–53
98. Ingenito EP, Loring SH, Moy ML, Mentzer SJ, Swanson SJ, Reilly JJ (2001) Interpreting improvement in expiratory flows after lung volume reduction surgery in terms of flow limitation theory. Am J Respir Crit Care Med 163:1074–1080
99. Kim V, Criner G, Abdallah H, Gaughan J, Furukawa S, Solomides C (2005) Small airway morphometry and improvement in pulmonary function after lung volume reduction surgery. Am J Respir Crit Care Med 171:40–47
100. Fessler H, Permutt S (1998) Lung volume reduction surgery and airflow limitation. Am J Respir Crit Care Med 157:715–722

101. Martinez F, Flaherty K, Iannettoni M (2003) Patient selection for lung volume reduction surgery. Chest Surg Clin N Am 13:669–685
102. Gierada D (2002) Radiologic assessment of emphysema for lung volume reduction surgery. Semin Thorac Cardiovasc Surg 14:381–390
103. Kazerooni E (1999) Radiologic evaluation of emphysema for lung volume reduction surgery. Clin Chest Med 20:845–861
104. Goldin J (2002) Quantitative CT of the lung. Radiol Clin North Am 40:45–58
105. Rogers RM, Coxson HO, Sciurba FC, Keenan RJ, Whittall KP, Hogg JC (2000) Preoperative severity of emphysema predictive of improvement after lung volume reduction surgery: use of CT morphometry. Chest 118:1240–1247
106. Slone RM, Pilgram TK, Gierada DS, Sagel SS, Glazer HS, Yusen RD, Cooper JD (1997) Lung volume reduction surgery: comparison of preoperative radiologic features and clinical outcome [see comments]. Radiology 204:685–693
107. Bloch K, Georgescu C, Russi E, Weder W (2002) Gain and subsequent loss of lung function after lung volume reduction surgery in cases of severe emphysema with different morphologic patterns. J Thorac Cardiovasc Surg 123:845–854
108. Sciurba F (2002) Preoperative predictors of outcome following lung volume reduction surgery. Thorax 57(Suppl II):ii47–ii52
109. Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R et al (2006) International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 25:745–755
110. Studer S, Levy R, McNeil K, Orens J (2004) Lung transplant outcomes; a review of survival, graft function, physiology, health-related quality of life and cost-effectiveness. Eur Respir J 24:674–685
111. DeMeester J, Smits J, Persijn G, Haverich A (1999) Lung transplant waiting list: differential outcome of type of end-stage lung disease, one year after registration. J Heart Lung Transplant 18:563–571
112. Demeester J, Smits J, Persijn G, Haverich A (2001) Listing for lung transplantation: life expectancy and transplant effect, stratified by type of end-stage lung disease, the Eurotransplant experience. J Heart Lung Transplant 20:518–524
113. Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ (1998) Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet 351:24–27
114. Charman SC, Sharples LD, McNeil KD, Wallwork J (2002) Assessment of survival benefit after lung transplantation by patient diagnosis. J Heart Lung Transplant 21:226–232
115. Stavem K, Bjortuft O, Borgan O, Geiran O, Boe J (2006) Lung transplantation in patients with chronic obstructive pulmonary diseaes in a national cohort is without obvious survival benefit. J Heart Lung Transplant 25:75–84
116. Gunes A, Aboyoun CL, Morton JM, Plit M, Malouf MA, Glanville AR (2006) Lung transplantation for chronic obstructive pulmonary disease at st Vincent's Hospital. Intern Med J 36:5–11
117. Madill J, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, Keshavjee S, Program TLT (2001) Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. J Heart Lung Transplant 20:288–296
118. Culver D, Mazzone P, Khandwala F, Blazey H, DeCamp M, Chapman J (2005) Discordant utility of ideal body weight and body mass index as predictors of mortality in lung transplant recipients. J Heart Lung Transplant 24:137–144
119. Kanasky W, Anton S, Rodrigue J, Perri M, Szwed T, Baz M (2002) Impact of body weight on long-term survival after lung transplantation. Chest 121:401–406
120. Shane E, Papadopoulos A, Staron R, Addesso V, Donovan D, McGregor C, Schulman L (1999) Bone loss and fracture after lung transplantation. Transplantation 68:220–227
121. Spira A, Gutierrez C, Chaparro C, Hutcheon M, Chan C (2000) Osteoporosis and lung transplantation: a prospective study. Chest 117:476–481
122. Aris RM, Neuringer IP, Weiner MA, Egan TM, Ontjes D (1996) Severe osteoporosis before and after lung transplantation. Chest 109:1176–1183

123. Martinez F, Kotloff R (2001) Prognostication in chronic obstructive pulmonary disease: implications for lung transplantation. Semin Respir Crit Care Med 22:489–498
124. Landbo C, Prescott E, Lange P, Vestbo J, Almdal T (1999) Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:1856–1861
125. Gray-Donald K, Gibbons L, Shapiro S, MacKlem P, Martin J (1996) Nutritional status and mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153:961–966
126. Nishimura K, Izumi T, Tsukino M, Oga T (2002) Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 121:1434–1440, On Behalf of the Kansai COPD Registry and Research Group in Japan
127. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T (2002) Analysis of the factors related to mortality in chronic obstructive pulmonary disease. Role of exercise capacity and health status. Am J Respir Crit Care Med 167:544–549
128. Groenewegen K, Schols A, Wouters E (2003) Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 124:459–467
129. Connors A Jr, Dawson N, Thomas C, Harrell F, Desbiens N, Fulkerson W, Kussin P, Bellamy P, Goldman L, Knaus W et al (1996) Outcomes following acute exacerbation of severe chronic obstructive lung disease. Am J Respir Crit Care Med 154:959–967
130. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, Coke MA, Garrity ER, Sweet SC, Heiney DA et al (2006) Development of the new lung allocation system in the United States. Am J Transplant 6:1212–1227
131. Celli B, Calverley P, Rennard S, Wouters E, Agusti A, Anthonisen N, MacNee W, Jones P, Pride N, Rodriguez-Roisin R et al (2005) Proposal for a multidimensional staging system for chronic obstructive pulmonary disease. Respir Med 99:1546–1554
132. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012
133. Martinez F, Foster G, Curtis J, Criner G, Weinmann G, Fishman A, DeCamp M, Benditt J, Sciurba F, Make B et al (2006) Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med 173:1326–1334
134. Kazerooni EA, Chow LC, Whyte RI, Martinez FJ, Lynch JP (1995) Preoperative examination of lung transplant candidates: value of chest CT compared with chest radiography. AJR Am J Roentgenol 165:1343–1348
135. Kazerooni EA, Hartker FW, Whyte RI, Martinez FJ, Lynch JP (1996) Transthoracic needle aspiration in patients with severe emphysema. A study of lung transplant candidates. Chest 109:616–619
136. Nathan S (2005) Lung transplantation. Disease-specific considerations for referral. Chest 127:1006–1016

15

Depression and Anxiety in COPD: Diagnosis and Management Issues

Soo Borson

Key Points:

- Depression, often with anxiety, is common in COPD, contributes to disability, and is detectable by simple screening tools.
- Mild mood symptoms often respond well to good medical management and pulmonary rehabilitation, but major depressive episodes and panic disorder should be diagnosed and specifically treated. Treatment outcome studies are too limited to provide guideline-level support for choosing among interventions.
- Current best practices include screening COPD patients for major depression and panic disorder, initiating specific treatment, and monitoring patient response at planned intervals. Persistently symptomatic patients should be referred to an appropriate mental health specialist.

Keywords Antidepressant • anxiety • anxiolytic • collaborative care • depression • disease management • family involvement • lung disease • pulmonary rehabilitation

Introduction

Clinically significant symptoms of depression and anxiety affect at least 40% of patients with COPD. When persistent, mood symptoms worsen quality of life and diminish motivation to sustain important disease-management activities such as regular exercise and a smoke-free lifestyle. Mild mood symptoms can, for many patients, be alleviated by optimizing management of lung and other comorbid disease and exercise-based pulmonary rehabilitation. A key to effective management of depression and anxiety is to distinguish such mild symptoms – that generally do not require a separate treatment – from those due to mood disorders that will likely persist or worsen unless specifically treated.

Major depression and panic disorder are two mood disorders that require specific treatment. Use of simple screening measures in primary care and pulmonary disease clinics would improve recognition of depression and panic disorder in COPD patients, and antidepressant therapy can be helpful for both conditions. However, studies evaluating the efficacy and proper selection of antidepressants in COPD patients are very limited in size and scope, and often inconclusive for methodological reasons. The best data support the efficacy of an older tricyclic antidepressant, nortriptyline; studies of newer, easier to

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_15,

use medications (selective serotonin reuptake inhibitors) have not established their value for either depression or panic disorder in COPD. In addition, many patients refuse antidepressants, and clinicians need access to nonpharmacological modalities of treatment for depressed and anxious patients. Collaborative models of care utilize depression screening followed by monitored treatment by the primary physician, and then by mental health specialty consultation and treatment for poor responders. Such models can be adapted to both primary and specialty medical settings where COPD patients are managed.

Overview: Depression and Anxiety in COPD

Many studies over the last 40 years have documented the common occurrence of depression and anxiety symptoms in patients with COPD. Precise prevalence figures vary between 40% for clinically significant depression (reviewed in [1, 2]) and over 80% [3] for any depressive and/or anxiety symptoms. There is general agreement among investigators that depression is associated with many different types of adverse outcomes in COPD. These include poorer quality of life, greater total symptom burden and functional disability, more persistent smoking, poorer outcomes of pulmonary rehabilitation, more hospital readmissions, longer lengths of stay, refusal of resuscitation as a future option, and shortened survival [1, 4–8].

There is much less consensus as to how depression and anxiety should be managed, and very little data demonstrating the effect of treatment for depression on relevant disability outcomes. In addition, little is known about how the long-term, changing trajectory of COPD relates to mood disorder risk, onset, and chronicity. Specific disease-related events are likely to heighten this risk. Good candidates include: the initial diagnosis of COPD, when the patient hears that he/she has an incurable, progressive condition; after acute exacerbations and hospitalizations; having a pattern of frequent exacerbations or an episode of respiratory failure and artificial ventilation; needing oxygen at night and with exercise; becoming permanently oxygen dependent; developing secondary heart failure; and approaching the end of life.

Although much remains to be learned about the relationship between mood disorders and COPD, the correct diagnosis has prognostic and therapeutic significance: among patients followed longitudinally after hospitalization for a COPD exacerbation, two-thirds with minor or subsyndromal depression remitted by 12 weeks, compared to only one-quarter with major depression [9]. At 24 weeks, still only 49% of those with major depression had remitted [9]. Nevertheless, most studies of mood in COPD do not distinguish mild or minor from major depression (and similarly, mild anxiety from panic disorder), confounding the results of intervention trials. We retain this distinction whenever relevant throughout the remainder of this chapter.

Diagnosing Depression and Anxiety

Diagnostic criteria for major depression are the same for chronically medically ill and medically healthy adults [10] and, though less well established, the same is true of anxiety disorders (see Table 15.1 for criteria). Simple, brief tools well within the scope of both primary and specialty care practice can screen, diagnose,

Table 15.1 DSM-IV TR criteria for major depression and panic disorder.

Major depression	Panic disorder
Five or more of the following symptoms are endorsed and have been present for at least 2 weeks and constitute a change from previous functioning (at least one symptom must be either depressed mood or loss of interest or pleasure) 1. Depressed mood most of the day, nearly every day; can be self-reported or reported by others 2. Marked decrease in interest or pleasure in activities (anhedonia); can be self-reported or reported by others 3. Significant change in weight 4. Sleep disturbance 5. Psychomotor disturbance 6. Fatigue or loss of energy nearly every day 7. Feeling worthless or having excessive guilt feelings 8. Decreased ability to concentrate, focus, make ordinarily easy decisions 9. Recurrent thoughts of death, suicidal thoughts with or without a plan or an attempt at suicide Mood symptoms cause distress and impaired social, occupational or other important daily function, and are not due to another physical or substance abuse issue. *In COPD[a]: Do not diagnose major depression during an acute respiratory exacerbation, or afterwards until respiratory function has stabilized for 2 weeks or more.*	Both of the following are present: 1. Recurrent panic attacks 2. At least one attack has been followed by at least 1 month of one or more of the following: (a) Near constant concern with having additional panic attacks (b) Worry about the implications of the attacks or their consequences (c) A significant change in behavior related to the attacks The patient may be afraid to leave home or be in large groups (agoraphobia, if present note separately) The panic attacks are not due to another physical or substance abuse issue *In COPD[a]: Do not diagnose panic disorder when attacks are caused by overuse of beta agonists, other pulmonary disease medications, a current exacerbation, or exercise (in patients with severe airflow limitation).*

[a]Limitations on use of diagnostic criteria are based on the author's clinical experience and are intended to avoid overdiagnosis. Other forms of mood disorder: *Minor depression: Symptoms of depression are present but do not meet criteria for MDD. General Anxiety Disorder: Excessive worry or anxiety, restlessness, easy fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbance*

and monitor treatment of depression and anxiety disorders. Among the many validated depression-screening tools, the most useful is the PHQ-9 [11]. Developed specifically for depression case-finding in general medical practice, it operationalizes the specific criteria required to diagnose major depression [12]. The PHQ-9 is a 9-item self-report scale that can be given by interview if necessary, and is downloadable free from the Internet. It offers good sensitivity and specificity for current major depression, but is also scored to identify minor (mild or subsyndromal) depression. The PHQ-9 can be used to track the course of depression over time and to measure treatment response. In addition to depression severity, it provides a patient with an estimate of the impact of depressive symptoms on everyday functioning; this feature has not been tested in patients with COPD, who often do not distinguish depression from the impact of lung disease [1]. A limitation of the PHQ-9 is lack of items reflecting duration depression; one small study in COPD reported a mean duration of major depression of over 3 years at the time of diagnosis [13].

In COPD, a substantial body of evidence points to the frequent co-occurrence of anxiety and depression [2, 3, 14] though they can occur as distinct symptom profiles. Three-quarters of a sample of moderate to severe COPD patients with major depres-

sion had concurrent panic disorder [13], and in a group of consecutive COPD patients attending a pulmonary clinic, the lifetime prevalence of major or chronic depression was 18% and of anxiety disorders 16%, including 8% with panic disorder [15]. For practical purposes, in COPD, major depression and panic disorder, as well as milder depressive and anxiety symptoms, may be considered distinct clinical entities within a related mood disorder spectrum.

Treatment

Table 15.2 summarizes the three types of interventions for which outcomes of depression and anxiety have been reported in COPD: psychological approaches, pharmacological treatments, and pulmonary rehabilitation. At least some studies of each modality report significant mood benefits, but many do not; the best outcomes are found in studies that specify depression diagnosis as an entry criterion and quantify outcome using the methods of psychiatric research rather than patient-rated scales alone. The aggregated evidence suggests that exercise-based, multimodal pulmonary rehabilitation should be the foundation of mood management for patients with COPD. Exercise itself can be sufficient treatment for major and minor depression in

Table 15.2 Summary of published intervention studies: depression and anxiety in COPD.

	Source	Sample	Intervention	Outcome
Psychosocial interventions	[16]	*N* = 14, mean age 61	4 weeks, relaxation ± pulmonary rehab	No effect
	[17]	*N* = 94, mean age 63	Stress management versus no treatment	No effect
	[18]	*N* = 89, mean age 67	Dyspnoea management versus general health education	No effect
	[19]	*N* = 10 anxious patients	6 session, cognitive behavioral therapy (CBT)	No effect
	[20]	*N* = 56 VA patients	Single-blind, single-session 2 h group CBT, homework 6 weekly follow-up calls versus 2 hour education plus calls	Depression and anxiety symptoms improved in intervention group
Antidepressant pharmacotherapy				
	[13]	*N* = 36 (30 completed), mean age 62 MDD, anxiety in ¾; moderate to severe COPD	12 week, RPCT of nortriptyline (NT)	Marked benefit of NT for depression, anxiety, self rated cognition, and somatic symptoms
	[21]	*N* = 60, "depressive neurosis"	3 week, RCT of imipramine + diazepam, + pulmonary medications versus pulmonary medications alone	Decreased depressive and anxious symptoms, drowsiness a common side effect
	[22]	*N* = 12	6 week, PCT of doxepin	No benefit

(continued)

Table 15.2 (continued)

	Source	Sample	Intervention	Outcome
	[23]	*N* = 27 (19 completed), Beck Depression Inventory >15, lung transplant patients	12 week RPCT of citalopram	No overall benefit, citalopram helped mildly depressed/ anxious patients (only in the least disabled)
	[24]	*N* = 23 (15 completed), CRQ scales	12 week RPCT of paroxetine	Significant improvement in emotional function and mastery among paroxetine completers
	[25]	*N* = 778 with MDD (179 with COPD), electronic pharmacy records	Track % receiving at least 72 days (≥ 80% of first 90 days) of prescribed antidepressant	COPD patients much less likely to have an adequate initial trial of an antidepressant
Pulmonary rehabilitation				
	[26]	*N* = 15, ages 46–71	28 weeks versus 14 weeks of an exercise program	Anxiety but not depressive symptoms improved
	[27]	*N* = 40, mean age 59	10 weeks of exercise, patient education +/– chest muscle training	Depression and anxiety improved in the exercise groups
	[28]	*N* = 89, mean age 66	24 weeks of exercise and education versus usual care	Depression and anxiety improved in intervention group
	[29]	*N* = 43, mean age 63	12 weeks of exercise and MD/RN visits versus usual care	Depression and anxiety improved in intervention group
	[30]	*N* = 119, mean age 63	8 weeks of pulmonary rehabilitation and 1 year of follow-up versus 4 educational sessions	No change in depression, but self-efficacy improved in rehab group
	[31]	*N* = 79, mean age 67	10 weeks of exercise, education and stress management versus 2 control conditions	Depression, anxiety and cognition improved in the intervention group
	[32]	*N* = 59 (30 intervention 29 control, all with COPD)	3 weeks of pulmonary rehabilitation versus usual care	Depression and functional status improved in intervention group
	[33]	*N* = 149 patients with COPD after an exacerbation	12 daily 3 h rehabilitation sessions	Depression, anxiety, function, activity related dyspnoea and fatigue improved in the intervention group
	[34]	*N* = 63 (COPD and MDD)	Median length of stay 16 days, inpatient pulmonary rehabilitation	32 responders, 25 in remission by Hamilton Depression Rating scale
	[35]	*N* = 40	16 weeks, randomized trial of pulmonary rehabilitation versus no intervention	Decrease in depression symptoms and hostility

Unless a specific depression or anxiety diagnosis is indicated, mood disorder classification if any is unknown. *MDD* Major depressive disorder

older adults [36], and exercise-based pulmonary rehabilitation produces consistently measurable mood benefits in COPD patients.

Because of the way medical practice is currently organized, treatment for mood disorder that is provided in physicians' offices will generally emphasize antidepressant pharmacotherapy, for which the formal evidence base is still surprisingly small. However, much larger studies of antidepressants for nonmood disorder indications such as smoking cessation have established their value in COPD, particularly for bupropion [37]. These studies did not selectively enroll depressed patients and most had a relatively small percentage of patients with clinical depression. Useful information about side effects of bupropion versus nortriptyline versus placebo is provided in one comparative smoking cessation trial [38]. However, evidence from a study of adherence to initial antidepressant treatment indicates that COPD patients with major depression are much less likely (OR 0.67) to achieve 80% of prescribed treatment days in the first 3 months than are depressed patients with other chronic medical diseases [25]. Data explaining this differential adherence were not available in this study; among the many possibilities that must be considered are behavioral differences in patients who develop COPD (e.g., neglect of other health-promoting behaviors such as smoking cessation) and higher rates of drug intolerance in patients with multiple concurrent medications and low physiological reserve, both of which are prevalent among patients with more severe COPD. Analysis of nonadherence due to antidepressant side effects needs to be evaluated as a function of COPD-related disease variables in future research.

Progress in reaching consensus and standardizing treatment of mood disturbances in COPD has been hindered by several key factors. Well-designed treatment trials using measures and outcomes accepted by both respiratory and psychiatric specialists are few. Lack of formal psychiatric diagnosis, relatively small sample sizes, and failure to consider key illness variables such as severity and course of lung disease, limit the prescriptive value of these studies. Finally, all available treatment studies lasted only weeks, a very short time measured against the years of illness most COPD patients experience, and the chronicity of many major depressive episodes in these patients.

Only two treatment studies have specified a diagnosis of major depression as an inclusion criterion. One, a small ($N=36$), 12-week, randomized placebo-controlled trial of nortriptyline, in medically stable outpatients with moderate to severe airflow limitation, showed robust treatment effects for depression, anxiety, somatic symptoms, and everyday (especially psychosocial) function [13].

The second study that selected patients with major depression ($N=63$), a nonrandomized descriptive study of the effect of multidimensional inpatient pulmonary rehabilitation, showed general improvement in function and significant depression benefits (39% remission and 51% improvement) after a median length of stay of 16 days [34]. The duration of major depression at the time of enrollment was not reported in that study, nor was whether admission to rehabilitation followed hospitalization for an acute exacerbation (in which case improvement in depression would be expected to occur as overall health improved).

There is a compelling need for longer-term studies of both antidepressant medications and pulmonary rehabilitation, as well as well-designed psychological and psychosocial interventions, to evaluate the durability of treatment response, regardless of modality. There is an equally important need for studies that ground depression and its treatment in the natural history of COPD as a chronic disease that confers ongoing risk for mood disorders.

What can we make of the data we have now? A reasonable and practical approach to managing mood disorders in COPD is shown in Fig. 15.1. Note that exercise-based pulmonary rehabilitation – or another way of delivering measured exercise on a regular

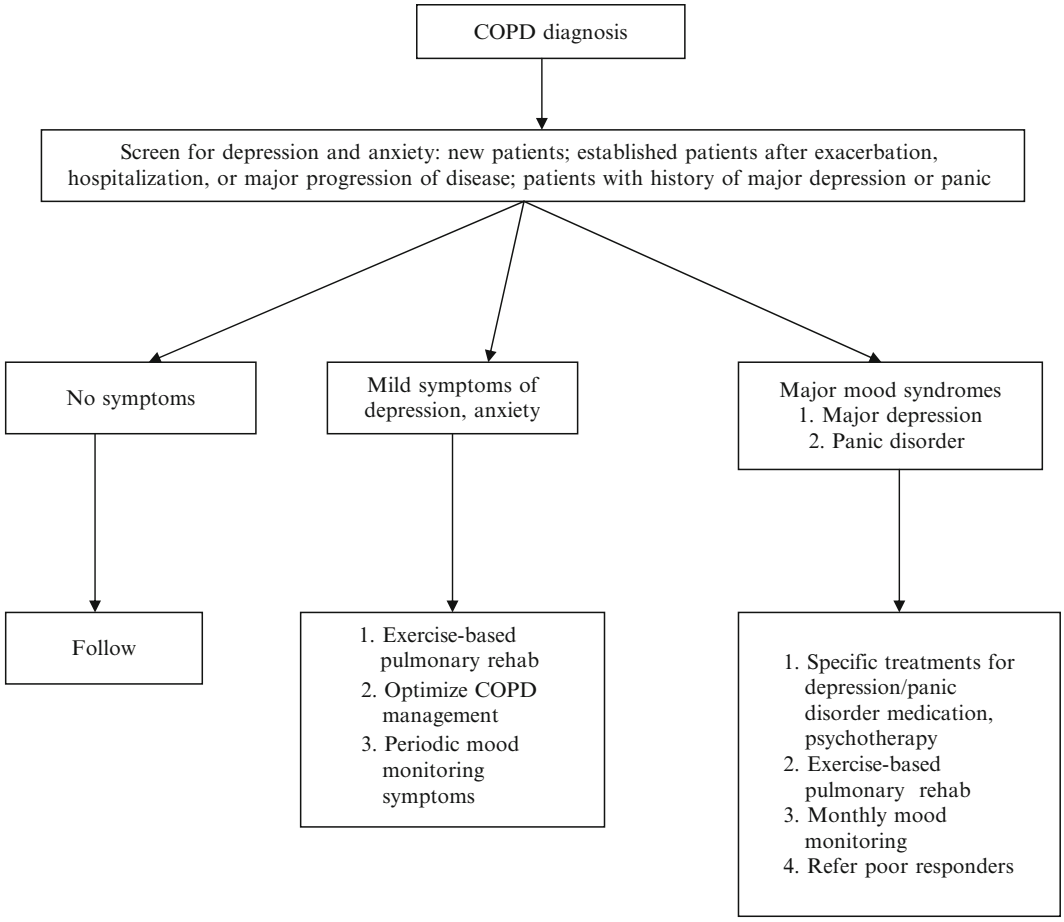


Fig. 15.1. Suggested algorithm for diagnosing and managing mood disorders in COPD

basis – is here considered essential for all eligible patients with minor or major mood disorders complicating COPD, with psychotherapeutic and/or pharmacological treatments applied in conjunction with focused disease management education and sustained physical activation.

Organizing Clinical Practice to Improve Mood Disorders in COPD Patients

The salience of depression and anxiety as predictors of important outcomes in COPD calls for making mood disorders a planned focus of disease management models. The PHQ-9 and related anxiety screens are appropriate for routine screening, monitoring, and evaluating treatment response [39]. Nonphysician staff in primary care and pulmonary disease specialty clinics can manage much of this activity, once a systematic, practice-wide commitment to the process has been established. Collaborative models of care focus on managing mood disorders as potentially chronic conditions, using an outcome-based, stepped-care approach. These models require specific patient-centered actions: identify those with major depression or panic disorder, make an explicit diagnosis in the medical record and on the problem list, schedule a focused "depression

visit" (or "panic visit"), educate patients about why treatment is important in managing their lung disease, and what their treatment options are. Eliciting patients' depression/panic treatment preferences is critical to build sufficient rapport for compliance with the selected treatment. Once chosen, implement the selected treatment, monitor response, and revise treatment to improve response, when needed, with the help of collaborating mental health providers.

Managing depression and panic in COPD patients is best achieved when a practice adopts a chronic care model that includes mood components. Chronic care models require creation of a patient registry to keep track of affected individuals over time. Patient registries for depression and panic in COPD, as for other chronic medical conditions, can be maintained by specially trained nurses, psychologists, or other nonphysician providers, who are trained as depression care managers. Psychiatrists are typically available for consultation regarding switching to more intensive, skilled interventions (e.g., additional pharmacotherapy and formal psychotherapy for patients who are not reaching therapeutic goals for mood disorders). Project IMPACT – Improving Mood-Promoting Access to Collaborative Treatment [40] – is an excellent model for building collaborative treatment teams that substantially improve depression outcomes in medical settings. Many papers from this large randomized trial, comparing collaborative care for depression with usual primary care, report marked improvements in depression and functional outcomes for older adults even in the presence of multiple comorbid conditions [41]. Although the model has been successfully implemented in replication studies across a range of primary care practice types and health systems, it may need specific adaptations for sicker patients with more severe chronic medical disease, such as COPD patients managed in pulmonary specialty clinics. An analysis of the translatability and sustainability of IMPACT is available in Blasinsky et al. [42].

Talking with Patients About Mood Problems

Many patients with COPD believe that depression and anxiety are inevitable components of lung disease and do not see mood disorder as independently treatable (13; unpublished qualitative data). This may be one reason for the striking finding [43] that many depressed COPD patients refuse antidepressant treatment. Educating patients about depression as a disorder that is common among people dealing with chronic medical diseases, about the potential to improve their health and day to day functioning as well as their mood if depression is a focus of treatment, and engaging close family members in encouraging and supporting treatment, are all useful interventions. The more confident a physician is in his/her ability to diagnose and manage depression, the more specific the treatment and monitoring plan proposed, and the more confidence that patient has in his/her relationship with the doctor, the more likely they are to respond positively and to accept the recommended intervention.

Conclusion

Depression and anxiety are common in COPD and adversely affect most important disease-related outcomes. Clinically significant mood disorders can be readily diagnosed using simple tools. Pulmonary rehabilitation including exercise is a maintstay

of mood management in COPD and should be made available to all patients capable of participating. Antidepressant medications benefit patients with depression and panic disorder complicating COPD, but evidence is too limited to direct choice of medication.

References

1. Borson S, Claypoole K, McDonald GJ (1998) Depression and COPD: treatment trials. Semin Clin Neuropsychiatry 3:115–130
2. Yohannes AM, Baldwin RC, Connoly MJ (2000) Depression and anxiety in elderly outpatients with COPD: prevalence, and validation of the BASDEC screening questionnaire. Int J Geriatr Psychiatry 15:1090–1096
3. Kunik ME, Azzam PN, Souchek J, Cully JA, Wray NP, Krishnan LL, Nelson HA, Stanley MA (2007) A practical tool for anxiety and depression in patients with chronic breathing disorders. Psychosomatics 48:16–21
4. Fan VA, Curtis JR, Tu S-P, McDonell MB, Fihn SD (2002) Using quality of life to predict hospitalization and mortality in patients with obstructive lung disease. Chest 122:429–436
5. Stapleton RD, Nielsen EL, Engleberg RA, Patrick DL, Curtis RC (2005) Association of depression and life-sustaining treatment preferences in patients with COPD. Chest 127:328–334
6. Cully JA, Graham DP, Stanley MA, Ferguson CJ, Sharafkhaneh A, Souchek J, Kunik ME (2006) Quality of life in patients with COPD and comorbid anxiety and depression. Psychosomatics 47:312–319
7. Garrod R, Marshall J, Barley E, Jones PW (2006) Predictors of success and failure in pulmonary rehabilitation. Eur Respir J 27:788–194
8. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P (2007) Depressive symptoms and COPD: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 167:60–67
9. Koenig HG (2006) Predictors of depression outcomes in medical inpatients with chronic pulmonary disease. Am J Geriatr Psychiatry 14:939–948
10. Simon GE, Von Korff M (2005) Medical co-morbidity and validity of DMS-IV depression criteria. Psychol Med 35:1–10
11. The PHQ-9. http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/ Accessed 22 March 2007
12. The American Psychiatric Association (2000) The diagnostic and statistical manual of mental disorders IV – text revision (DSM IV-TR). The American Psychiatric Association, Washington, DC
13. Borson S, McDonald GJ, Gayle T, Deffebach M, Lakshminarayan S, Van Tuinen C (1992) Improvements in mood, physical symptoms, and function with nortriptyline for depression in patients with COPD. Psychosomatics 33:190–201
14. Gudmundsson G, Gislason T, Janson C, Lindberg E, Ulrik CS, Brøndum E, Nieminen MM, Aine T, Bakke P (2006) Depression, anxiety and health status after hospitalization for COPD: a multicentre study in the Nordic countries. Respir Med 100:87–93
15. Karagji B, Rifkin A, Doddi S, Kolli R (1990) The prevalence of anxiety disorders in patients with COPD. Am J Psychiatry 147:200–201
16. Renfroe KL (1988) Effect of progressive relaxation on dyspnea and state anxiety in patients with COPD. Heart Lung 17:408–413
17. Blake RL, Vandiver TA, Braun S, Bertuso DD, Straub V (1990) A randomized controlled evaluation of a psychosocial intervention in adults with chronic lung disease. Fam Med 22:365–370
18. Sassi-Dambron DE, Eakin EG, Ries AL, Kaplan RM (1995) Treatment of dyspnea in COPD. A controlled clinical trial of dyspnea management strategies. Chest 107:724–729
19. Eiser N, West C, Evans S, Jeffers A, Quirk F (1997) Effects of psychotherapy in moderately severe COPD: a pilot study. Eur Respir J 10:1581–1584

20. Kunik ME, Braun U, Stanley MA, Wristers K, Molinari V, Stoebner D, Orengo CA (2001) One session cognitive behavioral therapy for elderly patients with COPD. Psychol Med 31:717–723
21. Sharma TN, Goyal RL, Gupta PR, Gautam S, Gulati R (1998) Psychiatric disorders in COPD with special reference to the usefulness if imipramine-diazepam combination. Indian J Chest Dis Allied Sci 30:263–268
22. Light RW, Merrill EJ, Despars J, Gordon GH, Matlipassi LR (1986) Doxepin treatment of depressed patients with COPD. Arch Intern Med 146:1377–1380
23. Silvertooth EJ, Doraiswamy PM, Clary GL, Babyak MA, Wilkerson N, Hellegars C, Palmer SM (2004) Citalopram and quality of life in lung transplant recipients. Psychosomatics 45:271–272
24. Lacasse Y, Beaudoin L, Rousseau L, Maltais F (2004) Randomized trial of paroxetine in end-stage COPD. Monaldi Arch Chest Dis 61:140–147
25. Pirraglia PA, Charbonneau A, Kader B, Berlowitz DR (2006) Adequate initial antidepressant treatment among patients with COPD in a cohort of depressed veterans. Prim Care Companion J Clin Psychiatry 8:71–76
26. Gayle RC, Spitler DL, Karper WB, Jaeger RM, Rice SN (1988) Psychological changes in exercising COPD patients. Int J Rehabil Res 11:335–342
27. Dekhuijzen PN, van Herwaarden CL, Cox NJ, Folgering HT (1990) Exercise training during pulmonary rehabilitation in COPD. Lung 168(Suppl):481–488
28. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH (1994) Randomised controlled trial of respiratory rehabilitation. Lancet 344:1394–1397
29. Wijkstra PJ, TenVergert EM, van der Mark TW, Postma DS, Van Altena R, Kraan J, Koeter GH (1994) Relation of lung function, maximal inspiratory pressure, dysponea, and quality of life with exercise capacity in patients with COPD. Thorax 49:468–472
30. Ries AL, Kaplan RM, Limberg TM, Prewitt LM (1995) Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with COPD. Ann Intern Med 122:823–832
31. Emery CF, Schein RL, Hauck ER, MacIntyre NR (1998) Psychological and cognitive outcomes of a randomized trial of exercise among patients with COPD. Health Psychol 17:232–240
32. Kozora E, Tran ZV, Make B (2002) Neurobehavioral improvement after brief rehabilitation in patients with COPD. J Cardiopulm Rehabil 22:426–430
33. Garuti G, Cilione C, Dell'Orso D, Gorini P, Lorenzi MC, Totaro L, Cirelli G, Clini E (2003) Impact of comprehensive pulmonary rehabilitation on anxiety and depression in hospitalized COPD patients. Monaldi Arch Chest Dis 59:56–61
34. Alexopoulos GS, Sirey JA, Raue PJ, Kanellopoulos D, Clark TE, Novitch RS (2006) Outcomes of depressed patients undergoing inpatient pulmonary rehabilitation. Am J Geriatr Psychiatry 14:466–475
35. Güell R, Resqueti V, Sangenis M, Morante F, Martorell B, Casan P, Guyatt GH (2006) Impact of pulmonary rehabilitation on psychosocial morbidity in patients with severe COPD. Chest 129:899–904
36. Sjosten N, Kivela SL (2006) The effects of physical exercise on depressive symptoms among the aged: a systematic review. Int J Geriatr Psychiatry 21:410–418
37. McRobbie H, Less M, Juniper Z (2005) Non-nicotine pharmacotherapies for smoking cessation. Respir Med 99:1203–1212
38. Wagena EJ, Knipschild PG, Huibers MJH, Wouters EFM, van Schayck CP (2005) Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with COPD. Arch Intern Med 165:2286–2292
39. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K (2004) Monitoring depression outcomes with the patient health questionnaire PHQ-9. Med Care 42:1194–1201
40. Unutzer J, Katon W, Callahan CM, Williams JW, Hunkeler E, Harpole L, Hoffing M, Della Penna RD, Noel PH, Lin EH, Arean PA, Hegel MT, Tang L, Belin TR, Oishi S, Langston C (2002) IMPACT investigators (improving mood-promoting access to collaborative treatment). Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. J Am Med Assoc 288:2836–2845

41. Harpole LH, Williams JW, Olsen MK, Stechuchak KM, Oddone E, Callahan CM, Katon WJ, Lin EH, Grypma LM, Unutzer J (2005) Improving depression outcomes in older adults with comorbid medical illness. Gen Hosp Psychiatry 27:4–12
42. Blasinsky M, Goldman HH (2006) Project IMPACT: a report on barriers and facilitations to sustainability. A report on barriers and facilitations to sustainability. Adm Policy Ment Health & Ment Health Serv Res 33:718–729
43. Yohannes AM, Connolly MJ, Baldwin RC (2001) A feasibility study of antidepressant drug therapy in depressed elderly patients with COPD. Int J Geriatr Psychiatry 16:451–454

16

Disease Management Programs for COPD

Jean Bourbeau, Amir Sharafkhaneh, and Sandra G. Adams

Key Points:

- To optimally manage COPD, healthcare providers must shift their focus from acute care to chronic care involving the community and health system including self-management education and support.
- To be successful (healthy behavior change for patients to control their disease), self-management education programs require fewer lectures, and must focus more on practice and acquisition of new skills, including decision making and problem solving, in order to have an impact on self-efficacy leading to behavioral changes.
- To be effective (improvement of patients' well being and reduction of healthcare utilization such as hospitalizations), self-management has to be supported by a delivery system designed to provide planned chronic care:
  (a) Team including a skilled health professional "case manager"
  (b) Continuous communication to effectively manage COPD in it trajectory
  (c) Properly trained professionals to support physicians and patients
  (d) Therapies supported by protocol (evidence-based practice guidelines)
- To prevent patient complications such as deterioration of quality of life and hospitalizations due to COPD exacerbations, action plans as part of a strategy promoting self-management education could play a key role in the future.

Keywords COPD • chronic care • patient education • self-management

Introduction

COPD is a chronic, progressive, and debilitating disease that presents with dyspnoea. Furthermore, the course of COPD is complicated by episodes of worsening respiratory status that result in seeking medical care and hospitalization. Worsening dyspnoea and COPD exacerbation episodes result in physical and psychological impairments [1]. Negative experiences caused by physical and psychological impairments diminish sense of control. In short, with worsening disease, COPD patients feel as though they are losing control of their lives and their confidence, and at times feel incapacitated in dealing with the disease. COPD patients progressively become less physically active [2], reduce their social contacts, and often become depressed [3], which creates a downward vicious circle [4]. Because COPD is one of the most common causes of emergency visits and

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD*: *A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_16,

hospitalizations, the healthcare system will continue to bear its weight into the future. More than 65% of COPD-related costs is due to hospitalizations [5].

Most COPD patients are managed by their primary care physicians. Efforts to improve care of the chronically ill must begin with the knowledge that the majority of COPD patients receive their care in family medicine practices. The medical system has been slow to respond to the concept of chronic disease management, and remains centered on acute care. However, recent changes in the philosophy of care from acute to chronic management have led to increased interest in education programs designed to encourage patient autonomy and responsibility in the management of their condition. Self-management interventions with action plans for acute episodes in asthma were proven effective to improve symptoms and are economically viable [6]. This approach is now advocated for the management of COPD patients.

In this chapter, we review the importance of shifting from an acute to a chronic care approach in the management of COPD. We look at characteristic components of the chronic care approach, such as self-management education in COPD patients, and features of a successful program. We also look at an action plan as part of a strategy promoting self-management education and emphasizing management of exacerbations.

Improving Chronic Illness Care: Shift of Focus from Acute to Chronic Care

An inordinate amount of healthcare resources are required to manage patients with COPD. Similar to many other chronic illnesses, COPD management is usually focused on acute disease *treatment* rather than on the more efficacious and cost-effective *prevention* of exacerbations [7]. In primary care, attention continues to focus on treatment, usually in the form of drug prescriptions. Time spent with patients on chronic conditions is not different from that on acute diseases (11 vs 9.7 min) [8].

Most of the care for COPD patients is tailored to treating acute exacerbations of COPD (AECOPD) episodes, while minimal effort is expended to educate patients in building the confidence and the specific skills to manage their disease on a daily basis and to prevent exacerbations. This may result in inappropriate resource utilization. Emphasizing the disconnection between current healthcare systems and "ideal" care that may be attainable for chronic illness management, the Institute of Medicine reported that "the current care systems cannot do the job," "trying harder will not work," but "changing care systems will" [9, 10]. Therefore, a shift of the paradigm for healthcare from acute to chronic care is required for the optimal management of patients with COPD (Table 16.1).

Concomitant comorbidities are common in patients with COPD (discussed in detail in other chapters); therefore, the allotted time during a clinical visit is often spent on addressing the most acute symptoms and concerns of the patient, leaving minimal to no time to address the optimal management of the patient's chronic illnesses. In the "Acute Care Model," the goals are generally short term, healthcare professionals assume the bulk of the responsibility to "fix" the acute problem, and the patient's role is often passive. In contrast, management in the "Chronic Care Model (CCM)" is focused on health promotion with long-term goals to reduce complications and improve quality of life. In the CCM, the healthcare provider understands that providing high-quality care is a process

Table 16.1 Shift of COPD management from acute to chronic care.

	Acute care model	Chronic care model
Focus	Symptoms, pulmonary function, and other lab results	Health promotion Self-management
Goals	Short-term: Reduce symptoms	Long-term: Prevent complications Reduce exacerbations Improve quality of life Reduce utilization of healthcare resources
Healthcare Professionals	Autocratic (reactive): Short-term vision: "fix" the acute problem Assume responsibility and control Minimal consideration of patient's concerns No emphasis on patient education	Facilitator (proactive): Long-term vision: understand that providing high-quality care is a process Self-management education to increase patient's skills, facilitate lifestyle changes, and promote autonomy To support and facilitate self-management, the facilitator must: • Have excellent communication skills • Have expertise in behavioral change • Evaluate patient's concerns, beliefs, readiness, and life experiences • Seek partnership with patient/family, healthcare team, and community resources
Patient/Family	Passive Role: Not part of decision making Minimal communication Poorly informed	Active Role: Engaged and actively participates in the care plan Communicates needs to healthcare provider Well informed

requiring excellent communication skills and active partnerships with the patient, family, healthcare team, and the community. In addition, the patient needs to be well informed, to seek autonomy through self-management, and actively participate in the care plan.

The CCM Components

The CCM identifies essential elements that encourage high-quality chronic disease care [11–13]. These CCM components (Fig. 16.1) involve the community and health system and include: (1) self-management support; (2) delivery system design; (3) decision support; and (4) clinical information systems.

The model fosters productive interactions between informed patients who actively participate in their care and experienced providers, resulting in a broadly applicable, higher quality, and possibly more cost-effective patient care environment.

A growing body of health service research points to the design of care delivery, not to the specialty of the physician, as the main determinant of effective chronic illness management. Utilizing resources within the community and maintaining support from the healthcare organization are key elements in this model. Incorporating community-based resources into clinical practice may allow healthcare providers to improve chronic care. Tapping into these community resources (e.g., a home health agency that provides a case manager, an existing pulmonary rehabilitation program, patient education material such as the self-management program(SMP) "Living Well with COPD" www.livingwellwithcopd.com (password: copd), classes such as the "Better Breathers Club," etc.) is particularly important for small practices with limited resources. To provide and sustain high-quality long-term improvements in chronic care, family physicians and health professionals within the healthcare organization must view

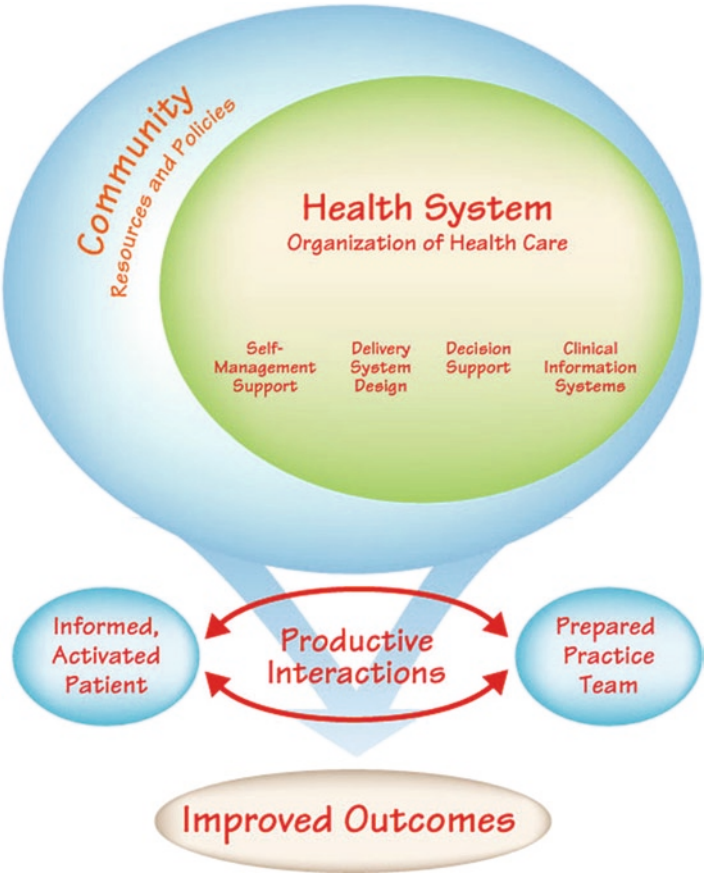


Fig. 16.1. Chronic care model components (From Wagner EH. http://www.improvingchronic-care.org)

chronic care as a priority. Therefore, the community and the health system form the foundation for the other components of the CCM.

Self-management Support

Because many aspects of chronic care management are under the direct control of patients, effective chronic care should ensure that patients and their families acquire the confidence and specific skills to manage their illness on a daily basis (self-management). This requires collaboration and should ideally be supported by a case manager whose role is to work with the primary care physician and healthcare team to optimize disease control and routinely assess difficulties and accomplishments. Case managers are used to empower patients with sufficient knowledge and confidence to take over the responsibility of managing the illness.

Three important aspects to address in any self-management intervention are: education (education on specific topics with required skills to cope with the disease on a day-to-day basis), behavioral support (providing tools to modify behavior), and motivational strategies (linking specific goals for behavioral changes to clinical information). For patients with COPD, some of the components of a comprehensive self-management support program include smoking cessation, adequate nutrition, active exercise program, medication compliance and proper inhaler technique, breathing techniques, control of anxiety related to shortness of breath, and tools to recognize and manage AECOPD

(i.e., an Action Plan). Style of teaching has to change from traditional, didactic to that of self-management. Self-efficacy, which is individuals' belief in their ability to execute necessary actions in response to specific situations, is considered in the Social Cognitive Theory as a predictor of behavioral change [14, 15]. The ongoing assessment of self-efficacy is critical to the success and improvement of chronic care.

Delivery System Design

Another component of the CCM is the delivery system design, which refers to the structure of the medical practice. To deliver effective chronic care, there must be a clear separation between delivering acute care, which is unpredictable, and providing planned chronic care. An integrated team with a skilled health professional "case manager" is a critical component of effective chronic disease care and self-management intervention [16, 17]. The case manager will ensure that patients acquire the confidence and specific skills to manage their disease on a daily basis. Key success to self-management includes a strong collaboration and good communication between the patient, the health professional case manager, and the medical team.

The case manager has to be knowledgeable about the specific aspects of each patient's medical condition in order to support the self-management process. Personnel should be trained to support the physician and the patient, arrange routine care to support complications/comorbidities of COPD (such as screening for depression and anxiety, scheduling regular bone densitometries for osteoporosis screening, and emphasizing and aiding smoking cessation efforts, etc.). The therapy has to be supported by protocol and follow-up with empowerment of self-health behaviors needed to effectively manage chronic disease such as COPD.

Decision Support

Decision support in the form of evidence-based practice guidelines should be incorporated into daily practice of chronic care; however, this is challenging in busy clinical practices. A practical strategy for implementing these guidelines for patients with COPD is to integrate automated clinical reminders in routine practice. In addition, specialist expertise in the management of COPD and associated comorbidities, as well as full specialty consultations, should be readily available by telephone. Shared care between family physicians and specialists produces the best outcomes [18, 19]. This model offers the optimal combination of knowledge and skills needed by chronically ill patients.

Clinical Information Systems

The final component in the CCM involves integrating a computerized clinical information system into clinical practice. This computerized system can be used to improve chronic care by keeping registries for planning individual and population-based care, implementing automated reminders for the primary care team to comply with clinical guidelines, and providing individual feedback to physicians and clinical practices regarding their performance in specific chronic illness care measures.

Self-management in COPD

Definition of Self-management Model (Self-efficacy)

A key element in effective disease management and chronic care is patient self-management education. Self-management applies to a formalized patient education program aimed at teaching skills needed to carry out medical regimens and guide

healthy behavior change for patients to control their chronic disease and improve their well-being. An SMP in any chronic disease is a process by which patients gain the knowledge, skills, and confidence (self-efficacy) to deal with their disease. Patients need to acquire the practical experience to deal with their disease during everyday life. In a successful COPD SMP, interventions designed to enhance patients' efficacy, beliefs, and confidence in their skills of managing their illness are as important as strategies to increase patients' knowledge of COPD. This is presented as a simple illustration in Fig. 16.2. This model has been the foundation of the development of the SMP "Living Well with COPD" [20].

We must consider and work on many factors in order to change patient behavior and impact patient health. Self-efficacy influences actions that individuals choose to perform and the effort they invest in managing their chronic illness. Individuals will choose an action only if they believe that they are capable of doing it and that they will benefit from it. As part of patient education, there are strategies to enhance self-efficacy: (1) past performance accomplishments; build on successful experiences; (2) peer observation; role models (group education); (3) verbal persuasion from health professionals; and (4) self-evaluation of physical/emotional state. Knowledge alone is clearly insufficient. Self-efficacy is the most important determinant of behavior change. The adage that "nothing succeeds like success" is crucial if we want lifestyle changes to occur.

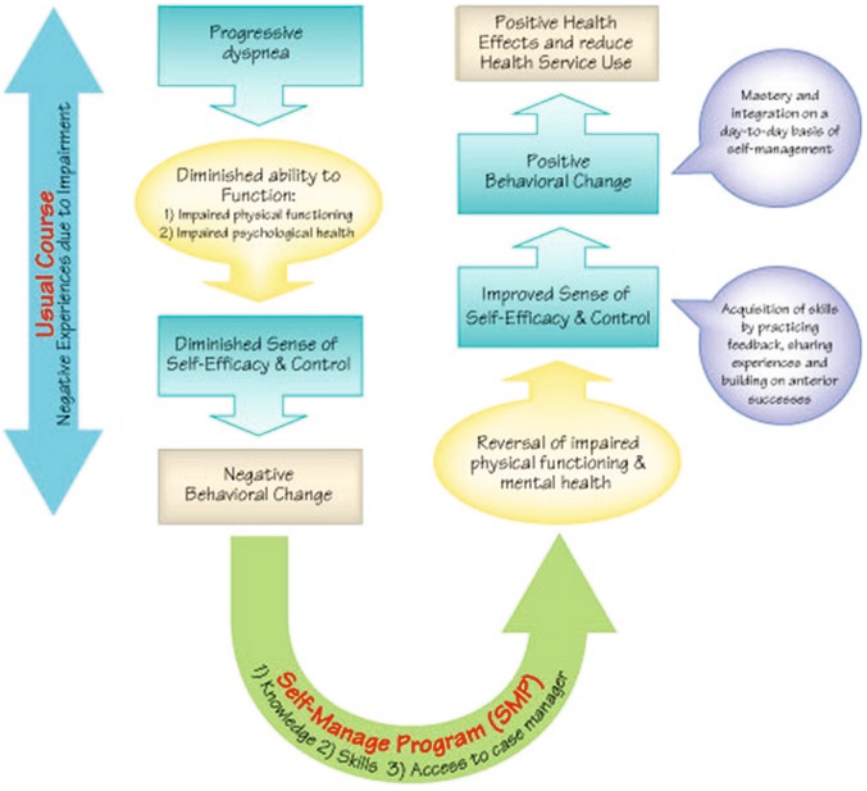


Fig. 16.2. Progressive course of COPD and effect of self-management program (*SMP*) associated with other components of the CCM model

Review of the Benefits of Self-management

Systematic reviews and clinical studies have demonstrated that implementing the CCM components in patients with chronic diseases such as diabetes, depression, asthma, and congestive heart failure is associated with significantly improved outcomes [21, 22].

Taylor and colleagues [23] evaluated RCTs of self-management in COPD and also found no difference in quality of life at 12 months, lung function, number of exacerbations, or mortality, but they reported that emergency visits "may be reduced." In a recent update of the Cochrane review about the effectiveness of self-management education in COPD, it was demonstrated that self-management education is associated with a clinically relevant and significant reduction in the probability of at least one COPD-related hospital admission with no evidence of detrimental effects on other outcomes [24].

Recently, a systematic review by Adams and colleagues evaluated studies in self-management in COPD taking a different approach. They divided the studies according to the presence of self-management alone or self-management associated with other components of the CCM model [25]. Pooled results from studies that implemented multiple components of the CCM demonstrated a significant reduction in healthcare utilization (unscheduled/emergency center visits, number of hospitalizations, and hospital length of stay) compared to the control group (Fig. 16.3). The trials that resulted in reduced healthcare utilization included two or more of the following components: (1) an extensive SMP with an individualized Action Plan, (2) delivery system with "advanced" access to care, which consisted of knowledgeable healthcare provider

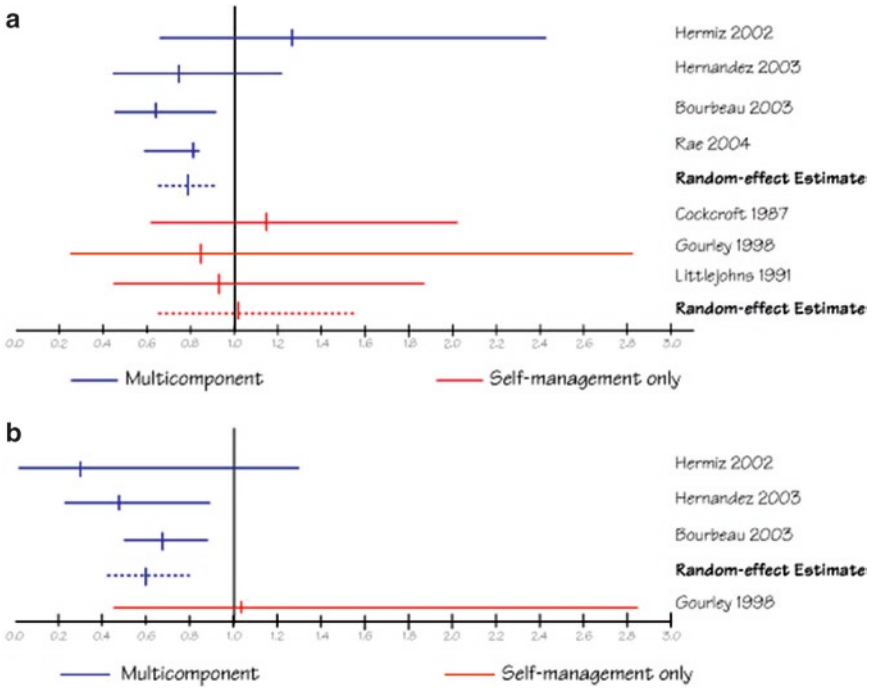


Fig. 16.3. Relative risk ratio of health service use between patients who have taken part in self-management alone or self-management associated with other components of the CCM model (**a**) Emergency/Unscheduled visits (**b**) Hospitalizations (relative risk ratio) (Adapted from [25])

"casemanager," (3) decision support with guideline-based therapy, and (4) a clinical registry system.

Other systematic reviews in COPD were more limited in their scope and focused on trials that predominantly involved self-management. Pooled results from these other reviews did not demonstrate significant improvement in outcomes. Another systematic review involved disease management programs in various chronic diseases, including COPD [17]. Only seven COPD studies met their inclusion criteria. They pooled results of three studies, which included only self-management interventions, and did not demonstrate improved outcomes. Many studies included in these reviews had incomplete descriptions of interventions and the self-management interventions were often limited in intensity (half of the studies included in the review by Adams and colleagues had an intervention duration <7.25 h). Cognitive–behavioral approaches to smoking cessation, medication and oxygen compliance, and exercise, which are known to be beneficial, had limited application in many studies. In addition, only seven studies included all three elements of self-management (education, behavioral changes, and motivation), whereas most studies were aimed at changing only the participants' knowledge of the disease (i.e., education alone is known to be necessary, but insufficient to change behavior) [25].

In many studies, the focus of self-management education is primarily on teaching topics specific to COPD (changing knowledge alone is insufficient) and not on the educational process (teaching self-management, emphasizing day-to-day controls and healthy behavior, and enhancing self-efficacy). Few studies emphasize continual communication which is key in successful SMPs. Pooled results from these reviews have failed to demonstrate significant improvement in outcomes. In fact, this may simply be a failure to intervene.

Building Self-management Strategies in COPD

Understanding the course of a chronic disease, its symptoms, and the way it affects a patient's life is essential to develop a successful SMP. Disease process and its treatment affect patients' ability to pursue a normal way of life. In COPD, dyspnoea limits patients' ability to be physically active and lead a productive life. This forces patients to modify and adjust their lifestyle by avoiding tasks that may result in dyspnoea. Patients become gradually more sedentary. In addition, the physical limitation often compromises mental health and results in anxiety and depression. Episodes of COPD exacerbations add to the impairment. An SMP needs to evaluate and address the effects of physical and psychological impairments on patients' daily lives and reduce the worsening effects of exacerbations. Finally, a successful SMP promotes the development of skills that are required for patients to cope with the disease, its complications, and the potential side effects of its therapy. This type of SMP aims at improving patients' self-confidence and self-efficacy and thus reversing the behavioral effects of the disease.

As mentioned in the previous sections, to be effective, the chronic care approach requires self-management support within a delivery system designed to provide planned chronic care. Self-management education includes a mutually understood care plan and careful and continuous communication with a case manager [16, 17, 26]. Building a successful self-management education program requires emphasis on the following two components: (1) the educational process "Self-management model"; (2) the educational topics "Intervention elements." Style of teaching has to change from traditional, didactic, to that of self-management. Health educators in self-management should ensure that patients acquire the confidence and the specific skills to manage their disease on a daily basis. Ideally this needs to be supported by a

Table 16.2 Self-management skills and healthy behaviors for COPD self-management.

Healthy behavior	Self-management skill (strategy)
Smoking cessation	Quit smoking and remain nonsmoker Avoid second-hand smoke
Proper prescription and use of medication	Take medication as prescribed on a regular basis and use proper inhalation techniques
Breathing techniques and positioning[a]	Use according to directives: • The pursed-lip breathing technique • The forward body positions
Regular exercise and physical activities	Maintain physical activities (activities of daily living, walking, climbing stairs, etc) Exercise regularly (according to a prescribed home exercise program and ideally following a pulmonary rehabilitation program)
Early recognition of exacerbation and prompt treatment.	Get your flu shot every year and your vaccine for pneumonia Identify and avoid factors that can make your symptoms worse Use your Plan of Action according to the directives (recognition of symptom deterioration and actions to perform) Contact your resource person when needed

[a]For some COPD patients, teaching cough techniques may also be needed

case manager whose role is to optimize disease control and follow-up with empowerment. Proven effective interventions should be the main focus of our self-management educational approach [27]. These educational topics (Table 16.2) are: (1) smoking cessation; (2) proper prescription and use of medication; (3) breathing techniques and positioning; (4) regular exercise and physical activities; and (5) early recognition and prompt treatment of exacerbation.

An example of a successful SMP is the one used in a study by Bourbeau and colleagues [28]. The program "Living Well with COPD" was multifaceted and delivered as part of the continuum of care. The program provides basic knowledge on COPD and its symptoms. It also suggests ways for patients to control their symptoms while effectively continuing to function. In addition, the program educates patients on COPD exacerbations and promotes early recognition and treatment. The program includes access to antibiotics and systemic steroid (self-initiated prescription) for early treatment of COPD exacerbations. A comprehensive program acknowledges all aspects of patients' health and life including elements that improve physical and emotional well being. The program promotes a healthy lifestyle through home exercise and healthy sleep and nutrition. It also explores leisurely activities as a means of improving emotional well being.

The program designed by Bourbeau and colleagues was supported by a case manager whose role was to optimize disease control and follow-up with empowerment. In order to assure an efficient follow-up, there was: (1) regular assessment of patients' general health condition and needs, (2) help provided to patients/families to ensure integration in daily life of skills and healthy behaviors learned, (3) written action plan given to patients with a self-administered prescription in case of a COPD exacerbation and support of its use until complete mastery of skills, and (4) referrals to proper hospital and community services, if needed. Goals and objectives were reviewed with patients.

For goals and objectives that were unmet, the educational plan was revised and education repeated through efficient interventions and methods.

Detailed information including patients' workbooks and brochure, and health professionals' teaching material such as the flip chart, the posters, and the reference guides are provided on the website www.livingwellwithcopd.com (password: copd) where all the resources can be accessed and downloaded for free. "Living Well with COPD" is a program designed to be delivered to patients under the guidance of healthcare professionals. This is why the access to the website is protected by a password.

The website will help you to continue improving the quality of the education provided to the patients and their families.

Action Plan in COPD

To date, treatment has focused mainly on drug therapy to decrease admission rates, reduce length of stay, and hasten recovery. More attention needs to be paid to early treatment of exacerbations to prevent complications such as deterioration in quality of life and hospitalizations. As Wilkinson et al. showed [29], patient recognition of COPD exacerbation and early treatment by their physician improved symptom recovery, reduced risk of hospital admission, and is associated with better health-related quality of life. SMPs have the potential to support the use of action plans, which include written guidelines on the recognition of worsening symptoms and early exacerbation management with self-initiated prescriptions of antibiotics and prednisone. While action plans were proven effective in the management of asthma [6], evidence supporting the use of action plans in COPD is limited.

A Cochrane review aimed specifically at action plans for COPD was recently published [30]. Studies considered for this review met the following criteria: (1) RCTs; (2) Patients with primary diagnosis of COPD; (3) The intervention was the use of an action plan, without a broader SMP, defined as the use of guidelines which outlined self-initiated interventions (such as antibiotics and prednisone) in response to alterations in the state of the patients' COPD that suggested the commencement of an exacerbation; the active intervention was compared to "usual care"; and (4) The outcomes included primary measures (hospital admissions, healthcare utilization, use of medications) and secondary measures (number and length of exacerbations, health-related quality of life [HRQL], lung function, symptoms, mortality). Three studies were included in the review [31–33]. All studies recruited patients through general practitioners. Two studies were prospective cluster randomized controlled trials and one was a parallel-group block randomized controlled study. Patients all had one or more exacerbations in the previous 12 months that required an increase in therapy. Allocation concealment grades were B (unclear). Furthermore, in one study GP practices were allocated by one of the investigators which might have introduced confounding factors between treatment methods, possibly diluting the effects of active intervention. The interventions all involved the use of an action plan and an information booklet. Patients received an individual education session usually by a nurse experienced in managing COPD. Self-administered prescriptions of antibiotics and prednisone were part of the action plan and education to patients. In two studies, patients were instructed to make early contact with their GP. Two studies had hospital admissions as an outcome measure. Weighted mean difference for hospital admissions over 12 months was 0.16 [95% CI: −0.09, 0.42]. The same two studies had ER visits as an outcome measure. Weighted mean difference for ER visits over 12 months was −0.01 [95% CI: −0.12, 0.10]. The use

of medication was reported in a variety of ways. One of the studies that measured use of medication over 6 months [34] showed an increase in the use of antibiotics by the group using an action plan, but the difference between groups was not as clear-cut for oral corticosteroid use. The two other studies [31, 32] both reported this outcome using continuous data over 12 months, which could be combined, showed no significant difference in medication use for either antibiotics or oral corticosteroids. Finally, the studies showed that patients provided with an action plan have a better knowledge of the importance of early intervention and how to implement appropriate treatment for an exacerbation.

New study results suggest that an action plan as part of a strategy promoting self-management education could play a key role in reducing emergency visits and hospitalization risk, as demonstrated in a subanalysis of a previously successful trial [28]. There were fewer exacerbations in the intervention group compared to the control group, for which both antibiotics and prednisone were used resulting in hospitalizations (16.5% vs. 35.1%, $p=0.001$) and emergency visits (33.1% vs 72.3%, $p<0.001$) [35], related to the fact that treatments were started earlier. In addition, 52.9% of patients recognized the onset of an exacerbation, and used antibiotics and prednisone, as taught in their self-management training, in the intervention group and 34.8% in the usual care group ($p < 0.01$).

An example of a written action plan from the SMP "Living Well with COPD" is presented in Fig. 16.4. One of the main goals of the written action plan is to prevent and manage exacerbations, thus preventing complications such as emergency visits and hospitalizations. Preventive measures such as optimal medication and vaccination must be part of the action plans. Patient and family's needs should be assessed (barriers to learning, existing knowledge, beliefs, and abilities) and realistic learning goals set. Patient and family have to be taught new knowledge and skills leading to expected healthy behaviors, using the action plan in the event of an exacerbation: (1) identify and avoid aggravating factors; (2) use action plan (recognition of symptom deterioration and actions to perform promptly including self-initiation of antibiotics and prednisone); and (3) contact the resource person when there is deterioration or whenever required. Finally, patients need to be followed up and to be properly evaluated. Important points to assess are: (1) patient's knowledge, level of self-efficacy, and comprehension; (2) possible barriers to integration of skills and behaviors learned. In case of negative results, it would be essential to readdress issues in order to reach the specific objectives. Access to a written action plan including information provided as part of the reference guides for health professionals is available on the website "Living Well with COPD" www.livingwellwithcopd.com (password: copd).

Summary

Clinical Implications

A shift from acute to chronic care is required for the optimal management of patients with COPD. The CCM components involve the community and health system and include self-management support with action plans (implementing strategies to change specific behavior in patients), delivery system design (structuring clinical practice to actively address chronic problems), decision support (using clinical practice guidelines to guide management), and clinical information systems (computerized registry, reminders, and providing feedback).

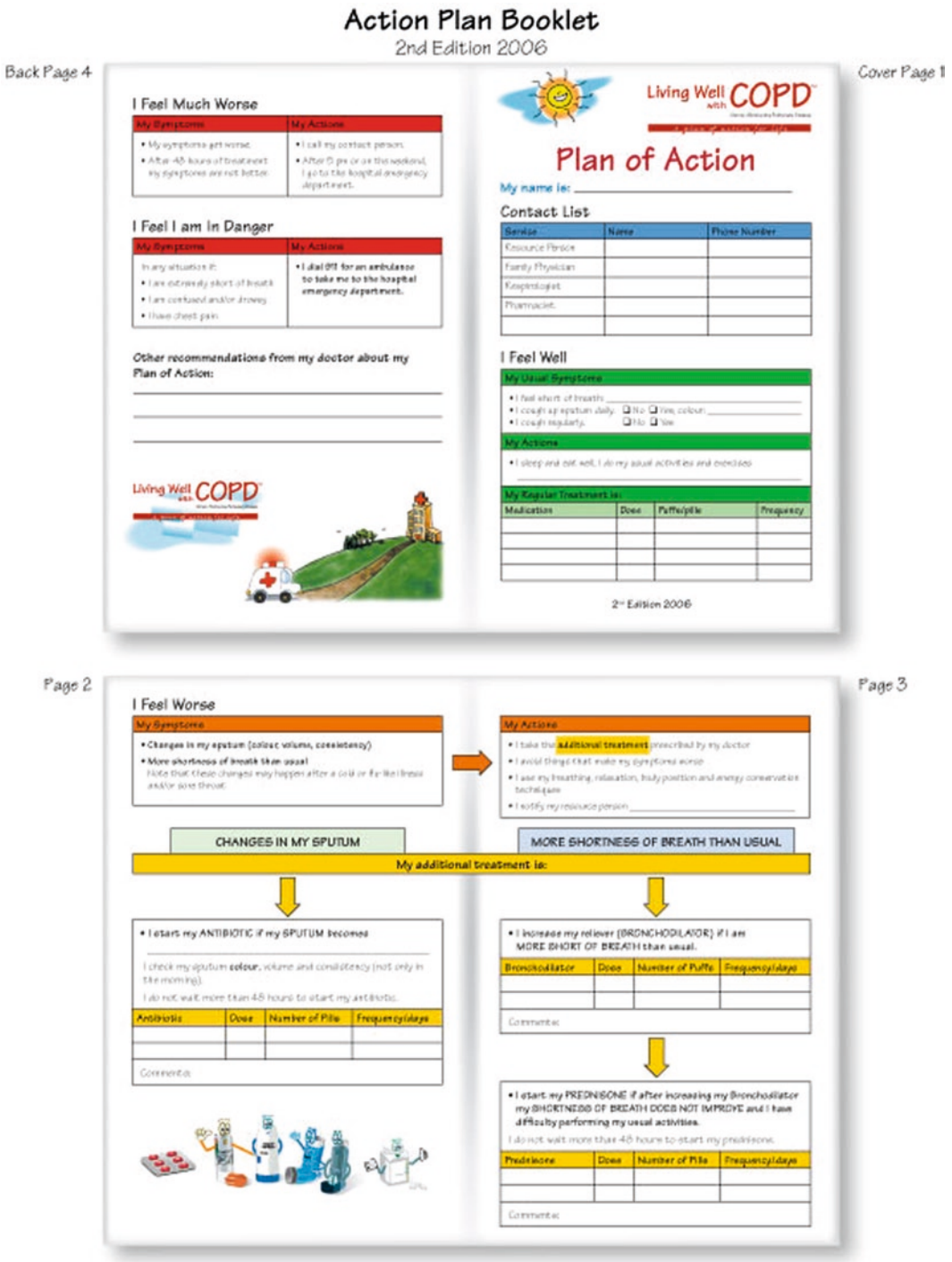


Fig. 16.4. Written action plan from the self-management program "Living Well with COPD" (www.livingwellwithcopd.com)

Self-management applies to a formalized patient education program aimed at teaching skills needed to carry out medical regimens and guide healthy behavior change for patients to control their chronic disease and improve their well-being. Self-management in any chronic disease is a process by which patients gain the knowledge, skills, and confidence (self-efficacy) to deal with their disease. Self-management requires an approach as part of a continuum of care that incorporates not only teaching various disease contents but also implementing strategies to change specific behavior in patients. Behavior modification implies the appropriate use of many disease-related skills (smoking cessation, proper prescription and use of medication, breathing techniques and positioning, regular exercise and physical activities, early recognition of exacerbation, and prompt treatment). Providing COPD patients with the self-management skills they need to properly manage their chronic disease should be considered as important as writing the correct prescription.

The use of action plans to help patients recognize symptom changes, to implement self-care and to self-initiate a customized prescription (antibiotics and corticosteroids) in the event of an exacerbation has been suggested as a promising strategy. Studies have shown that patients can learn how to recognize symptom changes and to react promptly. However, we have yet to prove that these changes to patients' behavior significantly reduce morbidity and use of costly health services such as emergency department visits and hospital admissions.

Future Research

Further research should be carried out to gain insight into healthy behavior change interventions in COPD, in order to design more effective SMPs. Future clinical trials need to be planned and designed more carefully; studies should also be powered properly. Studies claiming to assess self-management education in COPD should provide complete information allowing readers to evaluate if the intervention met the criteria for true self-management education. Studies need to assess if the intervention resulted in intended changes in patients' behavior. Standardized methods and properly designed studies need to be adopted if we want to ensure comparability of clinical trial results and move the field of COPD self-management into high-level evidence.

Considering the emerging evidence that action plans provide an effective approach to the early management of COPD exacerbations and could result in the intended changes in patients' behavior (timely self-administration of antibiotics and prednisone in the event of an exacerbation), further studies are also needed to investigate if the use of an action plan results in clinical benefits and reduction in the use of healthcare resources.

References

1. Schlecht NF, Schwartzman K, Bourbeau J (2005) Dyspnea as clinical indicator in patients with chronic obstructive pulmonary disease. Chron Respir Dis 2(4):183–191
2. Gift AG, Cahill CA (1990) Psychophysiologic aspects of dyspnea in chronic obstructive pulmonary disease: a pilot study. Heart Lung 19(3):252–257
3. Yohannes AM, Baldwin RC, Connolly MJ (2003) Prevalence of sub-threshold depression in elderly patients with chronic obstructive pulmonary disease. Int J Geriatr Psychiatry 18(5):412–416
4. Hajiro T, Nishimura K, Tsukino M et al (2000) Stages of disease severity and factors that affect the health status of patients with chronic obstructive pulmonary disease. Respir Med 94(9):841–846

5. Jansson SA, Andersson F, Borg S et al (2002) Costs of COPD in Sweden according to disease severity. Chest 122(6):1994–2002
6. Gibson PG, Powell H, Coughlan J et al (2003) Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev (1):CD001117
7. Wood R (2005) Improving chronic illness care [cited 20 Nov 2005]. Available from: http://www.improvingchroniccare.org. Johnson Foundation. Ref Type: Electronic Citation
8. Yawn B, Zyzanski SJ, Goodwin MA et al (2001) Is diabetes treated as an acute or chronic illness in community family practice? Diab Care 24(8):1390–1396
9. National Academy Press (US); Institute of Medicine (US). Committee on Quality of Health Care in America (2001) Crossing the quality chasm: a new health system for the 21st century. National Academy Press, Washington, Ref Type: Electronic Citation
10. Institute of Medicine (2005) Crossing the quality chasm: the IOM health care quality initiative. [Cited: 20 Oct 2005]. Ref Type: Electronic Citation
11. Wagner EH, Austin BT, Von Korff M (1996) Improving outcomes in chronic illness. Manag Care Q 4(2):12–25
12. Wagner EH (1998) Chronic disease management: what will it take to improve care for chronic illness? Eff Clin Pract 1(1):2–4
13. Wagner EH, Davis C, Schaefer J et al (1999) A survey of leading chronic disease management programs: are they consistent with the literature? Manag Care Q 7(3):56–66
14. Bandura A (1977) Social learning theory. Prentice Hall, Englewood Cliffs
15. Bandura A (1982) The assessment and predictive generality of self-percepts of efficacy. J Behav Ther Exp Psychiatry 13(3):195–199
16. Piette JD, Weinberger M, Kraemer FB et al (2001) Impact of automated calls with nurse follow-up on diabetes treatment outcomes in a Department of Veterans Affairs Health Care System: a randomized controlled trial. Diab Care 24(2):202–208
17. Weingarten SR, Henning JM, Badamgarav E et al (2002) Interventions used in disease management programmes for patients with chronic illness-which ones work? Meta-analysis of published reports. Br Med J 325(7370):925–928
18. Greenfield S (1999) The next generation of research in provider optimization. J Gen Intern Med 14(8):516–517
19. Nash DB, Nash IS (1997) Building the best team. Ann Intern Med 127(1):72–74
20. Bourbeau J, Nault D, Dang-Tan T (2004) Self-management and behaviour modification in COPD. Patient Educ Couns 52(3):271–277
21. Bodenheimer T, Wagner EH, Grumbach K (2002) Improving primary care for patients with chronic illness: the chronic care model, Part 2. J Am Med Assoc 288(15):1909–1914
22. Tsai AC, Morton SC, Mangione CM et al (2005) A meta-analysis of interventions to improve care for chronic illnesses. Am J Manag Care 11(8):478–488
23. Taylor SJ, Candy B, Bryar RM et al (2005) Effectiveness of innovations in nurse led chronic disease management for patients with chronic obstructive pulmonary disease: systematic review of evidence. Br Med J 331(7515):485–488
24. Effing T, Monninkhof E, van der Valk P, van der Palen J, van Herwaarden C, Partridge M et al (2007) Self-management education for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev (4):CD002990
25. Adams SG, Smith PK, Allan PF et al (2007) Systematic review of chronic care model in COPD prevention and management. Arch Intern Med 167:551–561
26. Simon GE, VonKorff M, Rutter C et al (2000) Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. Br Med J 320(7234):550–554
27. Nici L, Donner C, Wouters E et al (2006) American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173(12):1390–1413
28. Bourbeau J, Julien M, Maltais F et al (2003) Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med 163(5):585–591

29. Wilkinson TM, Donaldson GC, Hurst JR et al (2004) Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169(12):1298–1303
30. Turnock A, Walters EH, Walters J et al (2006) Action plans for chronic obstructive pulmonary disease. Cochrane Database Syst Rev: Reviews 2006 Issue 3
31. McGeoch GR, Willsman KJ, Dowson CA et al (2006) Self-management plans in the primary care of patients with chronic obstructive pulmonary disease. Respirology 2006; 11(5):611–618
32. McGlone S, Wood-Baker R, Walters EH (2004) The effect of a written action plan in COPD. Respirology 2(Suppl):A46
33. Watson JP, Nolan J, Elliott MW (1999) Autonomic dysfunction in patients with nocturnal hypoventilation in extrapulmonary restrictive disease. Eur Respir J 13(5):1097–1102
34. Watson P, Town G, Holbrook N et al (1997) Evaluation of a self-management plan for chronic obstructive pulmonary disease. Eur Respir J 10(6):1267–1271
35. Sedeno M, Nault D, Hamds D, Bourbeau J (2000) A self-management education program including an action plan for acute COPD exacerbations. COPD 6(5):352–358

17

General Management Issues in COPD: Sleep, Travel and Preoperative Management

Amir Sharafkhaneh, Mohammed Jamshidi, Hossein Sharafkhaneh, and Max Hirshkowitz

Key Points:

Sleep disorders in chronic obstructive pulmonary disease (COPD)

- Sleep disorders are prevalent in patients with COPD.
- Insomnia is reported in as much as 50% of patients with COPD.
- Optimal airway targeted pharmacotherapy of COPD may improve sleep in these patients.
- Attention should be paid to use of sedatives and narcotics in patients with COPD and insomnia as some of the medications may affect ventilation.
- OSA is not more frequent in COPD compared to a matched population without COPD, however, the severity of hypoxia or prevalence of hypoxia without OSA is more in COPD patients.

Travel and COPD

- Travel to high altitude or air travel may result in hypoxia in patients with COPD.
- Severity of hypoxia during the flight not only depends on the baseline arterial partial pressure of O_2 but also on severity of airflow obstruction and presence of other comorbid conditions.
- O_2 need during the flight or travel to high altitude can be determined either empirically or by hypoxia-altitude simulation test (HAST).
- Guidelines recommend having PaO_2 of 50–55 mmHg at high altitude and during the flight.

Perioprative care of COPD

- A comprehensive assessment by various practitioners involved in the operation is needed.
- Patient education and smoking cessation plays an important role in outcome of a surgery in these patients.

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8_17,

- Optimization of pharmacologic and non-pharmacologic therapies for COPD and other co-morbidities will improve outcomes of a surgery.
- Implementation of early post-op mobilization, incentive spirometry, and avoidance of shivering may help to avoid complications post surgery.

Keywords Air travel • insomnia • perioperative management • sleep apnea

Sleep Disorders in COPD

Sleep disorders such as insomnia, sleep apnea with a greater severity of arterial O_2 desaturations and restless leg syndrome are more common in patients with COPD. More than 50% of COPD patients complain from insomnia and more than 25% report daytime sleepiness [1]. Sleep in COPD patients is characterized by longer sleep onset latency, frequent arousals and awakenings, frequent sleep stage shifts and lower sleep efficiency [2]. Disturbed sleep in COPD patients is associated with the severity of airflow obstruction and decreased quality of life. In addition to idiopathic insomnia, patients with COPD may suffer from insomnia due to the disease or side effects of respiratory medications.

Normal Respiratory Physiology During Wakefulness, Sleep, and During the Transition from Wakefulness to Sleep

To better understand the mechanisms underlying COPD-related sleep disorders, it is first necessary to appreciate differences between wakefulness and sleep physiology. The dynamics of these physiological processes as one transits from wakefulness to sleep also influence the effects of obstructive lung disease on sleep and breathing. In the following sections we will detail normal sleep-wake physiological differences in respiratory function, control of ventilation, upper and lower airways functions, respiratory pump activity, and chemoreceptor sensitivity.

Control of Respiratory Function

The respiratory system's function is to provide the body with the required O_2 and remove CO_2 produced during the metabolism. Additionally, the respiratory system helps control acid–base balance. Regulation of respiratory systems function operates through a negative feedback loop. CO_2 elevation (hypercapnia) increases ventilation while CO_2 diminution (hypocapnia) decreases ventilation. This process involves both chemoreceptors and non-chemoreceptor sensory elements. The chemoreceptor component consists of both peripheral and central chemoreceptors. An estimated 30% of the CO_2 chemosensitivity and almost all of the hypoxic chemosensitivity is provided by the peripheral chemoreceptors [3]. Human peripheral chemoreceptors are located in the carotid body. The carotid body receptors respond to changes in O_2 and CO_2 levels in the blood.

CO_2 level is mainly regulated by central chemoreceptors located in the superficial layers of ventral medulla oblongata [4]. Information from sensory receptors is relayed to the medullary respiratory control center. Finally, the efferent arm of the feedback loop consists of motor output to upper airway (especially pharyngeal area), diaphragm, intercostals, and abdominal muscles through phrenic and intercostals nerves. In summary, the respiratory system under central control by medulla oblongata sustains ventilation and maintains O_2 and CO_2 within a normal range required by blood and tissues. This automatic control of ventilation persists throughout sleep

and wakefulness. However, during wakefulness, breathing can also be controlled voluntarily. For example, an awake individual can stop and take a breath whenever they wish. Thus, respiration can be affected by behavioral and voluntary input from higher areas of the brain, certainly during the awake state and possibly during rapid eye movement (REM) sleep.

Ventilation is under automatic control during sleep and thus, the response to CO_2 differs slightly during wakefulness, REM and non-REM (NREM) sleep. Of these three basic states, NREM has the lowest *set point* for balancing respiration. Most adults, when they fall asleep, go directly into NREM sleep. Therefore, the transition from wakefulness to sleep is marked by a *set point* drop in ventilation and corresponding changes in both CO_2 and O_2 levels. With initiation of sleep, minute ventilation falls about 0.5–1.5 L per minute [5, 6]. The minute ventilation reduction at sleep onset follows from decreased CO_2 production and O_2 uptake, absence of a wakefulness stimulus, reduced chemosensitivity, and increased upper airway resistance. Ventilatory response to hypercapnia diminishes as sleep deepens during NREM sleep. Similar reduction in minute ventilation is reported for REM sleep. Reduction of minute ventilation results in 2–8 mmHg elevation of partial pressure of CO_2 ($PaCO_2$); up to 10 mmHg reduction in partial pressure of O_2 (PaO_2); and less than 2% reduction of O_2 saturation [7, 8].

Upper Airway Function

During the transition from wakefulness to NREM and from NREM to REM sleep, upper airway resistance increases. This increase is mainly in the palatal or hypopharyngeal areas [8, 9]. The airway resistance increase is greater in snorers and obese subjects [10, 11], is highest during REM sleep [12], and apparently is induced by diminished upper airway muscle phasic activity and loss of upper airway protective reflexes [13]. With transition into REM sleep, the tonic activity of the upper airway muscles diminishes further; consequently, upper airway occlusion usually occurs more prominently during REM sleep.

Lower Airways Function

Lower airway resistance follows a circadian pattern, with highest values for normal individuals occurring in early morning hours [14]. Airways resistance follows a similar pattern in asthmatics, but with a higher amplitude [15]. The major mechanism of this change in airway caliber and increased resistance at night is a sleep-synchronized circadian rhythm largely due to changes in autonomic activity to the airways with increased cholinergic broncho-constrictor tone and decreased nonadrenergic noncholinergic bronchodilator function in the early morning hours [16].

Cough due to stimulation of airways is suppressed during sleep and only occurs with arousals [17].

Respiratory Pump

Input to respiratory muscles is controlled by the respiratory center in brain stem through phrenic and intercostals nerves. The phasic activity of respiratory pump is state dependent and therefore diminishes with initiation of sleep. However, phasic activity of the diaphragm is better maintained. With progression of sleep into REM, the tonic component of respiratory muscle pump decreases. The changes in muscle activity result in increased upper airway resistance and decreased minute ventilation.

Chemoreceptors

Hypoxic ventilatory response diminishes during sleep [18]. In NREM sleep, men show more reduction from wakefulness than women [19]. This difference is mainly due to

higher ventilatory drive during wakefulness in men. With progression to REM sleep, the hypoxic ventilatory drive further falls in both men and women [16].

Hypercapnic ventilatory response diminishes about 50% with transition from wakefulness to NREM sleep [7, 16, 20]. In REM sleep the ventilatory response falls even further; therefore, the lowest ventilatory response to hypercapnia occurs during REM sleep [7].

Overall, with transition from wakefulness to NREM sleep, the wakefulness stimulus and voluntary control of ventilation are lost, leaving automatic control to prevail. In addition, CO_2 production and O_2 uptake diminish, upper airway resistance increases, chemoreceptor response to hypercapnia and hypoxia falls, and operating lung volume decreases. Subsequently, $PaCO_2$ rises and PaO_2 falls. Combination of these changes can produce respiratory instability and predispose to periodic breathing and obstruction of upper airway during sleep. Loss of muscle tone with REM makes upper airway more prone to obstruction.

Sleep Disorders in Patients with COPD

Sleep-related breathing disorders include sleep apnea, nocturnal asthma, and COPD-related sleep disorder. While excessive sleepiness is the hallmark symptom of sleep apnea, patients with COPD usually complain of insomnia. Other sleep disorders described in association with COPD include restless legs syndrome and nightmares. Regardless of the cause, among many consequences is greatly decreased quality of life.

Insomnia

More than 50% of patients with COPD complain of insomnia and 25% report daytime sleepiness [1, 21]. Compared to patients that do not have respiratory disease, insomnia afflicts significantly more patients with chronic bronchitis, asthma and emphysema. Sleep in patients with COPD is characterized by longer sleep onset latency, frequent arousals and awakenings, frequent sleep stage shifts, and lower sleep efficiency [2]. Polysomnography shows sleep fragmentation with frequent arousals and diminished REM and slow wave sleep [22]. Disturbed sleep in patients with COPD is associated with the severity of expiratory airflow obstruction. The difficulties initiating and maintaining sleep in patients with COPD can arise from a variety of factors. Many patients with COPD are plagued by excess mucus production and coughing when trying to fall asleep. The coughing may punctuate brief episodes of light sleep with arousals. Sometimes patients will sleep in a recliner chair rather than laying flat. This can help by providing drainage but it also pulls the diaphragm down and facilitates some breathing mechanics. To make matters worse, restless legs syndrome (RLS) has been identified as a common additional barrier to sleep. RLS is characterized by *creepy-crawly* sensations in the extremities, particularly the calf muscles in legs. Some patients may describe it as feeling like “ants crawling up their legs” or “worms crawling through their muscles.” In some cases the sensation may be ach-like or painful. This disagreeable sensation worsens when the patient relaxes or is resting quietly. Moreover, the feelings are relieved by movement. Thus, RLS can provoke significant difficulty falling asleep and even sometimes falling back to sleep after nocturnal awakening. If and when the patient finally achieves sleep onset, increased expiratory airflow limitation produces lung hyperinflation and consequent increased dyspnoea later in the night. Periodic limb movement disorder (PLMD) is another pathophysiology associated with insomnia. It can consist of a simple dorsiflexion of the great toe during sleep that occurs repeatedly every 20–60 s (thus, it is periodic). However, the movement can involve the foot, ankle, knee, hip, and on

rare occasions, the upper extremities. The movements, in and of themselves, are not particularly pathophysiological; however, the activity is sometimes accompanied by CNS arousals that fragment and disturb sleep. Charokopos and colleagues reported significantly greater leg movement activity and leg movement associated arousals in patients with COPD [23]. The underlying mechanism connecting PLMD and COPD are not known.

Other exacerbating factors emerge, particularly during REM sleep. REM-related breathing mechanics changes occur in response to some muscle groups become hypotonic. As a result, minute ventilation declines, blood O_2 level drops, and inspiratory airway resistance increases. The resulting hypercapnia increases respiratory effort and activity sometimes leading to even greater lung hyperinflation. REM sleep is also marked by reduced functional residual capacity, ventilation/perfusion mismatches, and blunted response to CO_2.

When COPD is severe, the sleep-state alterations of breathing mechanics can induce severe hypoxemia, especially if the baseline O_2 saturation level is low. The lower the baseline O_2 saturation, the deeper and more rapid the desaturation event will be because oxyhemoglobin dissociation curve drops more steeply as the starting value diminishes. Finally, iatrogenic effects of the medications used to treat the COPD (for example, corticosteroids, methyl xanthenes, and β-agonists) must be taken into account [2, 24]. Such compounds have the potential to provoke insomnia in patients, regardless of their respiratory disease status.

Treatments for difficulty initiating and/or maintaining sleep include cognitive behavioral therapy for insomnia (CBT-I) and pharmacotherapy. CBT-I can be as effective as sedatives-hypnotics for treating primary insomnia [25]. However, to our knowledge, there are no published studies assessing efficacy and safety of CBT-I for treating COPD-related insomnia. In a small study of CBT in patients with COPD and anxiety or depression, CBT minimally but statistically significantly improved sleep efficiency [26]. Pharmacotherapy for insomnia involves using sedative-hypnotics that work via GABA-A receptor complex agonism (substances we traditionally think of as sleeping pills). Sedating antidepressants (that mainly work by central histamine (H_1) blockade) and melatonin receptor agonists (including melatonin) are also used.

The traditional sedative-hypnotics affect the GABA-A receptor complex most often achieve this outcome using benzodiazepines (BZD) and benzodiazepine receptor agonists (BZRAs). Most BZDs suppress respiration, decrease airway tone, inhibit arousals, and thereby may exacerbate hypoxemia. Triazolam, a very short acting BZD, has no obvious effect on respiration when used in single doses for patients with an awake supine O_2 Saturation of ≥90% and no CO_2 retention ($PaCO_2 \leq 45$). However, insomnia is chronic in patients with COPD and patient's moderate or worse disease will not reliably meet such criteria. BZRAs (imadazopyridines, cyclopyrrolones, and pyrazolopyrimidines) appear to be a better choice. The imadazopyridine zolpidem was tested in patients with more severe lung function abnormality and reportedly was safe and effective [25]. Thus, if a sedative-hypnotic is desired to treat insomnia in a patient with supine O_2 Saturation of ≤90%, zolpidem is clearly the first choice. Other BZDs, including Triazolam, should be used with extreme caution. Some antidepressants are quite sedating (e.g., amitriptyline, doxepin, trazodone) and have been used, sometimes to good effect. Most recently, the melatonin receptor agonist ramelteon was tested in mild to moderate COPD and found not to impair breathing but did improve sleep [27]. Total sleep time and sleep efficiency increased, and the number of awakenings decreased. Furthermore, blood O_2 level remained constant and there was no significant change in O_2 desaturation events. It should be noted that these patients were screened and excluded if they had clinical levels of obstructive sleep apnea. More recently,

results of a randomized controlled trial of ramelteon's effects on sleep in patients with moderate to severe COPD were presented at the 53 rd International Respiratory Congress of the American Association for Respiratory Care [28]. In addition to not adversely affecting O_2 saturation levels throughout the night, polysomnographically measured total sleep time, sleep efficiency, and sleep latency all significantly improved ($p=0.019$, $p=0.019$, and $p=0.051$, respectively). Thus, the current available data suggest that zolpidem and ramelteon may be safe in more advanced form of COPD. However, practitioner should exercise caution and properly follow patients with advanced COPD when a hypnotic-sedative is started [29–32].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is characterized by increased upper airway resistance; however, unlike COPD the increase occurs mostly during breathing's inspiratory phase. The increased resistance produces airflow limitation or cessation due to partial or complete collapse of the upper airway during sleep. If breathing ceases for 10 s, or more, the event is classified as an apnea episode. Episodes of airway narrowing without full cessation of airflow are classified as hypopnea. These hypopnea episodes are associated with decreased tidal volume and increasing respiratory effort; however, what makes them pathophysiological is their association with either oxyhemoglobin desaturations, respiratory effort related arousals, or both. Repeated hypoxemia or continual brief arousals fragmenting sleep produce a host of other problems by interfering with the sleep process and thereby undermining its functions.

When a patient has both COPD and sleep apnea, a so called *overlap syndrome*, they will likely have severe arterial O_2 desaturations. Most of these patients are chronically on the steep part of the oxyhemoglobin dissociation curve such that even a short or partial reduction in ventilation produces a precipitous fall in blood O_2 concentration. While the prevalence of sleep apnea in COPD patients does not differ compared to non-COPD population [33], in our experience the degree of apnea is less severe (in terms of the number of respiratory events per hour). However, patients with the *overlap syndrome* have more profound O_2 desaturation compared to patients with sleep apnea and no COPD. One might speculate that because the blood O_2 level consequence of each event are so severe, we only sleep patients with fewer nocturnal apnea and hypopnea events because mortality prevents the disease from progressing. Recent data from Marin and colleagues showed increased mortality and admission to hospital because of COPD exacerbation in patients with overlap syndrome not treated with CPAP compared to patients with only COPD or patients with overlap syndrome who were treated with CPAP [34].

Arterial O_2 desaturation can occur in patients with COPD who do not have obvious sleep apnea but rather have sleep-related hypoventilation. Again, low baseline saturation levels place these patients on the steep portion of oxyhemoglobin dissociation curve and even the usual REM sleep associated reduction in minute ventilation can provoke decreased arterial saturation [35, 36]. In addition, decreased functional residual capacity with transition to sleep may aggravate ventilation/perfusion mismatch and results in more O_2 desaturations. Nocturnal hypoxia is associated with increased daytime and nocturnal pulmonary artery pressure [37]. Further, nocturnal hypoxemia may increase mortality especially during acute exacerbations of COPD [38, 39].

Standard of care for treating obstructive sleep apnea is positive airway pressure therapy (PAP). PAP involves administering a fan or turbine generated flow using an interface (like a nasal or full-face mask). This positive pressure is adjusted to match

and offset the negative intrathoracic pressure responsible for collapsing the airway (i.e. PAP creates a pneumatic splint). The process of adjusting pressures until one is found that maximally improves breathing is called titration and is usually performed during an overnight sleep study in a laboratory.

Titration and finding an adequate pressure may be more difficult in patients with overlap syndrome than with simple obstructive sleep apnea. Patient with COPD sometime have greater difficulty adjusting to PAP therapy. Therefore, surgical interventions are sometimes considered, including uvulopalatalpharyngealplasty, maxillomandibular advancement, and tracheostomy. Additionally, desaturation events may continue at clinically significant rates and during REM sleep notwithstanding optimal PAP titration. In these cases, supplemental O_2 is often co-administered. In patients with COPD without frank sleep apnea or with isolated nocturnal O_2 desaturations, nocturnal O_2 therapy is recommended when complications of hypoxaemia like polycythaemia or cor pulmonale are present [40]. However, optimization of medical treatment may improve oxygenation [41–43].

In addition to these treatments, patients should be cautioned to avoid CNS depressants and alcohol because they can (a) decrease respiratory drive, (b) increase airway collapsibility, and (c) raise arousal threshold. We instruct patients to avoid driving or operating heavy equipment when sleepy or fatigued, avoid sleeping supine, extend sleep schedule to avoid sleep deprivation, and treat allergies and sinusitis aggressively.

Travel and Residence at High Altitude

With advancement of technology, human travel becomes easier every day. Individuals can travel hundreds of miles in matter of hours. This specifically is true with the use of airplanes. The current commercial planes are pressurized at 2,400 m or 8,000 ft above sea level (cabin altitude). Although, this level may not create any problem for travelers with normal lungs, it may result in hypoxia during the flight for patients with various respiratory disorders. Further, temporary or permanent residence in high altitude may affect oxygenation in patients with COPD. In this section we will review effects of high altitude on respiratory system in patients with COPD.

Effects of Altitude on Respiratory System

Fractional concentration of O_2 in the air (21%) and saturated vapor pressure of water at body temperature do not change with increasing altitude. However, as is shown in equation 1, drop in barometric pressure with increasing altitude affects the O_2 pressure in the air [44]. For Each 1,000 ft increase in altitude inspired PO_2 drops by 4 mmHg [45]. At the cabin altitude (8,000 ft), the inspired gas PO_2 will equivalent to amount of O_2 in fractional concentration of 16% (reduced from 21%) of sea level atmospheric pressure [44]. Table 17.1 shows the change in PO_2 with altitude.

$$Inspired\ gas\ P_{O_2} = 0.21\left(Barometric\ pressure - 47\right) mmHg$$

Acute hypoxia results in hyperventilation by stimulation of carotid bodies. The hyperventilation increases alveolar and arterial PO_2. In most normal individuals, arterial PO_2 remains at 50–60 mmHg or O_2 saturation of 80–90% at an altitude of 8,000–10,000 ft [45]. In a study of normal individuals, O_2 saturation dropped to less

Table 17.1 O_2 level at various altitude (Modified from Nunn's applied physiology [44]).

Altitude (ft)	Pressure (mmHg)	Inspired PaO_2 (mmHg)	Equivalent O_2% at sea level	% O_2 required
0	760	149	21	21%
2,000	707	138	19.4	22.6
6,000	609	118	17.8	26.5
8,000[a]	564	108	16.6	28.8
10,000	523	100	14.0	31.3
18,000[b]	379	69	9.7	44.8
30,000[c]	226	37	5.2	83.2

[a] Cabin altitude
[b] Highest permanent habitation
[c] Mount Everest

than 90% in half of the subjects at the cabin altitude [46]. In contrast to normal individuals, arterial PCO_2 does not decrease with acute exposure to 8,000 ft in patients with COPD [45]. Thus, in patients with respiratory conditions, the O_2 drop may be more pronounced during air travel or ascend to high altitude [47]. A 5% drop in O_2 concentration in patients with severe COPD may induce a 25–30 mmHg drop in PO_2 and this may cause significant arterial O_2 desaturation. Consequently, some of the COPD patients may require supplemental O_2 during the air travel.

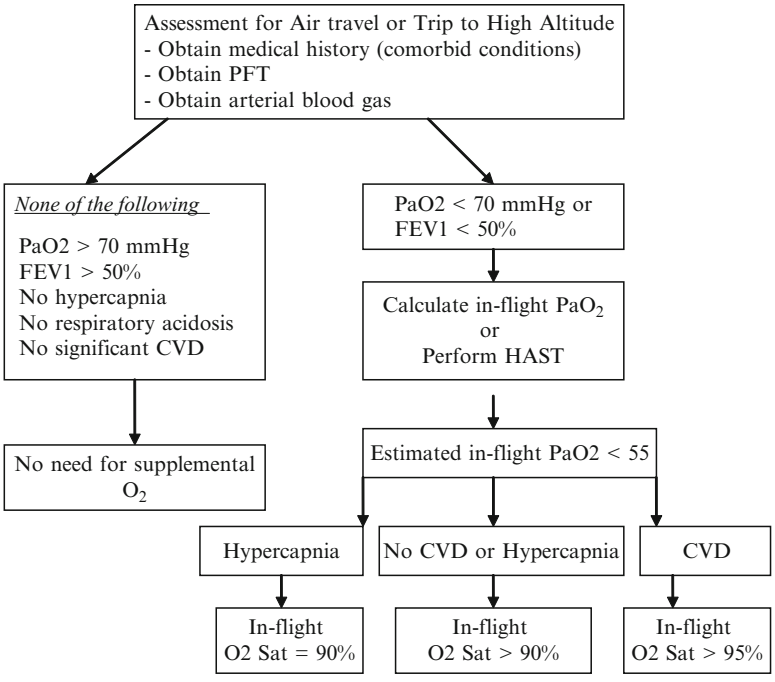
Evaluation and Prescription for Supplemental O2 at High Altitude

Several factors like severity of lung disease, presence of hypercapnia and presence of cardiovascular comorbid conditions influence need for supplemental O_2 at high altitude. A preflight PaO_2 of less than 70 mmHg is considered an indication for supplemental O_2 at high altitude [47]. A recent simulation study in patients with severe COPD (mean FEV1 30% of predicted) showed that sea level resting PaO_2 of more than 70 mmHg does not exclude in-flight severe hypoxemia [48]. In this group, light physical activity (equivalent to walking) caused worsening of hypoxemia [48]. Thus, in COPD patients with borderline PaO_2, a 6 min walk test showing drop in O_2 may identify the patients that may need in flight supplemental O_2.

The amount of O_2 prescribed depends on FEV1, PaO_2 (partial pressure of O_2 in arterial blood) at sea level and presence of hypercapnia and comorbid cardio- and cerebro-vascular diseases. The in-flight PaO_2 can be calculated with the following equation [49]:

$$PaO_2\left(Altitude\right) = 0.453\left[PaO_2\ sea\ level\right] + 0.386\left[FEV1\%\ predicted\right] + 2.44$$

Guidelines recommend maintaining PaO_2 above 50–55 mmHg during the flight [40]. For patients who are already on supplemental O_2, the flow should be adjusted accordingly to provide a PaO_2 of 55–60 mmHg or O_2 saturation of 90% at cabin altitude. The level aimed also depends on presence of hypercapnia or other comorbid conditions. In the presence of hypercapnia, flow of O_2 should be adjusted for an in-flight O_2 saturation of 90% (PaO_2 of 55–60 mmHg). In the presence of cardiac and cerebrovascular disease, in-flight O_2 saturation of >95% should be aimed. One liter/min O_2 flow rate can increase inspired PO_2 by 20 mmHg [45]. Alternatively a hypoxia-altitude simulation test (HAST) can be used to assess the need for supplemental O_2 during the flight and the amount required [45]. HAST is a normobaric test that uses hypoxic breathing mixture (15% O_2) to simulate a cabin altitude of 8,000 ft [45]. Figure 17.1 shows a simple algorithm for evaluation of need for in-flight supplemental O_2.



PaO2 Arterial pressure of O2
FEV1 Forced expired volume in one second
HAST Hypoxia altitude simulation test
CVD Cardiovascular disease

Fig. 17.1. The flow chart for evaluation of altitude hypoxia.

Preoperative Care of Patient with COPD

Chronic obstructive pulmonary disease (COPD) affects as many as 10% of the world's population older than 40 years of age. It is the fourth leading cause of death. COPD has increasing prevalence and mortality rates and has resulted in substantial human and economic burden. Post-operative complications in COPD patients can reach 30% and varies based on the type of procedures and the duration of general anesthesia. The most frequent life threatening complications include hypoxemia (fatal respiratory failure), arrhythmia (ACS and/or CHF), hypotension, acute over chronic bronchitis, pneumonia, and cardiac arrest.

COPD patients not only suffer from many years of smoking addiction but also other co-morbidities related or unrelated to nicotine use. Depending on the severity of airflow obstruction of these patients, the type (general vs vascular) surgical procedures, the location of incisions (thoracic, abdominal, extremities) and the general anesthesia duration several key management points need to be addressed prior to an elective procedure. This requires a passionate, aggressive and collaborative effort of all treating physicians (Primary MD, Pulmonologist, Cardiologist, Anesthesiologist, Pain Specialist and Surgeon) and nursing staff to create and fulfill an optimal management strategy to reduce post-operative complications and increase recovery. Experience with major surgical procedures in patients with severe COPD including lung volume reduction surgery

indicate that preoperative optimization of patient's health status combined with careful perioperative strategy results in improved outcome [50–52]. Intraoperative management of patients with COPD is beyond scope of this chapter and will not be discussed.

Pre-Operative and Perioperative Strategies for Elective Major Surgical Procedures in COPD Patients

Patients with COPD undergoing an elective surgical procedure should be evaluated and optimized in advance of the operation. All the members of the management team including pulmonary, anesthesiology, surgical and rehabilitation practitioners should evaluate the patient and become familiar with the patients detailed medical history. Review of comorbid medical and psychiatric conditions are very important as the prevalence of cardiovascular and psychiatric comorbid conditions are high in COPD patients. Pre-operative cardiac risk determination, based on American College of Cardiology guidelines, and optimization of patient's cardiac status and hypertension if present may help to reduce risk of peri-operative acute coronary syndrome or CHF. Arterial blood gas measurement in patients with moderate to severe COPD is helpful to establish the baseline value. A chest x-ray will help to evaluate for thoracic malignancies as patients with COPD are at increased risk for lung cancer [40].

Preparation of patients for surgery includes optimization of expiratory flow. Long acting bronchodilators (like tiotropium, salmeterol and formoterol) and combined beta-agonist/inhaled corticosteroid improve various outcomes including lung function, exercise capacity and quality of life and reduce exacerbations in patients with severe COPD. In the immediate perioperative period, short acting beta-agonists (such as albuterol or salbutamol) and anticholinergics (ipratropium bromide) via nebulizer can relieve bronchoconstriction and may reduce the risk of pneumonia post operatively [53]. Prophylactic use of systemic corticosteroids may be beneficial in patients who have received long-term systemic corticosteroids within the past year [54]. Use of preventive measures for deep vein thrombosis including compression devices and heparin is recommended [55]. Unfractionated heparin as well as low molecular weight heparin provides superior prophylaxis compared to compression devices. The decision to start prophylactic anticoagulation depends on the patient related risk factors [56]. Important risk factors include age over 40 years, previous venous thromboembolism, obesity, varices, and estrogen use [57]. Another important consideration is prevention of aspiration of oropharengeal and gastric contents into the lungs. The aspiration can cause pneumonitis, hypoxia and adult respiratory distress syndrome (ARDS). The American Society of Anesthesiologists recommends administration of acid suppressants in patients who are at high risk of aspiration [58]. The patients at increased risk of aspiration include those with increased gastric acid (like patients with gastric ulcer, gastritis and esophagitis), increased intragastric pressure, gastric or intestinal hypomotility, gastrointestinal structural disorders (such as impaired lower esophageal sphincter in Hiatal hernia and GERD), impaired gag reflex, epiglottic dysfunction, swallowing difficulty), neuromuscular incoordination, and depressed sensorium. Further, the placement of nasogastric and endotracheal tubes may predispose patients to aspiration [58].

Severe COPD patients may benefit from a pulmonary rehabilitation before surgery. Importantly, smoking may increase operative risk and hamper recovery [50], thus, smoking cessation (2–4 weeks for general and 6–12 weeks prior to thoracic operations) is very important. Additionally, teaching the patients about chest physiotherapy and use of incentive spirometry preoperatively may reduce post operative respiratory

complications [52]. Patient education about the disease and the operation will help to reduce patients' anxiety [55].

Post-operative Management of Elective Surgical Procedures in COPD Patients

Main goal in patients with COPD is immediate extubation after completion of surgery and anesthesia in recovery room. Evaluation of vital signs including blood pressure, pulse rate, respiratory rate and O_2 saturation is helpful in planning early extubation. Serum electrolyte measurements are useful in detecting any electrolyte abnormalities that may prevent optimum muscle function and hamper successful extubation, as is hemoglobin measurement in identifying excessive blood loss. In addition, an EKG will help to identify any possible ischemia in patients with known coronary artery disease. Some centers continue invasive or non-invasive cardiac output monitoring during the immediate postoperative period to detect early postoperative deterioration in cardiorespiratory function.

Due to underlying ventilatory problem in patients with COPD, extubation can be attempted even in the presence of higher arterial CO_2 pressure ($PaCO_2$) level. The proper anesthesia management and an experienced team are crucial for achieving this goal. Because postoperative shivering increases CO_2 production and O_2 consumption, postoperative shivering in patients with severe COPD may induce a metabolic demand that is larger than the ventilatory capacity and may lead to acute respiratory failure and the need for mechanical ventilation [59]. After extubation, positioning the patient in an upright or semi-upright position may help diaphragm movement and improve efficacy of spontaneous ventilation [55]. Furthermore, use of non-invasive ventilatory support should be considered in case of rising $PaCO_2$ level after extubation if the patient is awake. Close attention to prevention of aspiration is crucial at this stage (see above).

Chest wall or abdominal pain after surgical incision impairs proper ventilation and adequate clearing of secretion, which in turn may result in hypoventilation, hypoxia and respiratory failure [59]. Many centers prefer epidural pain control to systemic narcotic use due to the latter's effects on control of breathing. In patients with severe COPD, involvement of a pain expert can improve pain control and reduce the deleterious effects of narcotics.

While the use of postoperative incentive spirometry and chest physiotherapy in patients undergoing lung resection is commonplace, prospective data examining its effectiveness is sparse. Varela et al. reviewed clinical outcomes and costs of 119 patients undergoing lobectomy who received incentive spirometry as well as chest physiotherapy and 520 historical controls who did not receive this care. The study reported significant reductions in length of stay, atelectasis, and cost in the chest physiotherapy group compared to controls [60].

Early postoperative mobilization of patients should be instituted whenever feasible to help reduce the incidence of atelectasis, minimize use of narcotic analgesics, reduce recovery time and prevent muscle atrophy.

Summary

COPD patients are at higher risk for peri-operative morbidity and mortality. A well coordinated team of physicians and supportive staff that can provide a comprehensive management strategy in peri-operative period will reduce the complications and will optimize recovery in patients with COPD.

References

1. Klink M, Quan SF (1987) Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 91(4):540–546
2. George CF, Bayliff CD (2003) Management of insomnia in patients with chronic obstructive pulmonary disease. Drugs 63(4):379–387
3. Yoshiyuki H, Hiroaki T (1999) Chemical control of breathing. In: Altose MD, Yoshikazu K (eds) Control of breathing in health and disease. Marcel Dekker, New York, pp 41–87
4. Mitchell RA (1969) Respiratory chemosensitivity in the medulla oblongata. J Physiol 202(1):3P–4P
5. Hudgel DW, Martin RJ, Johnson B, Hill P (1984) Mechanics of the respiratory system and breathing pattern during sleep in normal humans. J Appl Physiol 56(1):133–137
6. Chokroverty S (1999) Physiologic changes in sleep. In: Chockroverty S (ed) Sleep disorders medicine, basic science, technical considerations, and clinical aspects. Butterworth Heinemann, Boston, pp 95–126
7. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW (1982) Respiration during sleep in normal man. Thorax 37(11):840–844
8. Lopes JM, Tabachnik E, Muller NL, Levison H, Bryan AC (1983) Total airway resistance and respiratory muscle activity during sleep. J Appl Physiol 54(3):773–777
9. Hudgel DW, Hendricks C (1988) Palate and hypopharynx – sites of inspiratory narrowing of the upper airway during sleep. Am Rev Respir Dis 138(6):1542–1547
10. Dempsey JA, Smith CA, Harms CA, Chow C, Saupe KW (1996) Sleep-induced breathing instability. University of Wisconsin-Madison Sleep and Respiration Research Group. Sleep 19(3):236–247
11. Skatrud JB, Dempsey JA (1985) Airway resistance and respiratory muscle function in snorers during NREM sleep. J Appl Physiol 59(2):328–335
12. Orem J, Lydic R (1978) Upper airway function during sleep and wakefulness: experimental studies on normal and anesthetized cats. Sleep 1(1):49–68
13. Krieger J (2000) Respiratory physiology: breathing in normal subjects. In: Krieger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W.B. Saunders, Philadelphia, pp 229–241
14. Lewinsohn HC, Capel LH, Smart J (1960) Changes in forced expiratory volumes throughout the day. Br Med J 1(5171):462–464
15. Hetzel MR, Clark TJ (1980) Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. Thorax 35(10):732–738
16. Douglas NJ (2000) Asthma. In: Kryger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W.B. Saunders, Philadelphia, pp 995–964
17. Douglas NJ (2000) Respiratory physiology: control of ventilation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W.B. Saunders, Philadelphia, pp 221–228
18. Hedemark LL, Kronenberg RS (1982) Ventilatory and heart rate responses to hypoxia and hypercapnia during sleep in adults. J Appl Physiol 53(2):307–312
19. White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW (1982) Hypoxic ventilatory response during sleep in normal premenopausal women. Am Rev Respir Dis 126(3):530–533
20. Bulow K (1963) Respiration and wakefulness in man. Acta Physiol Scand Suppl 209:1–110
21. Klink ME, Sethi GK, Copeland JG, Quan SF (1993) Obstructive sleep apnea in heart transplant patients. A report of five cases. Chest 104(4):1090–1092
22. Cormick W, Olson LG, Hensley MJ, Saunders NA (1986) Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. Thorax 41(11):846–854
23. Charokopos N, Leotsinidis M, Pouli A, Tsiamita M, Karkoulias K, Spiropoulos K (2008) Periodic limb movement during sleep and chronic obstructive pulmonary disease. Sleep Breath 12(2):155–159
24. Kutty K (2004) Sleep and chronic obstructive pulmonary disease. Curr Opin Pulm Med 10(2):104–112

25. Girault C, Muir JF, Mihaltan F, Borderies P, De La GB, Verdure A et al (1996) Effects of repeated administration of zolpidem on sleep, diurnal and nocturnal respiratory function, vigilance, and physical performance in patients with COPD. Chest 110(5):1203–1211
26. Hynninen MJ, Bjerke N, Pallesen S, Bakke PS, Nordhus IH (2010) A randomized controlled trial of cognitive behavioral therapy for anxiety and depression in COPD. Respir Med 104(7):986–994
27. Kryger M, Wang-Weigand S, Zhang J, Roth T (2007) Effect of Ramelteon, a selective MT(1)/MT (2)-receptor agonist, on respiration during sleep in mild to moderate COPD. Sleep Breath. 2008 12(3):243–50
28. Roth T (2007) A study of the safety of Ramelton in subjects with moderate to severe COPD. 53 rd international respiratory congress of the American association of respiratory care, Orlando, Florida

Ref Type: Slide

29. Greenberg J, Goss JB (2009) Therapies for insomnia and comorbid chronic obstructive pulmonary disease with a focus on ramelteon (rozerem). Pharm Ther 34(9):502–508
30. Kryger M, Roth T, Wang-Weigand S, Zhang J (2009) The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. Sleep Breath 13(1):79–84
31. Kryger M, Wang-Weigand S, Zhang J, Roth T (2008) Effect of ramelteon, a selective MT(1)/MT (2)-receptor agonist, on respiration during sleep in mild to moderate COPD. Sleep Breath 12(3):243–250
32. Roth T (2009) Hypnotic use for insomnia management in chronic obstructive pulmonary disease. Sleep Med 10(1):19–25
33. Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, O'Connor GT, Punjabi NM, Shahar E. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003;167:7–14
34. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR (2010) Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea. The overlap syndrome. Am J Respir Crit Care Med 200912-1869OC
35. Hudgel DW, Martin RJ, Capehart M, Johnson B, Hill P (1983) Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. J Appl Physiol 55(3):669–677
36. Phillips BA, Cooper KR, Burke TV (1987) The effect of sleep loss on breathing in chronic obstructive pulmonary disease. Chest 91(1):29–32
37. Levi-Valensi P, Weitzenblum E, Rida Z, Aubry P, Braghiroli A, Donner C et al (1992) Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. Eur Respir J 5(3):301–307
38. Fletcher EC, Miller J, Divine GW, Fletcher JG, Miller T (1987) Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tensions above 60 mm Hg. Chest 92(4):604–608
39. Connaughton JJ, Catterall JR, Elton RA, Stradling JR, Douglas NJ (1988) Do sleep studies contribute to the management of patients with severe chronic obstructive pulmonary disease? Am Rev Respir Dis 138(2):341–344
40. Celli BR, MacNee W (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 23(6):932–946
41. Mulloy E, McNicholas WT (1993) Theophylline improves gas exchange during rest, exercise, and sleep in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 148 (4 Pt 1):1030–1036
42. Martin RJ, Bartelson BL, Smith P, Hudgel DW, Lewis D, Pohl G et al (1999) Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD. Chest 115(5):1338–1345

43. McNicholas WT, Calverley PMA, Lee A, Edwards JC (2004) Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. Eur Respir J 23(6):825–831
44. Lumb AB (2000) High altitude and flying. In: Lumb AB (ed) Nunn's applied respiratory physiology. Elsevier, Edinburgh, pp 357–374
45. Gong H Jr (1992) Air travel and oxygen therapy in cardiopulmonary patients. Chest 101(4):1104–1113
46. Cottrell JJ, Lebovitz BL, Fennell RG, Kohn GM (1995) Inflight arterial saturation: continuous monitoring by pulse oximetry. Aviat Space Environ Med 66(2):126–130
47. Cottrell JJ (1988) Altitude exposures during aircraft flight flying higher. Chest 93(1):81–84
48. Christensen CC, Ryg M, Refvem OK, Skjonsberg OH (2000) Development of severe hypoxaemia in chronic obstructive pulmonary disease patients at 2, 438 m (8, 000 ft) altitude. Eur Respir J 15(4):635–639
49. Dillard TA, Beninati WA, Berg BW (1991) Air travel in patients with chronic obstructive pulmonary disease. Arch Intern Med 151(9):1793–1795
50. Warner MA, Offord KP, Warner ME, Lennon RL, Conover MA, Jansson-Schumacher U (1989) Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: a blinded prospective study of coronary artery bypass patients. Mayo Clin Proc 64(6):609–616
51. Gracey DR, Divertie MB, Didier EP (1979) Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease: a prospective study. Chest 76(2):123–129
52. Celli BR, Rodriguez KS, Snider GL (1984) A controlled trial of intermittent positive pressure breathing, incentive spirometry, and deep breathing exercises in preventing pulmonary complications after abdominal surgery. Am Rev Respir Dis 130(1):12–15
53. Garibaldi RA, Britt MR, Coleman ML, Reading JC, Pace NL (1981) Risk factors for postoperative pneumonia. Am J Med 70(3):677–680
54. Bingol H, Cingoz F, Balkan A, Kilic S, Bolcal C, Demirkilic U et al (2005) The effect of oral prednisolone with chronic obstructive pulmonary disease undergoing coronary artery bypass surgery. J Card Surg 20(3):252–256
55. Shen KR, Swanson SJ (2004) Perioperative complications and their management. In: Fessler HE, Reilly JJ, Sugarbaker DJ (eds) Lung volume reduction surgery for emphysema. Marcel Dekker, New York, pp 273–288
56. Gutt CN, Oniu T, Wolkener F, Mehrabi A, Mistry S, Buchler MW (2005) Prophylaxis and treatment of deep vein thrombosis in general surgery. Am J Surg 189(1):14–22
57. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr et al (2001) Prevention of venous thromboembolism. Chest 119(1 Suppl):132S–175S
58. Pisegna JR, Martindale RG (2005) Acid suppression in the perioperative period. J Clin Gastroenterol 39(1):10–16
59. Dureuil B (2002) Management of COPD patients undergoing surgery. In: Similowski T, Whitelaw WA, Derenne JP (eds) Clinical management of chronic obstructive pulmonary disease. Marcel Dekker, New York, pp 871–894
60. Varela G, Ballesteros E, Jimenez MF, Novoa N, Aranda JL (2006) Cost-effectiveness analysis of prophylactic respiratory physiotherapy in pulmonary lobectomy. Eur J Cardiothorac Surg 29(2):216–220

Index

N.A. Hanania and A. Sharafkhaneh (eds.), *COPD: A Guide to Diagnosis and Clinical Management*, Respiratory Medicine, DOI 10.1007/978-1-59745-357-8,