American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation

Linda Nici, Claudio Donner, Emiel Wouters, Richard Zuwallack, Nicolino Ambrosino, Jean Bourbeau, Mauro Carone, Bartolome Celli, Marielle Engelen, Bonnie Fahy, Chris Garvey, Roger Goldstein, Rik Gosselink, Suzanne Lareau, Neil MacIntyre, Francois Maltais, Mike Morgan, Denis O'Donnell, Christian Prefault, Jane Reardon, Carolyn Rochester, Annemie Schols, Sally Singh, and Thierry Troosters, on behalf of the ATS/ERS Pulmonary Rehabilitation Writing Committee

This Joint Statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, December 2005, and by the ERS Executive Committee, November 2005

SECTION 1: INTRODUCTION AND DEFINITION

Since the last statements on pulmonary rehabilitation by the American Thoracic Society (ATS; 1999) and the European Respiratory Society (ERS; 1997), there have been numerous scientific advances both in our understanding of the systemic effects of chronic respiratory disease as well as the changes induced by the process of pulmonary rehabilitation. Evidence-based support for pulmonary rehabilitation in the management of patients with chronic respiratory disease has grown tremendously, and this comprehensive intervention has been clearly demonstrated to reduce dyspnea, increase exercise performance, and improve health-related quality of life (HRQL). Furthermore, an emerging literature is beginning to reveal its effectiveness in reducing health care costs.

The impressive rise in interest in pulmonary rehabilitation is likely related to both a substantial increase in the number of patients being referred as well as the establishment of its scientific basis by the use of well-designed clinical trials that use valid, reproducible, and interpretable outcome measures. Advances in our understanding of the pathophysiology of chronic respiratory conditions are extending the scope and applicability of pulmonary rehabilitation.

Individuals with chronic obstructive pulmonary disease (COPD) still comprise the largest proportion of those referred for pulmonary rehabilitation. However, it has become clear that regardless of the type of chronic respiratory disease, patients experience a substantial morbidity from secondary impairments, such as peripheral muscle, cardiac, nutritional, and psychosocial dysfunction, as well as suboptimal self-management strategies. Therefore, pulmonary rehabilitation may be of value for all patients in whom respiratory symptoms are associated with diminished functional capacity or reduced HRQL.

The timing of pulmonary rehabilitation depends on the clinical status of the individual patient and should no longer be viewed as a "last ditch" effort for patients with severe respiratory

This Statement was endorsed by the American Association of Cardiovascular and Pulmonary Rehabiliation, May 2006.

Am J Respir Crit Care Med Vol 173. pp 1390–1413, 2006
DOI: 10.1164/rccm.200508-1211ST
Internet address: www.atsjournals.org

impairment. Rather, it should be an integral part of the clinical management of all patients with chronic respiratory disease, addressing their functional and/or psychologic deficits. Patient education is more than simply providing didactic information. It involves a combination of teaching, counseling, and behavior modification techniques to promote self-management skills and self-efficacy. Patient education should also integrate end-of-life decision making into the overall treatment strategy.

In light of the recent advances in our understanding of the science and process of pulmonary rehabilitation, the ATS and the ERS have adopted the following definition: "Pulmonary rehabilitation is 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." Pulmonary rehabilitation programs involve patient assessment, exercise training, education, nutritional intervention, and psychosocial support. 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, family, and health care providers. These strategies address both the primary and the secondary impairments associated with the respiratory disease.

This document has been developed by an international committee and has been endorsed by both the ATS and the ERS. It places pulmonary rehabilitation within the concept of integrated care. The World Health Organization has defined integrated care as "a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion" (1). Integration of services improves access, quality, user satisfaction, and efficiency of medical care. As such, pulmonary rehabilitation provides an opportunity to coordinate care and focus on the entire clinical course of an individual's disease.

Building on previous statements (2, 3), this document presents recent scientific advances in our understanding of the multisystemic effects of chronic respiratory disease and how pulmonary rehabilitation addresses the resultant functional limitations. It was created as a comprehensive statement, using both a firm evidence-based approach and the clinical expertise of the writing committee. As such, it is complementary to two current documents on pulmonary rehabilitation: the American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) evidence-based guidelines (4), which formally grade the level of scientific evidence, and the AACVPR Guidelines for Pulmonary Rehabilitation Programs (5), which give practical recommendations.

SECTION 2: EXERCISE PERFORMANCE: LIMITATIONS AND INTERVENTIONS

Introduction

Exercise intolerance is one of the main factors limiting participation in activities of daily living among individuals with chronic respiratory disease. While there is a growing body of evidence defining the mechanisms of exercise limitation in all respiratory disease, the majority of the literature to date has focused on individuals with COPD (6). In addition, virtually all randomized controlled trials of exercise training have been in this population. Most of the evidence presented here concentrates on COPD, with discussion on exercise limitation and exercise training in other chronic respiratory diseases included, where available.

The cardinal symptoms of chronic respiratory disease that limit exercise in most patients are dyspnea and/or fatigue, which may result from ventilatory constraints, pulmonary gas exchange abnormalities, peripheral muscle dysfunction, cardiac dysfunction, or any combination of the above. Anxiety and poor motivation are also associated with exercise intolerance. Although it is commonly accepted that anxiety and depression have an impact on symptom perception (7, 8) and hence may contribute to exercise intolerance, a direct association between emotional status and exercise tolerance has not been established (9). Further research is needed to unravel the potential interaction between mood disturbances and exercise limitation.

In the next section, the physiologic factors limiting exercise tolerance are discussed together with the most potent intervention to improve exercise tolerance: exercise training. Identifying one variable limiting exercise in patients with COPD is often difficult. Many factors may contribute directly or indirectly to exercise tolerance. Because of this, separating the various mechanisms contributing to exercise intolerance is often a largely academic exercise. For example, deconditioning and hypoxia contribute to excess ventilation, resulting in an earlier ventilatory limitation. By consequence, exercise training and oxygen therapy could delay ventilatory limitation during exercise without altering lung function or the maximum ventilatory capacity. Analyzing the limiting factors may uncover otherwise hidden exercise-related issues, such as hypoxemia, bronchospasm, dysrhythmias, musculoskeletal problems, or cardiac ischemia (10).

Factors Contributing to Exercise Intolerance in Chronic Respiratory Disease

Ventilatory limitation. In COPD, ventilation during exercise is often higher than expected because of increased dead-space ventilation, impaired gas exchange, and increased ventilatory demands related to deconditioning and peripheral muscle dysfunction. Furthermore, maximal ventilation during exercise is often limited by the mechanical constraints imposed by the lung pathophysiology. Prominent among these constraints and typically seen in emphysematous patients is the delay of normal emptying of the lungs during expiration due to flow limitation (11, 12), which is aggravated during exercise (13). This leads to dynamic hyperinflation (14), resulting in increased work of breathing, increased load on the respiratory muscles (15, 16), and the intensified perception of respiratory discomfort.

Gas exchange limitations. Hypoxia may directly or indirectly limit exercise tolerance. Hypoxia directly increases pulmonary ventilation through augmenting peripheral chemoreceptor output and indirectly through stimulation of lactic acid production. Lactic acidemia contributes to muscle task failure and increases pulmonary ventilation, as buffered lactic acid results in an increase in carbon dioxide production (17). Supplemental oxygen therapy during exercise in hypoxemic and even in nonhypoxemic patients with COPD allows for higher intensity training, probably through several mechanisms, including a dose-dependent decrease in dynamic hyperinflation by lowering respiratory rate, a decrease in pulmonary artery pressures, and a decrease in lactic acid production (14, 18–22).

Cardiac dysfunction. The cardiovascular system is affected by chronic lung disease in a number of ways, the most important being an increase in right ventricular afterload imposed by an elevated pulmonary vascular resistance from direct vascular injury (23, 24), hypoxic vasoconstriction (25), and/or increases in effective pulmonary vascular resistance due to erythrocytosis (26). An overloaded right ventricle, in turn, leads to right ventricular hypertrophy, which, if severe or left untreated, may result in right ventricular failure (27). These right ventricular effects can also compromise left ventricular filling through septal shifts

that further reduce the ability of the heart to meet exercise demands (28). Other complications include the detrimental effects of tachyarrythmias resulting from a dilated or hypertrophied myocardium. Air trapping and the consequent rise in right atrial pressure may further compromise cardiac function during exercise (29). Under these conditions, exercise-related left ventricular dysfunction, occult at rest, may be observed (30). Several studies have demonstrated substantial physiologic benefits after relatively high levels of exercise training (31–34), but it is difficult to determine the additional contribution of enhanced cardiovascular function to the improvements documented in peripheral muscle function. The role of exercise training in improving cardiovascular function in patients with chronic respiratory disease is largely undefined, and should be studied.

Finally, inactivity can lead to cardiovascular deconditioning, which further limits exercise tolerance. It is important to recognize that a substantial amount of the increase seen in exercise tolerance after exercise training probably reflects improvements in cardiovascular function.

Skeletal muscle dysfunction. An outline of possible skeletal muscle abnormalities in chronic respiratory disease is given in Table 1. Weight loss and consequent peripheral muscle wasting occurs in approximately 30% of outpatients with COPD (35). Peripheral muscle dysfunction may also be attributable to inactivity-induced deconditioning, systemic inflammation, oxidative stress, blood gas disturbances, corticosteroid use, and reductions in muscle mass (36). The quadriceps muscle has frequently been studied in COPD because it is readily accessible and is a primary muscle of ambulation. However, the generalization of these findings to patients with less severe disease or to other skeletal muscles is unclear. Upper limb skeletal muscle strength and mechanical efficiency may be better preserved, although this is controversial (37–39). For example, unlike the situation in the quadriceps, citrate synthase (an enzyme of the citric acid cycle) activity of the deltoid muscle is relatively preserved in severe COPD (40). At present, there are no studies in which muscle biopsies from upper and lower limbs obtained from the same subjects with chronic respiratory disease have been compared.

A reduced capacity for muscle aerobic metabolism may influence exercise tolerance in several ways. Increased lactic acidosis for a given exercise work rate, a common finding in COPD (31, 41), increases ventilatory needs (31). This imposes an additional burden on the respiratory muscles already facing increased impedance to breathing. Premature muscle acidosis, a contributory factor to muscle task failure and early exercise termination in healthy subjects, may be an important mechanism contributing

TABLE 1. PATHOPHYSIOLOGIC ABNORMALITIES IN CHRONIC RESPIRATORY DISEASE AND POSSIBLE MECHANISMS FOR IMPROVEMENT AFTER EXERCISE TRAINING

	Pathophysiologic Abnormality	References	Changes with Exercise Training	References
Body composition	↓ Lower limb muscle cross-sectional area ↓ Fat-free mass and ↓ fat mass ↓ % Fat-free mass and =/↑ fat mass	35	↑ With resistance training ↑ Fat-free mass and fat mass with rehabilitation and nutritional supplementation ↑ Fat-free mass and ↓ fat mass with rehabilitation (resistance + endurance combined Enhanced ↑ fat-free mass with testosterone (1) and anabolic steroids	360, 194, 361
Lower limb muscle fiber type, size	↓ % Fiber type I and myosin heavy chain (advanced disease) ↑ % Fiber type IIX ↓ Fiber cross-sectional area linked to muscle atrophy	40, 158, 362–367	= Fiber-type proportion ↑ Fiber cross-sectional area	362
Capillarization	↓ Capillary contacts to fiber cross-sectional area, especially in patients developing fatigue during exercise	45, 362	↑ Capillary contacts proportional to increase in fiber cross-sectional area	362
Muscle metabolic capacity	↓ Capacity of oxidative enzymes: citrate synthase, 3-hydroxyacyl-CoA dehydrogenase, succimic acid dehydrogenase, cytochrome C oxidase ↑ Cytochrome-c oxidase activity in hypoxemic patients	41, 368, 369	↑ Capacity of oxidative enzymes after endurance training	63
Metabolism at rest/after exercise	Rest: ↓ intracellular pH, ↓ [PCr] and [ATP], ↑ lactate and inosine monophosphate; ↓ glycogen stores in hypoxemic patients; ↓ glycogen stores related to physical activity level; ↓ uncoupling protein-3 content Exercise: rapid decline in muscle intracellular pH, phosphocreatine/inorganic phosphate [PCr/Pi] even in patients with relatively preserved submaximal oxygen delivery	42, 61, 68, 370–373	↓ Lactic acidemia at iso work rate Normalization of decline in intracellular pH and PCr/Pi. Faster PCr-recovery.	31, 61
Inflammatory state	↑ Inflammatory/apoptotic markers may occur in skeletal muscle in subpopulations of wasted COPD	374, 375	No effect shown or not studied	
Redox state	Glutathione levels normal to moderately reduced ↑ Oxidative stress in the skeletal muscle of COPD patients after quadriceps exercise	363, 376–378	↑ Oxidized gluthatione in contrast to observations in healthy subjects. Partially reversed by antioxidant therapy (N-acetyl cysteine)	379

to exercise intolerance in COPD (42). This is exacerbated by a tendency to retain CO_2 during exercise, further increasing acidosis. Improving peripheral skeletal muscle function is therefore an important goal of exercise training programs.

Leg fatigue also contributes to poor exercise tolerance in chronic respiratory disease, and in some patients is the main limiting symptom (43, 41). This could be related to the fact that the peripheral muscle alterations described in Table 1 render these muscles susceptible to contractile fatigue (44). Recently, the impact of leg fatigue on the exercise response to acute bronchodilation in patients with COPD has been evaluated (45). In patients who developed leg fatigue during exercise, ipratropium failed to increase endurance time despite an 11% improvement in FEV_1. This study provides indirect evidence of the role of peripheral muscle dysfunction in exercise intolerance in some patients with COPD.

Respiratory muscle dysfunction. The diaphragms of patients with COPD adapt to chronic overload and show a greater resistance to fatigue (46, 47). As a result, at identical absolute lung volumes, their inspiratory muscles are capable of generating more force than that in healthy control subjects (48, 49). This occurs early in the course of the disease, even before adaptations in the skeletal muscle are seen (50). However, these patients often have hyperinflation, which places their respiratory muscles at a mechanical disadvantage. Despite these adaptations in the diaphragm, both functional inspiratory muscle strength (52) and inspiratory muscle endurance (53) are compromised in COPD. As a consequence, respiratory muscle weakness, as assessed by measuring maximal respiratory pressures, is often present (51–54). This contributes to hypercapnia (55), dyspnea (56, 57), nocturnal oxygen desaturation (58), and reduced exercise performance (41). During exercise it has been shown that patients with COPD use a larger proportion of their maximal inspiratory pressure than healthy subjects, probably due, in large part, to increased respiratory muscle loading from dynamic hyperinflation (59). A last factor that may link the respiratory muscles to exercise limitation is the increase in systemic vascular resistance as the load on the diaphragm increases (60). This may lead to a "steal" effect of blood from the peripheral muscles to the diaphragm, although no convincing data are available to confirm this.

Exercise Training to Improve Exercise Performance

Introduction. Exercise training, widely regarded as the cornerstone of pulmonary rehabilitation (73), is the best available means of improving muscle function in COPD (61–63) and (probably) other chronic respiratory diseases. It is indicated for those individuals with chronic respiratory disease who have decreased exercise tolerance, exertional dyspnea or fatigue, and/or impairment of activities of daily living. Patients with COPD after acute exacerbations are excellent candidates for exercise training (64). Exercise training programs 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 (65, 66), decrease symptoms (67), and improve cardiovascular function. Patients with severe chronic respiratory disease can sustain the necessary training intensity and duration for skeletal muscle adaptation to occur (63, 68). Before exercise training and during a thorough patient assessment, clinicians must establish optimal medical treatment, including bronchodilator therapy, long-term oxygen therapy, and treatment of comorbidities. A thorough patient assessment may also include a maximal cardiopulmonary exercise test to assess the safety of exercise, the factors contributing to exercise limitation, and the exercise prescription (69). Table 1 summarizes the effects of exercise training on different aspects of skeletal muscle dysfunction.

Improvements in skeletal muscle function after exercise training result in gains in exercise capacity despite the absence of changes in lung function. Moreover, the improved oxidative capacity and efficiency of the skeletal muscles lead to less alveolar ventilation for a given work rate. This may reduce dynamic hyperinflation, thereby reducing exertional dyspnea.

Exercise programs in COPD.

Program duration and frequency. The minimum duration of exercise training in pulmonary rehabilitation has not been extensively investigated. Outpatient exercise training with two or three weekly sessions for 4 weeks showed less benefit than similar training for 7 weeks (70, 71). Furthermore, 20 sessions of comprehensive pulmonary rehabilitation has been demonstrated to show considerably more improvement in multiple outcomes than 10 sessions (72). Short-term, intensive programs (20 sessions condensed in 3–4 weeks) have also been shown to be effective (73). It is generally believed that longer programs yield larger, more endurable training effects (74–76).

Patients should perform exercise at least three times per week, and regular supervision of exercise sessions is necessary to achieve optimal physiologic benefits (77, 78). Because of program constraints, twice-weekly supervised exercise training and one or more unsupervised session at home may be an acceptable alternative (79), although it is unclear whether this is as effective. Once-weekly supervised sessions appear to be insufficient (80).

Intensity of exercise. Although low-intensity training results in improvements in symptoms, HRQL, and some aspects of performance in activities of daily living (81, 82), greater physiologic training effects occur at higher intensity (31). Training programs, in general, should attempt to achieve maximal physiologic training effects (83), but this approach may have to be modified because of disease severity, symptom limitation, comorbidities, and level of motivation. Furthermore, even though high-intensity targets are advantageous for inducing physiologic changes in patients who can reach these levels, low-intensity targets may be more important for long-term adherence and health benefits for a wider population.

In normal subjects, high-intensity training can be defined as that intensity which leads to increased blood lactate levels (31). However, in the pulmonary rehabilitation patient population, there is no generally accepted definition of high intensity, since many are limited by respiratory impairment before achieving this physiologic change. A training intensity that exceeds 60% of the peak exercise capacity is empirically considered sufficient to elicit some physiologic training effects (84), although higher percentages are likely to be more beneficial and are often well tolerated. In clinical practice, symptom scores can be used to adjust training load (85, 86); these scores are anchored to a stable relative load and can be used throughout the training program (87). A Borg score of 4 to 6 for dyspnea or fatigue is usually a reasonable target. Alternatively, heart rate at the gas exchange threshold or power output has also been used to target training intensity (83).

Specificity of exercise training. Pulmonary rehabilitation exercise programs have traditionally focused on lower extremity training, often using a treadmill or stationary cycle ergometer. However, many activities of daily living involve upper extremities. Because improvement is specific to those muscles trained, upper limb exercises should also be incorporated into the training program (88). Examples of upper extremity exercises include an arm cycle ergometer, free weights, and elastic bands. Upper limb exercise training reduces dyspnea during upper limb activities and reduces ventilatory requirements for arm elevation (89, 90).

Endurance and strength training. Endurance training in the form of cycling or walking exercises is the most commonly applied exercise training modality in pulmonary rehabilitation (33, 34, 91, 92). Optimally, the approach consists of relatively long exercise sessions at high levels of intensity (> 60% maximal work rate). The total effective training time should ideally exceed 30 minutes (93). However, for some patients, it may be difficult to achieve this target training time or intensity, even with close supervision (34). In this situation, interval training may be a reasonable alternative.

Interval training is a modification of endurance training where the longer exercise session is replaced by several smaller sessions separated by periods of rest or lower intensity exercise. Interval training results in significantly lower symptom scores (79) despite high absolute training loads, thus maintaining the training effects (79, 94, 95).

Strength (or resistance) training also appears to be worthwhile in patients with chronic respiratory disease (96). This type of training has greater potential to improve muscle mass and strength than endurance training (96–100), two aspects of muscle function that are only modestly improved by endurance exercises. Training sessions generally include two to four sets of 6 to 12 repetitions at intensities ranging from 50 to 85% of one repetition maximum (101). Strength training may also result in less dyspnea during the exercise period, thereby making this strategy easier to tolerate than aerobic training (96).

The combination of endurance and strength training is probably the best strategy to treat peripheral muscle dysfunction in chronic respiratory disease, because it results in combined improvements in muscle strength and whole body endurance (62), without unduly increasing training time (99).

Practice guidelines:

1. A minimum of 20 sessions should be given at least three times per week to achieve physiologic benefits; twice-weekly supervised plus one unsupervised home session may also be acceptable.
2. High-intensity exercise produces greater physiologic benefit and should be encouraged; however, low-intensity training is also effective for those patients who cannot achieve this level of intensity.
3. Interval training may be useful in promoting higher levels of exercise training in the more symptomatic patients.
4. Both upper and lower extremity training should be utilized.
5. The combination of endurance and strength training generally has multiple beneficial effects and is well tolerated; strength training would be particularly indicated for patients with significant muscle atrophy.

Special Considerations for Exercise Training in Patients without COPD

To date, there are no formal evidence-based guidelines regarding the exercise prescription or response to exercise training for patients with respiratory disorders other than COPD. Therefore, recommendations for pulmonary rehabilitation of these diseases must rely on expert opinion based on knowledge of the underlying pathophysiology and clinical experience. Safety considerations as well as individual patient needs and goals of rehabilitation must guide the exercise prescription and implementation of the training program. Careful consideration of the multiple factors contributing to exercise limitation is essential for each patient. To follow are some unique features for rehabilitation among patients without COPD.

When treated appropriately, patients with asthma are often not ventilatory-limited and therefore can usually achieve substantial physiologic training benefit from high-intensity training. To minimize exercise-induced bronchospasm during exercise training, preexercise use of bronchodilators and an adequate period of gradual warm-up exercise are indicated. Cardiopulmonary exercise testing may be used to evaluate for exercise-induced bronchoconstriction (102). Patients with cystic fibrosis should exercise at stations a few feet apart from other participants to avoid cross-contamination with bacterial pathogens that may be antibiotic resistant (103, 104). In addition, patients and staff members must also pay close attention to hygiene techniques. Patients should maintain the protein and caloric intake necessary to meet the metabolic demand posed by exercise training (105), and precautions should be taken to maintain adequate fluid and salt intake (102, 106–108). Pulmonary rehabilitation has been shown to improve exercise capacity in patients with bronchiectasis (109). For patients with advanced interstitial lung disease, particular emphasis should be placed on pacing and energy conservation, because dyspnea may be severe and oxygen desaturation during exercise may be difficult to correct with supplemental O_2. Walking and low-impact and water-based exercise may be ideal for severely obese patients. Persons with neuromuscular disease–related respiratory disorders may require adaptive assistive equipment to optimize functional status. Exercise should be undertaken in a manner that maintains muscle conditioning while avoiding excess muscular fatigue (110).

Until recently, severe pulmonary hypertension was considered a contraindication to exercise training. However, a closely supervised program with attention to the nature and intensity of exercise may be useful before transplantation or for the treatment of functional limitation. High-intensity exercise is generally not recommended for this population. Low-intensity aerobic exercise, pacing, and energy conservation techniques are recommended. Telemetry monitoring may be indicated for those patients with known arrhythmias. Cessation of exercise is especially important if the patient develops chest pain, lightheadedness, or palpitations. Activities such as weight lifting, which lead to increased intrathoracic pressure, should be avoided because of the risk of syncope and circulatory collapse. Blood pressure and pulse should be monitored closely during exercise, and care should be taken to avoid falls for patients receiving anticoagulation medication. Extreme caution must be used to avoid interruption of continuous intravenous vasodilator therapy and to ensure adequate oxygenation.

Additional Strategies to Improve Exercise Performance

Maximizing pulmonary function before starting exercise training. In patients with airflow limitation, bronchodilators may reduce dyspnea and improve exercise tolerance (111). These beneficial effects may be mediated not only through reducing airway resistance but also through the reduction of resting and dynamic hyperinflation (112–115). Thus, the effectiveness of bronchodilators should not be judged only by the improvement in FEV_1, as improvements in markers of hyperinflation, such as the inspiratory capacity, may be more relevant to the observed clinical benefit during exercise.

Bronchodilator therapy may be especially effective in enhancing exercise performance in those patients less limited by contractile muscle fatigue (45, 116). With optimal bronchodilation, the primary cause of exercise limitation may change from dyspnea to leg fatigue, thereby allowing patients to exercise their peripheral muscles to a greater degree (115). This nicely illustrates the potential synergy between pharmacologic and nonpharmacologic treatments. Optimizing bronchodilation within the context of a pulmonary rehabilitation program for COPD

results in greater improvement in exercise performance, probably by allowing patients to exercise at higher intensities (117).

Practice guideline: In individuals with airflow limitation, optimal bronchodilator therapy should be given prior to exercise training to enhance performance.

Oxygen. Patients who are receiving long-term oxygen therapy should have this continued during exercise training, but may need increased flow rates. Oxygen supplementation as an adjunct to exercise training has been tested in two distinct populations: those with and those without exercise-induced hypoxemia. In hypoxemic patients, randomized controlled trials compared exercise training with supplemental oxygen to training with room air. In one study, oxygen supplementation led to significant improvement in exercise tolerance and dyspnea (18). In three others, there were no significant between-group differences in exercise tolerance, dyspnea, or HRQL (118–120).

In nonhypoxemic patients, oxygen supplementation also allowed higher training intensities and enhanced exercise performance in the laboratory setting, even without desaturation, probably mediated through a reduced ventilatory response (19). There was a trend for a greater improvement in some aspects of quality of life in oxygen-trained patients, although the study was probably underpowered for this outcome. In another study, the prescription of supplemental oxygen for mild hypoxemia outside of the pulmonary rehabilitation setting did not show any increase in exercise tolerance or HRQL (121). These studies provide important information but do not enable the clinician to predict individual responses to oxygen therapy based on exercise-induced desaturation (122).

Practice guideline: Oxygen supplementation during pulmonary rehabilitation, regardless of whether or not oxygen desaturation during exercise occurs, often allows for higher training intensity and/or reduced symptoms in the research setting. However, at the present time, it is still unclear whether this translates into improved clinical outcomes.

Noninvasive mechanical ventilation. Noninvasive positive-pressure ventilation (NPPV) reduces breathlessness and increases exercise tolerance in certain patients with chronic respiratory disease, probably through reducing the acute load on the respiratory muscles (123–129). In patients with COPD with chronic respiratory failure, a novel form of noninvasive ventilatory support, proportional assist ventilation, enabled a higher training intensity, leading to a greater maximal exercise capacity and evidence of true physiologic adaptation (130–132). In one study, the addition of nocturnal domiciliary NPPV in combination with pulmonary rehabilitation in severe COPD resulted in improved exercise tolerance and quality of life, presumably through resting the respiratory muscles at night (133).

Practice guideline: In selected patients with severe chronic respiratory disease and suboptimal response to exercise, NPPV may be considered as adjunctive therapy since it may allow for greater training intensity through unloading respiratory muscles. Because NPPV is a very difficult and labor-intensive intervention, it should be used only in those with demonstrated benefit from this therapy. Further studies are needed to further define its role in pulmonary rehabilitation.

Respiratory muscle training. Adding inspiratory muscle training to standard exercise training in patients with poor initial inspiratory muscle strength has been shown in some studies to improve exercise capacity more than exercise training alone (134–138). In patients with less respiratory muscle weakness, evidence for the addition of inspiratory muscle training to regular exercise training is lacking. Three types of inspiratory muscle training have been reported: inspiratory resistive training (139), threshold loading (140, 141), and normocapnic hyperpnea (142–144). At present, there are no data to support one method over the other.

Practice guideline: Although the data are inconclusive, inspiratory muscle training could be considered as adjunctive therapy in pulmonary rehabilitation, primarily in patients with suspected or proven respiratory muscle weakness.

Neuromuscular electrical stimulation. Neuromuscular electrical stimulation (NMES) involves passive stimulation of contraction of the peripheral muscles to elicit beneficial training effects. It has been used in patients with severe peripheral muscle weakness, such bed-bound patients receiving mechanical ventilation who have marked peripheral muscle dysfunction (145, 146). The application of NMES combined with active limb mobilization significantly improved muscle strength and exercise capacity and reduced days needed for patients to transfer from the bed to the chair (147). In one study, patients who were deemed by the investigators to be poor candidates for standard pulmonary rehabilitation were able to participate in regular rehabilitation after 6 weeks of NMES (145). One of the potential advantages of NMES is that it can be applied in the home setting. Larger studies are needed to further define its indications and applications.

Practice guideline: NMES may be an adjunctive therapy for patients with severe chronic respiratory disease who are bed-bound or suffering from extreme skeletal muscle weakness.

SECTION 3: BODY COMPOSITION: ABNORMALITIES AND INTERVENTIONS

The Scope of Body Composition Abnormalities in Chronic Lung Disease

Body composition abnormalities are probably prevalent in all advanced respiratory disease. However, most literature, to date, has focused on individuals with COPD. Therefore, most of the information given below relates to this disease. Individuals with moderate to severe COPD are frequently underweight, including up to one-third of outpatients (148, 149) and 32 to 63% of those referred for pulmonary rehabilitation or those participating in clinical trials (150–154). Muscle wasting associated with COPD is more common in, but by no means limited to, underweight patients. At a minimum, simple screening should be a component of comprehensive pulmonary rehabilitation. This can be most easily accomplished by calculating body mass index (BMI), which is defined as the weight in kilograms divided by the height in meters squared. On the basis of 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 chronic lung disease.

Measurement of body weight or BMI, however, does not accurately reflect changes in body composition in these patients. Body weight can be divided into fat mass and fat-free mass (FFM). FFM consists of body cell mass (organs, muscle, bone) and water. Under clinically stable conditions, measurement of FFM can be used to estimate body cell mass. The loss of FFM, which is characteristic of the cachexia associated with chronic lung diseases, such as COPD, can be estimated using skinfold anthropometry, bioimpedance analysis (which determines FFM) (155), or dual-energy X-ray absorptiometry (DEXA; which determines lean nonfat, nonbone mass) (156). Although reductions in FFM are usually associated with weight loss, the former may even occur in weight-stable patients. Loss of FFM is significantly

related to selective atrophy of muscle fibers, particularly type II fibers (68, 157, 158).

In the last two decades, several studies have defined and quantified depletion of FFM. Patients can be considered to be depleted based on the FFM index (FFM/height^2), with values below 16 kg/m^2 for men and 15 kg/m^2 for women (159). In European studies, using these criteria, 35% of patients with COPD admitted for pulmonary rehabilitation and 15% of outpatients with COPD were characterized as depleted (160–162), underscoring its high prevalence in chronic lung disease.

Patients with COPD and reduced FFM have lower exercise tolerance as measured using either 12-minute walk distance (163, 160) or $\dot{V}O_2$max (164, 165) than those with preserved FFM. In addition, peripheral muscle strength is decreased in patients with COPD (38, 166–168, 163), although it is seen in some muscle groups more than others (169). Because muscle power is directly proportional to its cross-sectional area, loss of muscle mass would be expected to impair muscle strength. Indeed, the finding that strength per kilogram of limb FFM is similar in patients with COPD and control subjects supports the concept that loss of muscle mass is a major determinant of limb weakness (166). Reduced FFM in COPD is also associated with impaired respiratory muscle strength (167, 168), although a proportion of the apparent weakness of these muscles is undoubtedly due to mechanical disadvantage due to changes in chest wall shape and hyperinflation (170).

Underweight patients with COPD have significantly greater impairment in HRQL than those with normal weight (171). Moreover, those with depletion in lean body mass have greater impairment in this outcome area than those without depletion (171). Because normal-weight patients with COPD and low FFM have more impairment in HRQL than underweight patients with normal FFM, this body composition abnormality appears to be an important predictor of HRQL, independent of weight loss (163).

In COPD, there is an association between underweight status and increased mortality (172–174), independent of the degree of airflow obstruction (172). Perhaps more importantly, weight gain in those with a BMI below 25 kg/m^2 was associated with decreased mortality (172, 175). Because the midthigh muscle cross-sectional area (using computed tomography scanning) in severe COPD was demonstrated to be a better indicator of prognosis than BMI (176), the loss of muscle mass rather than body weight may be a better predictor of mortality. Normal-weight patients with COPD and depleted FFM may have a comparable mortality risk to underweight patients with depleted FFM.

Weight loss may be caused by increased energy and substrate metabolism or reduced dietary intake, and muscle wasting is the consequence of an imbalance between protein synthesis and protein breakdown. Impairment in total energy balance and protein metabolism may occur simultaneously, but these processes can also be dissociated because of altered regulation of substrate metabolism. Hypermetabolism may be the consequence of low-grade systemic inflammation in COPD (177, 178). Total energy expenditure, which reflects the metabolic state of the individual, includes resting energy expenditure and activity-related energy expenditure. In sedentary individuals, resting energy expenditure is the major component of total energy expenditure, and this has been found to be elevated in 25% of patients with COPD (179). Activity-related energy expenditure is also elevated in COPD, but there may be different mechanisms that underlie these metabolic alterations in subgroups of patients (154). Table 1 summarizes the effects of body composition on different aspects of skeletal muscle dysfunction.

Interventions to Treat Body Composition Abnormalities

Introduction. The rationale for addressing and treating body composition abnormalities in patients with chronic lung disease is based on the following: (*1*) the high prevalence and association with morbidity and mortality; (*2*) the higher caloric requirements from exercise training in pulmonary rehabilitation, which may further aggravate these abnormalities (without supplementation); and (*3*) the enhanced benefits, which will result from structured exercise training.

Although the etiology of the weight loss and muscle wasting in chronic respiratory disease is complex and not yet fully understood, different physiologic and pharmacologic intervention strategies have been used to reverse wasting of fat mass and FFM. The duration of most of these interventions has been 2 to 3 months; limited information is available regarding longer term therapy. Assessment of body composition is indicated in the assessment and diagnostic workup of the individual patient to target the therapeutic intervention to the pattern of tissue wasting.

Caloric supplementation. Caloric support is indicated to match elevated energy requirements to maintain or restore body weight and fat mass. This is especially important for chronic respiratory patients, since some may suffer from involuntary weight loss and/or exhibit a decreased mechanical efficiency during exercise. Adequate protein intake is crucial for stimulation of protein synthesis to maintain or restore FFM not only in underweight but also in normal-weight patients. The increased activity-related energy requirements during pulmonary rehabilitation must also be met, even in normal-weight individuals (180).

Caloric supplementation intervention should be considered for the following conditions: a BMI less than 21 kg/m^2, involuntary weight loss of more than 10% during the last 6 months or more than 5% in the past month, or depletion in FFM or lean body mass. Nutritional supplementation should initially consist of adaptation in the patient's dietary habits and the administration of energy-dense supplements.

In early controlled clinical trials, oral liquid dietary supplementation (without exercise) was able to restore energy balance and increase body weight in underweight patients with COPD (181–183). These early intervention studies did not assess the ratio of fat mass to FFM. In most outpatient settings, however, nutritional supplementation alone has not been successful in inducing significant weight gain (184). Several factors may contribute to this, including a reduction in spontaneous food intake (180, 185, 186), suboptimal implementation of nutritional supplements in daily meal and activity pattern (185), portion size and macronutrient composition of nutritional supplements (187), and the presence of systemic inflammation (186). Addressing these factors by integrating nutritional intervention into a comprehensive rehabilitation program should improve outcome. For example, two controlled studies have demonstrated that nutritional supplementation combined with supervised exercise training increased body weight and FFM in underweight patients with COPD (168, 188). From these studies, it can be anticipated that the combined intervention can result in a 2:1 ratio of gain in FFM to gain in fat mass.

Physiologic interventions. Strength training may selectively increase FFM by stimulation of protein synthesis via insulin-like growth factor 1 (IGF-1) or targets downstream of IGF-1 signaling. In patients with COPD and a normal body composition, 8 weeks of whole body exercise training increased body weight as a result of modest increases in FFM, whereas body fat tended to decrease (189). Enhanced bilateral midthigh muscle cross-sectional area, assessed by computed tomography, was seen after 12 weeks of aerobic training combined with strength

training in normal-weight patients with COPD (190). However, BMI did not change. This different response in BMI could be related to differences in dietary intake between study groups (191).

Pharmacologic interventions. Several pharmacologic strategies have been used in an attempt to induce weight gain and, specifically, increase FFM in COPD. Anabolic steroids have been investigated most extensively, either as single therapy (192) or combined with pulmonary rehabilitation (184, 168). In general, treatment duration ranged from 2 to 6 months. Anabolic steroids may improve outcome of pulmonary rehabilitation through various mechanisms: (*1*) stimulation of protein synthesis either directly or indirectly by interaction with the IGF-1 system, (*2*) regulation of the myostatin gene, (*3*) antiglucocorticoid action, and (*4*) erythropoietic action. Low-dose anabolic steroids, given either by intramuscular injection or orally administered, increase FFM, but not fat mass, generally without harmful effects (193). In male patients with low testosterone levels, testosterone administration resulted in an increase in muscle mass. This effect was augmented by concomitant resistance training, and resulted in increased strength (194). It is not clear whether anabolic therapy will lead to improvements in exercise capacity or health status. Specific indications for this treatment are not yet defined.

Growth hormone, which is a potent stimulator of systemic IGF-1 levels, has been shown to increase lean body mass in a small number of underweight patients with COPD participating in a pulmonary rehabilitation program (195). The modest improvement in body composition was associated with increases in exercise performance. However, this therapy is expensive and has been associated with a number of undesirable side effects, such as salt and water retention, and impairment in glucose metabolism. Currently, studies are ongoing to investigate the efficacy and safety of growth hormone–releasing factors to improve body composition and functional capacity in COPD.

The progestational agent megesterol acetate has been shown to increase appetite and body weight, and stimulate ventilation in chronic wasting conditions such as AIDS and cancer. In underweight patients with COPD, 8 weeks of this drug resulted in a treatment–placebo difference of 2.5 kg weight. However, this favorable change in weight was mainly fat mass (196).

On the basis of the current studies, it appears that several physiologic and pharmacologic interventions are able to modulate either fat mass or FFM in patients with COPD. Although these interventions appear to be safe in the short term, further studies are needed to evaluate long-term effects. Further studies are also necessary to develop optimal strategies for pharmacologic interventions for muscle wasting in chronic lung disease. These will include combining exercise training with pharmacologic therapy, targeting specific subpopulations (disease severity and tissue depletion pattern), and determining whether improvement in body composition translates into functional benefits and prolonged survival.

Special Considerations in Obesity

The respiratory disturbances associated with obesity cause an increased work and oxygen cost of breathing (197), with impaired exercise tolerance, disability, and impaired quality of life (198–200). Significant abnormalities of respiratory function can result from obesity alone, even in the absence of underlying parenchymal lung or restrictive chest wall disease. Respiratory disturbances associated with obesity include impaired respiratory mechanics with low lung volumes and decreased respiratory system compliance, increased small airway resistance, and alterations in both breathing pattern and respiratory drive (197, 201). Patients with "obesity hypoventilation syndrome" have resting daytime hypoxemia and hypercarbia, impaired central respiratory drive with decreased ventilatory responsiveness to CO_2, and nocturnal alveolar hypoventilation (197, 201). Persons with "simple obesity" may also have hypoxemia greater than expected for age, due to poor expansion of the lung bases, but maintain normal daytime P_{CO_2}. Obstructive sleep apnea and nocturnal alveolar hypoventilation are also extremely common in obese persons, and can result in pulmonary hypertension and cor pulmonale (197, 202). Obesity is also associated with an increased risk of thromboembolic disease, aspiration, and complications from mechanical ventilation (197). Many morbidly obese individuals eventually develop overt respiratory and/or cardiac failure.

Pulmonary rehabilitation is an ideal setting in which to address the needs of people with obesity-related respiratory disorders and individuals with lung disease in whom obesity is also contributing to functional limitation. Specific interventions may include nutritional education, restricted calorie meal planning, encouragement for weight loss, and psychologic support. Although there is no established target for the amount of weight loss to be achieved after pulmonary rehabilitation, comprehensive rehabilitation of obese persons can lead to weight loss, and improved functional status and quality of life (203–205).

Practice guideline: Pulmonary rehabilitation programs should address body composition abnormalities, which are frequently present and underrecognized in chronic lung disease. Intervention may be in the form of caloric, physiologic, pharmacologic, or combination therapy.

SECTION 4: SELF-MANAGEMENT EDUCATION

Introduction

Patient education remains a core component of comprehensive pulmonary rehabilitation, despite the difficulties in measuring its direct contribution to overall outcomes (5, 206, 207). Education permeates all aspects of pulmonary rehabilitation, beginning at the time of diagnosis and continuing through end-of-life care. It is a shared responsibility among the patient, family, primary care physician, specialist, and nonphysician health care providers.

The style of teaching used in pulmonary rehabilitation is changing from traditional didactic lectures to self-management education (208). Although the former provides information related to the patient's condition and his or her therapy, the latter teaches self-management skills that emphasize illness control through health behavior modification, thus increasing self-efficacy, with the goal of improving clinical outcomes including adherence (Figure 1) (209, 210). Self-efficacy refers to the belief that one can successfully execute particular behaviors to produce certain outcomes (211). Strategies to enhance self-efficacy are listed in Table 2.

Curriculum Development

The curriculum of an individualized educational program is based on addressing knowledge deficits of the patients and their significant others. These specific educational requirements and the patients' goals are determined at the time of their initial evaluation and are reevaluated during the program. Self-management interventions emphasize how to integrate the demands of the disease into the daily routine. Educational topics are listed in Table 3. For patients with disorders other than COPD, it is important that the pulmonary rehabilitation staff understand the pathophysiology and the appropriate therapeutic interventions required for each diagnostic group.

Prevention and early treatment of respiratory exacerbations, informed end-of-life decision making, breathing strategies, and bronchial hygiene techniques are important educational issues to be included in pulmonary rehabilitation. Health professionals

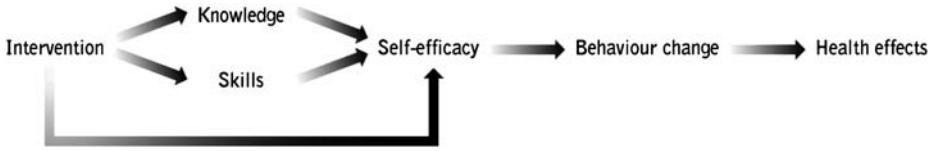

Figure 1. Causal chain of behavior modification. Reprinted by permission from Reference 210.

should always be aware of those patients who still require smoking cessation interventions.

Prevention and early treatment of exacerbations. Self-management should include instruction in the prevention and early treatment of respiratory exacerbations. An exacerbation can be defined as a sustained worsening of the patient's symptoms from that beyond normal day-to-day variation (212). Exacerbations can result in a more rapid decline of lung function (213), increased peripheral muscle weakness (214), decreased quality of life (215), increased health care costs (216, 217), and increased mortality (218). It has been demonstrated that early therapy speeds exacerbation recovery (219) and reduces health care utilization (220). Patients should be instructed to respond early in the course of an exacerbation by activating their predetermined action plan. The action plan can range from initiating a predetermined medication regimen to alerting the health care provider. An example of an action plan can be found at www.livingwellwithcopd.com . Initiating pulmonary rehabilitation immediately after the COPD exacerbation may reduce subsequent health care utilization (64).

End-of-life decision making. Prognostic uncertainty as well as health care provider reluctance form barriers that hinder the discussion of end-of-life decision making. Pulmonary rehabilitation has been identified as an appropriate setting for the discussion of advance care planning and palliative care (221, 222).

Breathing strategies. Breathing strategies refer to a range of techniques, including pursed-lip breathing, active expiration, diaphragmatic breathing, adapting specific body positions, and coordinating paced breathing with activities. These techniques aim to improve regional ventilation, gas exchange, respiratory muscle function, dyspnea, exercise tolerance, and quality of life (223).

Pursed-lip breathing attempts to prolong active expiration through half-opened lips, thus helping to prevent airway collapse. Compared with spontaneous breathing, pursed-lip breathing reduces respiratory rate, dyspnea, and Pa_{CO_2}, while improving tidal volume and oxygen saturation in resting conditions (224). Though these have not been convincingly demonstrated to result in enhanced exercise performance, many patients with chronic lung disease use this technique instinctively and report decreased dyspnea with its use.

Active expiration and body positioning techniques attempt to decrease dyspnea, possibly by improving the length–tension relationships or geometry of the diaphragm. Diaphragmatic breathing techniques require the patient to move the abdominal wall out during inspiration and to reduce upper rib cage motion. The goal is to improve chest wall motion and the distribution of ventilation, thereby decreasing the energy cost of breathing. To date, evidence from controlled studies does not support the use of diaphragmatic breathing in patients with COPD (225, 226). Forward leaning has been noted clinically to be effective in COPD and is probably the most adopted body position (227). Use of a rollator/walker while ambulating allows forward leaning with arm support, decreases dyspnea, and increases exercise capacity (228, 229).

As with the development of all aspects of the patient's self-management education curriculum, the breathing strategies must be individualized. Patients will usually adopt the techniques most effective in reducing symptoms (230).

Bronchial hygiene techniques. For some patients, mucus hypersecretion and impaired mucociliary transport are distinctive features of their lung disease. Instruction in the importance of bronchial hygiene and training in drainage techniques are appropriate for these patients. A recent review concluded that the combination of postural drainage, percussion, and forced expiration improved airway clearance, but not pulmonary function, in patients with COPD and bronchiectasis (231). Use of a positive expiratory pressure mask and assisted coughing were more effective than assisted coughing alone in patients with COPD during an exacerbation (232). Short-term crossover trials suggest that airway clearance regimens have beneficial effects in cystic fibrosis. However, based on a Cochrane review, there is currently no robust scientific evidence to support the hypothesis that chest physiotherapy for the purpose of clearing airway secretions has a beneficial effect in patients with cystic fibrosis (233).

Benefits of Self-Management Education

Self-management improves health status and lowers health service use in many chronic diseases. Recently, a multicenter randomized clinical trial (220) provided evidence that a multicomponent, skill-oriented self-management program that incorporated an exacerbation action plan and home exercise reduced hospitalizations, emergency visits, and unscheduled physician visits, and improved HRQL. However, the beneficial effects of comprehensive self-management were not replicated in another randomized trial (234). Self-management might be especially beneficial for

TABLE 2. STRATEGIES TO ENHANCE SELF-EFFICACY

Strategy	Example
Personal experience and practice	Practice self-management skills during rehabilitation sessions; when possible, practice in home environment, and readdress skills as the patient's disease process changes
Feedback and reinforcement	Receive critique at each visit or telephone contact of patient's ability to effectively use self-management skills; patients need reassurance and reinforcement
Analysis of causes of failure	Address prior negative experiences; reinforce skills that lead to positive outcomes
Vicarious experience	Share experiences; learning from a peer who succeeds in changing the behavior enhances self-efficacy expectations

Adapted from Reference 210.

TABLE 3. EXAMPLES OF EDUCATIONAL TOPICS

Breathing Strategies
Normal Lung Function and Pathophysiology of Lung Disease
Proper Use of Medications, including Oxygen
Bronchial Hygiene Techniques
Benefits of Exercise and Maintaining Physical Activities
Energy Conservation and Work Simplification Techniques
Eating Right
Irritant Avoidance, including Smoking Cessation
Prevention and Early Treatment of Respiratory Exacerbations
Indications for Calling the Health Care Provider
Leisure, Travel, and Sexuality
Coping with Chronic Lung Disease and End-of-Life Planning
Anxiety and Panic Control, including Relaxation Techniques and Stress Management

patients with reduced health status and/or a high frequency of exacerbations. This is a fruitful area for research.

Adherence to Therapeutic Interventions and Transference of Education and Exercise to the Home Setting

Adherence is defined by the World Health Organization as the extent to which a person's behavior corresponds with agreed-on recommendations by the health care provider. Adherence to therapeutic interventions is a crucial health behavior in the management of chronic respiratory disease. The most effective adherence-enhancing interventions are designed to improve patient self-management capabilities (235). The degree of adherence is enhanced when the relationship between the patient and the health care provider is a partnership. Pulmonary rehabilitation is a venue that supports the strengthening of this partnership.

Although the short-term benefits of pulmonary rehabilitation with a supervised exercise training program are well established, challenges remain in understanding and promoting long-term self-management and adherence to exercise in the home setting. Most of our knowledge in exercise behavior comes from emerging research in chronic disease populations, not specifically in patients with chronic respiratory disease. In longitudinal studies of the elderly (236, 237), exercise self-efficacy and estimate of expected benefits from regular exercise were predictors of exercise adherence. Confusion and depression were predictors of poor adherence to a home-based strength-training program (238). In a review of 27 cross-sectional and 14 longitudinal studies of individuals 65 years or older, it was shown that educational level and past exercise behavior correlate positively with the performance of regular exercise (239). Conversely, perceived frailty and poor health were the greatest barriers to adopting an exercise and maintenance program. This is in agreement with a qualitative study conducted specifically in patients with COPD (240). This qualitative study demonstrated that barriers to lifestyle changes frequently reported by patients were progression of COPD and associated comorbid conditions.

A recent study compared enhanced to conventional follow-up strategies at completion of a comprehensive pulmonary rehabilitation program (241). Adherence with exercise was high shortly after completion of the rehabilitation program, but dropped off in both groups over the next 6 months. The most consistently reported reasons for nonadherence were chest infection and disease exacerbation. Although not the primary focus of the study, the description of adherence to home exercise and reasons for nonadherence provide important insight into the patterns and predictors of physical activity behavior modification after rehabilitation. Longer lasting programs seem to enhance long-term effects (76, 242).

Adherence to therapeutic interventions, including exercise programs, is a crucial health behavior in the management of chronic respiratory disease. Instruction in individualized self-management skills is a cornerstone in the promotion of long-term adherence.

Practice guidelines:

1. The educational component of pulmonary rehabilitation should emphasize self-management skills.
2. Self-management should include an action plan for early recognition and treatment of exacerbations and discussions regarding end-of-life decision making.
3. In selected patients, instruction in breathing strategies and bronchial hygiene techniques should be considered.
4. The transference of educational training and exercise adherence to the home setting should be emphasized.

SECTION 5: PSYCHOLOGIC AND SOCIAL CONSIDERATIONS

Introduction

Chronic respiratory disease is associated with increased risk for anxiety, depression, and other mental health disorders (243, 244). Psychologic and social support provided within the pulmonary rehabilitation setting can facilitate the adjustment process by encouraging adaptive thoughts and behaviors, helping patients to diminish negative emotions, and providing a socially supportive environment.

Patients often experience fear and anxiety in anticipation of, and in association with, episodes of dyspnea (245). This heightened physiologic arousal can precipitate or exacerbate dyspnea and contribute to overall disability. Frustration with poor health and the inability to participate in activities can present in the form of irritability, pessimism, and a hostile attitude toward others. In the later stages of respiratory disease, progressive feelings of hopelessness and inability to cope often occur. Patients with chronic respiratory disease who have positive social support have less depression and anxiety than those who do not (246). Those with a history of preexisting mental health disorders often have the greatest difficulty adjusting to chronic respiratory disease. Most at risk are those with a major depressive or anxiety disorder, previous adjustment or personality disorder, alcohol or drug abuse, or history of psychosis.

Depressive symptoms are common in patients with moderate to severe COPD, with an approximate prevalence rate of 45% (247). The tendency for depressed patients to withdraw from social interactions increases feelings of isolation and depression for both the patient and their loved ones. Sexual activity is also limited by depression and physical restrictions. Subthreshold depression (clinically relevant depression that does not fit operational criteria) is seen in 25% of elderly patients with COPD (248). Both depression and anxiety in the elderly are significantly undertreated (247, 249). Even when appropriate treatment is recommended, many patients refuse anxiolytics or antidepressant medication because of fear of side effects, embarrassment, denial of illness, worries about addiction, cost concerns, or a frustration with taking too many medications (250).

Mild to moderate neuropsychologic impairments may exist as a result of depression as well as disordered gas exchange. These deficits contribute to difficulties in concentration, memory disturbances, and cognitive dysfunction (251), and may lead to difficulty solving common problems in daily living, missed office or clinic appointments, or failure to adhere to the medical and self-management plans (252). Oxygen supplementation should be considered in those patients with documented hypoxemia.

Assessment and Intervention

The initial patient assessment should include a psychosocial evaluation. The interview should allow adequate time for patients to openly express concerns about the psychosocial adjustment to their disease. Questions should cover perception of quality of life, ability to adjust to the disease, self-efficacy, motivation, adherence, and neuropsychologic impairment (e.g., memory, attention/concentration, problem-solving abilities). Common feelings and concerns that are expressed in this component of the evaluation include the following: guilt, anger, resentment, abandonment, fears, anxieties, helplessness, isolation, grief, pity, sadness, stress, poor sleep, poor marital relations, and failing health of the spouse caretaker (253). If possible, interviewing the significant caregiver (with the patient's consent) may help to explore issues related to dependency, interpersonal conflict, and intimacy. Screening questionnaires, such as the Hospital Anxiety and Depression Questionnaire or the Beck Depression Inventory, may aid in the recognition of significant anxiety and depression (254, 255). When a patient seems to be depressed, psychologic counseling should be considered.

Developing an adequate support system is a most important component of pulmonary rehabilitation (256). Patients with chronic respiratory disease will benefit from supportive counseling to address their concerns, either individually or in a group format. Treating depression may make a significant difference in the patient's quality of life (257). However, although 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 before the start of the program.

Patients should be taught to recognize symptoms of stress and be capable of stress-management techniques. Relaxation training can be accomplished through techniques such as muscle relaxation, imagery, or yoga. Relaxation tapes, supplemented through biofeedback, may be provided for home use. Relaxation training should be integrated into the patient's daily routine, for tackling dyspnea and controlling panic. Useful crisis management skills include active listening, calming exercises, anticipatory guidance regarding upcoming stressors, problem solving, and identifying resources and support systems.

The sensitive topic of sexuality is often of central importance to quality of life (258). A number of factors may determine how sexual functioning is affected by chronic illness: the patient/spouse relationship, degree of affection, communication, and the level of satisfaction with a partner. Although general information may be provided during patient education in a small-group format, specific questions and concerns are generally best addressed in a one-on-one or couples format. For those having significant interpersonal or family conflicts, referral to a clinical social worker, psychologist, or other counselor for family/relationship counseling is recommended.

Practice guidelines:

1. Screening for anxiety and depression should be part of the initial assessment.
2. Although mild or moderate levels of anxiety or depression related to the disease process may improve with pulmonary rehabilitation, patients with significant psychiatric disease should be referred for appropriate professional care.
3. Promotion of an adequate patient support system is encouraged.

SECTION 6: OUTCOMES ASSESSMENT

Introduction

Outcomes assessment in pulmonary rehabilitation may be evaluated from three different perspectives: those of the patient, the program, and society. This section will discuss patient-centered outcomes. Program audit and societal outcomes (health care utilization) are covered later in this document.

Patient-centered outcome assessment can range from unstructured clinical assessments to the use of specific, validated tests and instruments, such as a field test of exercise performance or an HRQL questionnaire. These are useful in assessing change among a group of individuals enrolled in a rehabilitation program. Although the utility of these structured assessments in the evaluation of the specific patient has not received much critical study, clinical experience seems to suggest they may also be useful in this setting. In addition, some of the measures used for outcome analysis may also be useful in the initial assessment of the patient. For example, a cardiopulmonary exercise test is useful to determine the mechanism of exercise intolerance, to generate an exercise prescription, to determine the need for oxygen supplementation, and to detect contraindications to a training program.

Patients are referred to pulmonary rehabilitation for several reasons: they do not feel their symptoms (dyspnea or fatigue) have sufficiently improved from medications alone, they are dissatisfied with their ability to perform activities of daily life, and/or they are dissatisfied with their quality of life. Thus, for pulmonary rehabilitation, the important patient-centered outcomes should reflect the following: (*1*) control of symptoms, (*2*) the ability to perform daily activities, (*3*) exercise performance, and (*4*) quality of life. The effect of pulmonary rehabilitation on these outcomes has been studied with numerous instruments, many of which are described on the website of the ATS: http://www.atsqol.org/qinst.asp. In addition, the AACVPR Guidelines for Pulmonary Rehabilitation Programs provides practical recommendations for using outcome measures (5).

Family members are affected by the patient's condition through role changes, impact on social activities, emotional stress, and financial burden. Little is known about the specific impact of pulmonary rehabilitation on family dynamics.

Like many treatment modalities, pulmonary rehabilitation has made significant progress in evaluating patient outcomes; however, understanding outcomes evaluations continues to require scrutiny. For example, programs should not only determine how much individual patients benefit from rehabilitation but should also identify what component(s) of the process led to these benefits. Meaningful conclusions regarding the benefits of the program require robust evaluative instruments. It is generally recommended that outcomes such as dyspnea, activity, and exercise capabilities should be evaluated, because these areas should improve with pulmonary rehabilitation.

Although an emerging body of literature suggests that pulmonary rehabilitation is beneficial in patients with disorders other than COPD (102, 103, 110, 259–268), this level of evidence has not reached the magnitude of that for COPD. Many of the outcome tools used in pulmonary rehabilitation have only been tested in COPD and require validation studies to establish their effectiveness. Generic questionnaires such as the Medical Outcomes Study Short Form 36 (SF-36) may be appropriate in these patients (269).

Patients with interstitial lung disease may achieve substantial gains in functional status by virtue of improving knowledge and skills for coping with symptoms, using energy conservation and pacing techniques, or using assistive equipment for activities of daily living. Persons with respiratory impairment related to advanced degenerative neuromuscular disease may have limited tolerance for traditional exercise training, but may achieve improved functional status through education, secretion clearance techniques, pacing and energy conservation techniques, use of adaptive assistive equipment, and NPPV. Thus, health care

providers must think broadly regarding ways in which pulmonary rehabilitation may benefit patients with non-COPD diagnoses. Age- and disease-appropriate outcomes assessment tools must be considered (270).

The outcome measures described in this section are most commonly used in pulmonary rehabilitation and many have been designed primarily for patients with COPD. Further research is needed to develop outcome assessment tools that are specific for respiratory diseases other than COPD. In the absence of disease-specific outcome tools, the assessment should focus on the symptoms and functional limitations of that population.

Symptom Evaluation

The two major symptoms in patients referred to pulmonary rehabilitation are dyspnea and fatigue (271–274). These symptoms are complex, with multiple mechanisms of action (275, 276), and comprehensive reviews are available elsewhere (76, 275, 277). By nature, symptoms are subjective and require self-reporting. In the pulmonary rehabilitation setting, dyspnea or fatigue can be assessed in two ways: (*1*) in "real time" or (*2*) through recall (278). Each approach may yield differing results.

Real-time evaluation of symptoms will only answer the question of how short of breath or fatigued the patient is at the moment of testing. The Borg scale (279) and the Visual Analog Scale (280) are most commonly used for this purpose, with either useful in assessing dyspnea or fatigue during exercise testing or training.

Recall of symptoms, such as dyspnea or fatigue, is usually accomplished through the use of questionnaires. Some questionnaires require patients to rate their overall dyspnea experience, whereas others ask about dyspnea related to activities. Although most have adequate psychometric properties, some were initially developed for research purposes and thus are not "user friendly" in the pulmonary rehabilitation setting. Technical issues that should be taken into account when selecting a questionnaire in the rehabilitation setting are as follows: length of time to complete/administer the questionnaire, administration requirements (can it be completed by the patient or does it require administration by another), complexity of scoring, cost of purchase, and whether written permission is required to use the questionnaire. Other considerations should be the context in which the symptom is measured, how the questions about symptoms are worded, and the timeframe over which the symptom is measured.

Cough and sputum production are other important symptoms in patients referred for pulmonary rehabilitation. Information about cough and sputum is usually included in subscales of selected questionnaires and addressed in educational sessions as appropriate to the population receiving rehabilitation. Questionnaires are now available that measure in detail the impact of cough on health status (281, 282), but their usefulness in pulmonary rehabilitation outcomes assessment is unclear.

Performance Evaluation

An important goal of rehabilitation is to improve the patient's ability to engage in activities of daily living. Because improvements in exercise capacity do not necessarily translate into increases in activities of daily living, assessment of functional performance is important. Assessment of performance can be accomplished by direct observation or by patient report. It is possible, for example, to observe patients performing activities and note the rate, speed, or efficiency with which an activity is performed. However, this is time consuming, difficult to standardize, and often impractical. Most pulmonary rehabilitation programs rely on patient self-reports to assess activity levels using both the patient's report on the intensity of dyspnea with activities and the degree to which a patient may perform activities in a real-life situation (283).

An emerging method of evaluating activities in the nonlaboratory setting is the use of activity monitors or motion detectors (284). Activity monitors can be used in the rehabilitation setting to provide an objective measure of patients' daily activity (285). Monitors range from simple, such as a pedometer, which evaluates the number of steps a patient takes, to more complex devices that measure movement in three planes, such as a triaxial accelerometer. These devices are generally less sensitive to arm activities than activities requiring lower extremity movement. Some patients may overestimate their activity levels when assessed with questionnaires as compared with directly with video or triaxial accelerometers (286). The role of activity monitors in clinical pulmonary rehabilitation assessment requires further study.

Exercise Capacity

Measurement of exercise capacity can be accomplished in several ways, including field tests, activity monitors, and cardiopulmonary exercise testing. Field tests have several advantages: they are simple to perform with little additional equipment, are conducted in a nonlaboratory setting, and are responsive to the pulmonary rehabilitation intervention. They are either self-paced, such as the 6-minute walk test (6MWD) (287–290), or externally paced tests, such as the incremental and endurance shuttle walk tests (291, 292). Both tests measure distance walked. The 6MWD has been shown to have the most variability in its administration (293–296), which can be minimized using published guidelines that standardize the performance of this test (290). Although these tests are good objective measures for programs, it is unclear how they translate into improvement in day-to-day activities.

Although cardiopulmonary exercise testing can be of considerable help in the initial assessment of exercise limitation and formulating the exercise prescription, it can also be useful in outcome assessment. Physiologic measurements provide valuable insight into mechanisms of exercise intolerance. Cardiopulmonary exercise testing can be incremental to maximal symptom limitation or at a constant work rate. Because of its complexity and costs, use of this methodology in outcome assessment is often restricted to specialized centers.

Quality-of-Life Measurements

Quality of life can be defined as "the gap between that which is desired in life and that which is achieved" (297). HRQL focuses on those areas of life that are affected by health status, and reflects the impact of respiratory disease (including comorbidities and treatment) on the ability to perform or enjoy activities of daily living (298). A particularly important factor that negatively affects HRQL in COPD is a high frequency of disease exacerbations (215, 299).

Individual components of quality of life include symptoms, functional status, mood, and social factors. Questionnaires can measure these components individually or with a composite score. The value of measuring each component separately is that each can be evaluated in more detail and its unique contribution can be identified. Both generic (300, 301) and respiratory-specific (302, 303) questionnaires are available for use in the pulmonary rehabilitation setting. There are well-validated generic and specific quality-of-life tools; these tools are available on the ATS website at http://www.atsqol.org/. The two most widely used respiratory-specific HRQL questionnaires are the Chronic Respiratory Disease Questionnaire (CRQ) (302) and the Saint George's Respiratory Questionnaire (SGRQ) (303). Although generic HRQL questionnaires usually are less discriminative and

show less ability to detect changes occurring spontaneously or with therapy, the SF-36 has demonstrated improvement after pulmonary rehabilitation (304). Both the CRQ and SGRQ have shown beneficial change after pulmonary rehabilitation (76, 305–307), and both have established thresholds for clinical significance (308, 309). However, as stated earlier, the value of these questionnaires in the individual patient has not been adequately addressed. The CRQ has historically been administered to the patient and research results have been based on operator-administered questionnaires. However, recently, self-administered versions of this questionnaire have been developed (310, 311).

Outcomes in Chronic Respiratory Failure

Chronic respiratory diseases, either obstructive or restrictive, can be complicated by chronic respiratory failure. When chronic respiratory failure occurs, there is an increase in the impact of the disease on the patient's daily life and well-being. A significant reduction in the ability to perform daily activities is one of the main consequences (312, 313). Consequently, quality-of-life measurements that reflect this effect on activities of daily living are important outcomes in this patient population.

Earlier noncontrolled studies assessed the efficacy of pulmonary rehabilitation in improving outcomes for very severe respiratory patients (314, 315). A more recent prospective, controlled, randomized study compared the effects of early comprehensive rehabilitation added to standard therapy versus progressive ambulation plus standard therapy in patients admitted to a respiratory intensive care unit (316). Pulmonary rehabilitation dramatically improved exercise tolerance and dyspnea in this subset of patients; however, quality of life was not measured. To date, no data are available on the effect of pulmonary rehabilitation on quality of life in patients with chronic respiratory failure. It is important, however, to describe the applicability of the different questionnaires to this subgroup of very severe respiratory patients.

Generic questionnaires explore many domains of health status, such as emotional functioning (e.g., mood changes), activities of daily living, ability to maintain social relationships, and performance of leisure activities (e.g., hobbies) (317). Because they are not specifically designed for respiratory disease or chronic respiratory failure, they contain few items of relevance to patients with chronic respiratory failure. As a consequence, generic instruments may not be sufficiently sensitive to detect clinically significant changes after treatment. Only the SF-36 has been used in patients on long-term ventilation (318–320). However, these studies demonstrate that, although the SF-36 is used in and broadly applicable to patients on mechanical ventilation, for many dimensions it is not sensitive enough to differentiate between patients on mechanical ventilation and other conditions.

The CRQ (302) and the SGRQ (303) have been used in severely impaired patients with COPD: the CRQ in those with severe COPD without chronic respiratory failure (321) and the SGRQ in those either on ventilators or with very severe disease (322–324). Because the above questionnaires were not specifically developed for patients with chronic respiratory failure, they may not be sufficiently sensitive to detect changes among these patients, thus limiting their discriminative and evaluative properties. Recently, the Maugeri Foundation Respiratory Failure Questionnaire (MRF28) was developed specifically for individuals with chronic respiratory failure (325). Limited data are available with the MRF28 (326, 327), and it has not been used in patients undergoing a rehabilitation program.

Practice guideline: Assessment of patient-centered outcomes, such as symptoms, performance in daily activities, exercise capacity, and HRQL, should be an integral component of pulmonary rehabilitation.

SECTION 7: PROGRAM ORGANIZATION

Introduction

Pulmonary rehabilitation is a service that complies with the general definition of rehabilitation and achieves its therapeutic aims through a permanent alteration of lifestyle. In practice, the details of program construction and setting will vary with different cultures and health care systems. There is no internationally recognized formula for the design of a program, because its structure may reflect the commissioning policy or health care needs of its country. There may therefore be significant differences in approach depending on whether an individual or population approach is taken. In some countries, the process is focused on the individual and the program is configured to provide optimum benefit for that patient. In other countries, especially where resources are limited, programs may be configured to provide maximum benefit for the population by using the minimum rehabilitation necessary to obtain a satisfactory result. Whatever strategy is adopted, the program should be structured to deliver individualized content in a manner that includes patient and family and results in a lifestyle change that can sustain the improvements for as long as possible. As with any health care process, the providers should be able to demonstrate their effectiveness through the audit of process and program outcomes. In addition, they will need to take account of staffing needs and health and safety issues. This section discusses such issues involved in program organization other than content and individual outcome assessment.

Patient Assessment and Selection

Pulmonary rehabilitation should be considered for all patients with chronic respiratory disease who have persistent symptoms, limited activity, and/or are unable to adjust to illness despite otherwise optimal medical management. Evidence on the selection of patients who might benefit is mostly derived from patients with COPD, with limited studies describing rehabilitation in other chronic lung diseases (5). The benefits are likely to be similar in patients with comparable disability from a spectrum of respiratory diseases. Gains can be achieved from pulmonary rehabilitation regardless of age, sex, lung function, or smoking status. Pulmonary rehabilitation is generally considered a necessary component before and after lung volume reduction surgery and lung transplantation (328). Peripheral muscle weakness is a positive predictor of successful outcome (329).

Nutritional status and peripheral muscle weakness may also influence the outcome of rehabilitation (186, 330, 331), and severe nutritional depletion and low FFM may be associated with an unsatisfactory response to rehabilitation. Because there are no clear data that define a threshold of disability for selection, a simple dyspnea rating, such as the Medical Research Council dyspnea scale, may be a general indicator for when rehabilitation can be beneficial (grades 3–5) (332). There may also be some specific indications for rehabilitation before transplantation or lung volume reduction surgery (333).

Exclusions. Exclusion criteria include significant orthopedic or neurologic problems that reduce mobility or cooperation with physical training. In addition, poorly controlled coexisting medical conditions, especially psychiatric or unstable cardiac disease, may limit participation, thereby making the patient an unsuitable candidate. Some centers disqualify current smokers; however, there is no evidence that short-term outcomes are different in smokers and nonsmokers.

Adherence. Patient motivation is required to achieve the fullest benefit from pulmonary rehabilitation. Data are limited on predictors of nonadherence. Predictors of reduced long-term adherence include social isolation and continued smoking (334).

Many programs report dropout rates on the order of 20%, often due to intercurrent illness or logistical difficulty. Long-term adherence with lifestyle changes, especially maintenance of regular exercise, is very important in pulmonary rehabilitation and probably contributes to the decline in benefits after 18 to 24 months. Maintenance of long-term adherence is discussed later in this section.

Hypoxemia. Patients who are hypoxemic at rest or with exercise should not be excluded from rehabilitation but should be provided with ambulatory oxygen during the exercise sessions. Oxygen supplementation in this setting should not only promote patient safety; it may also allow for increased levels of exercise training. In a research setting, providing supplemental oxygen to nonhypoxic patients with COPD during exercise training enhanced the improvement in exercise performance (19, 20). It remains to be determined whether this would be beneficial in clinical practice.

Timing. Rehabilitation is generally completed during a period of clinical stability rather than during a respiratory exacerbation. However, the institution of pulmonary rehabilitation during or immediately after an exacerbation has a rationale and has been demonstrated to have benefit (64, 335–337). The precise timing of the intervention after an exacerbation has yet to be established. This is an area of current research interest.

Program Setting

Principles of pulmonary rehabilitation apply regardless of location; consequently, it has been shown to be effective across various settings. Properly conducted pulmonary rehabilitation offers clinical benefit in all settings that have so far been studied; however, few clinical trials offer direct comparison among various settings.

Inpatient pulmonary rehabilitation may consist of a planned program to which a patient is directly admitted, or inpatient care provided during an admission for acute exacerbation. This clinical setting is better suited to patients with severe deconditioning and lack of support for home management or limited transportation to outpatient settings. Inpatient rehabilitation can provide similar benefits to outpatient settings (305). Potential disadvantages of inpatient pulmonary rehabilitation include the proportionally high cost and lack of coverage by insurance in some countries.

Outpatient pulmonary rehabilitation is the most widely available of settings and may be hospital or community based. Potential advantages include cost-effectiveness, a safe clinical environment, and availability of trained staff. The majority of studies describing the benefits of pulmonary rehabilitation are derived from hospital-based outpatient programs.

Home-based rehabilitation may offer the greatest convenience for the patient and may prolong its benefit (337–339). In severely disabled patients, home rehabilitation may not be as effective (306). Potential disadvantages of home-based rehabilitation include the possible lack of opportunity for group support, limited presence of a multidisciplinary team, variable availability of exercise equipment, lack of safe facilities, and cost of visits by health care professionals.

Program Structure and Staffing

Pulmonary rehabilitation is delivered by a multidisciplinary team whose structure varies according to patient population, program budget, reimbursement, as well as the availability of team members and resources. The team is headed by a medical director together with a program coordinator. In the United States, the AACVPR provides recommendations for programs through its Guidelines for Pulmonary Rehabilitation Programs (5). Staffing requirements vary by jurisdiction: 1:4 for the exercise classes and 1:8 for education in the United States, and 1:8 for exercise and 1:16 for education in the United Kingdom (332). Although pulmonary rehabilitation is safe, it is recommended that the staff have training in resuscitation techniques and that appropriate equipment and expertise is available on site.

Pulmonary rehabilitation begins with the patient assessment, followed by the formal pulmonary rehabilitation program, and then development of strategies to maintain the benefits through lifestyle changes. Although short-term benefits may be obtained from even brief 2-week inpatient programs, conventional rehabilitation programs are generally 8 to 12 weeks in duration, depending on individual patient characteristics and the continued response to therapy. Longer programs may have longer lasting effects.

Program Audit and Quality Control

Good results can be obtained from simple programs, but more sophisticated services can provide greater flexibility in physical training, research opportunities, and the ability to deal with the more complex patients.

Most patients who enter pulmonary rehabilitation will benefit from it, and the number needed to treat to obtain a clinically meaningful response is low. The common patient-centered outcomes of health status and physical performance should be recorded to quantify the performance of the program as a whole. Minimum datasets need to be agreed on nationally to allow some quality control and pooling of data to facilitate comparison of outcomes across centers. Examples of local benchmarking already exist (340).

Aside from the pooling of patient-centered outcomes, there are also some program organization evaluations that ensure quality control and continuous quality improvement. These include a record of program attendance, adherence to home exercise prescription, hospital admissions, clinic visits, and patient satisfaction surveys.

Long-term Strategies

The immediate aims of pulmonary rehabilitation are to reduce symptoms, improve physical functioning, and enhance HRQL. Its long-term aims are to maintain these benefits and see them translated into reduced health care resource utilization, especially through hospital admission prevention, reduced length of hospital stay, and improved self-management, limiting dependence on medical care.

The duration of benefit of pulmonary rehabilitation (concept of lifestyle change). Limited studies suggest that the benefits of pulmonary rehabilitation decline toward baseline after 6 to 12 months, but remain improved compared with control subjects after 1 year (341–346). HRQL benefits appear better preserved than exercise performance, sometimes being sustained 2 years after the intervention (242, 347, 348). In some studies, these benefits appear to be maintained in the absence of any specific maintenance therapy, suggesting that a change in lifestyle alters behavior.

Program structure and the effect of program duration. Pulmonary rehabilitation can be delivered in a variety of structured programs that may themselves have an influence on the degree or duration of long-term benefit. Short-duration inpatient programs may result in physical performance improvement within 2 weeks (349). Strict comparisons of dose–response or duration of benefit of different physical training regimes have not yet been made, and the rate of improvement in exercise performance and quality of life may differ (70). It is possible that improvements may continue to develop after the completion of a program, but observation of these effects has not yet been determined.

Maintaining the benefit of pulmonary rehabilitation. Strategies to maintain the benefits of rehabilitation include continuous rehabilitation, maintenance programs, and repeated courses. Continuing rehabilitation for a prolonged period only seems to have a small additional benefit (350), and one study identified minor gains in 6-minute walk performance and other measures of disability in patients who attended for 18 months compared with 3 months (351). More research in this area is needed. There have been other studies of specific maintenance interventions after a conventional course of rehabilitation but as yet there is no broad consensus as to their benefit. It is not clear what form maintenance therapy should take or how it should be applied. Monthly interventions and telephone support appear to show benefit while they are applied but their effect wears off rapidly with discontinuation (352). Repeating a course of rehabilitation does seem to have the ability to reproduce the short-term gain but does not result in long-term advantage (353).

Other methods of support (relatives, patient support groups, community schemes, etc.). There are a variety of approaches for supporting patients after pulmonary rehabilitation, including changing the attitude of caregivers, attendance at self-help support groups, or exercise sessions in community centers. There are not yet any substantive data to support the use of these activities, but they are worthy of consideration.

SECTION 8: HEALTH CARE UTILIZATION

Patients with chronic respiratory disease are heavy users of health care and social services resources worldwide. Although the major goals of pulmonary rehabilitation programs are to reduce levels of morbidity and to improve activity as well as participation in patients with chronic respiratory disease, their role in the management of these patients must also be validated by cost-effectiveness. Pulmonary rehabilitation's role in decreasing utilization of health care resources is an important potential benefit.

Pulmonary rehabilitation is an effective intervention in patients disabled by chronic respiratory disease; however, there are relatively few studies that evaluate its effect on health care utilization. An 18-session, 6-week outpatient pulmonary rehabilitation program decreased inpatient hospital days and decreased the number of home visits when compared with standard medical management (307). A comprehensive cost-effectiveness analysis of the addition of this multidisciplinary pulmonary rehabilitation program to standard care for patients with chronic disabling respiratory disease concluded that the program was cost-effective and produced cost per Quality-adjusted-life-years (QALY) ratios within the bounds considered to be cost-effective and therefore likely to result in financial benefits to the health care system (354).

Patients with COPD who receive an education intervention with supervision and support based on disease-specific self-management principles have decreased hospital admissions, decreased emergency department visits, and reduced number of unscheduled physician visits (220). This approach of care through self-management strategies is of interest because it does not require specialized resources and could be implemented within normal health care practice. In a before–after designed study, a community-based, 18-session, comprehensive pulmonary rehabilitation program was associated with an average reduction of total costs of $344 per person per year. This was associated with decreased health service utilization, reduced direct costs, and improved health status of patients with COPD, regardless of disease severity (355).

The California Pulmonary Rehabilitation Collaborative Group of 10 outpatient pulmonary rehabilitation programs (340) provides further evidence of the effectiveness of rehabilitation as practiced in a variety of settings with a heterogeneous group of patients with chronic lung disease. This study, which did not contain a control group, demonstrated considerable use of health care resources during the 3 months preceding rehabilitation, as evidenced by a mean of 2.6 hospital days, 0.4 urgent care visits, 4.4 physician visits, and 2.9 telephone calls. Over the 18 months of follow-up evaluation, patients reported fewer hospital days, visits, and telephone calls. Further comparisons of the costs of various approaches to pulmonary rehabilitation in combination with short-term and long-term outcomes are needed to allow for accurate assessments of cost-effectiveness, which should contribute to informed decisions made to reduce health care costs while making pulmonary rehabilitation more widely available.

SECTION 9: CONCLUSIONS AND FUTURE DIRECTIONS

In a relatively short period of time, pulmonary rehabilitation has become recognized as a cornerstone in the comprehensive management of patients with COPD. This is evident by its prominent position in statements such as the ATS/ERS Standards for the Diagnosis and Management for Patients with COPD (207) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document (206). The evidence for improvement in exercise endurance, dyspnea, functional capacity, and quality of life is stronger for rehabilitation than for almost any other therapy in COPD, and documentation of its favorable effect on health care utilization is increasing. The success of pulmonary rehabilitation stems from its favorable influence on systemic effects and comorbidities associated with chronic lung disease. Because these impairments are present to some extent in all chronic lung disease, pulmonary rehabilitation should be effective in diseases other than COPD.

The science and implementation of pulmonary rehabilitation need to develop along several lines in the next few years. First, pulmonary rehabilitation should be made available to all patients who need it. This will require the education of health care professionals at all levels of training as to the rationale, scope, and benefits of pulmonary rehabilitation, with a goal of incorporating it into the mainstream of medical practice. In addition, concerted efforts are needed to encourage health care delivery systems to provide this therapy and make it affordable. Recent studies that demonstrate that long-term benefits (including health care resource reductions) are attainable with relatively low-cost interventions should help with these efforts (220, 307, 340, 354).

Second, more research is needed to optimize the effectiveness of pulmonary rehabilitation, including more efficient ways of targeting it to the unique needs of the individual patient. These include, for instance, defining the optimal intensity and duration of exercise training and defining the effects of the nonexercise components of comprehensive pulmonary rehabilitation. Adjunctive strategies, such as hormonal therapy, supplemental oxygen administration to nonhypoxemic patients, and noninvasive ventilation, are being developed; their effectiveness must be established. The scientific rationale for pulmonary rehabilitation in respiratory diseases other than COPD is present; its effectiveness must be established through clinical trials.

Third, we need to develop ways to maintain the benefits of pulmonary rehabilitation, especially through improving long-term self-management and adherence to the exercise regimen in the home setting. Even if pulmonary rehabilitation is offered, a considerable number of patients choose not to participate (210, 305); little is known about the reasons for this choice. More information is needed on the reasons for and predictors of nonadherence and nonparticipation to develop effective strategies in this regard.

Finally, more concerted efforts are needed to evaluate the effect of pulmonary rehabilitation on survival, because it is entirely possible that it may favorably influence this outcome. Pulmonary rehabilitation improves dyspnea, exercise capacity, and quality of life, each of which are recognized predictors of mortality (356–359). A large prospective, controlled trial would be necessary to examine this possible effect.

These guidelines provide reasons for optimism. A considerable body of theoretical and practical knowledge has already been developed since the last statement, resulting in the establishment of pulmonary rehabilitation as a science. We look forward to refining its process, improving its efficiency, optimizing its benefits, and expanding its scope.

This statement was prepared by an *ad hoc* subcommittee of the Assembly on Nursing, Pulmonary Rehabilitation Section.

Members of the subcommittee are:
Linda Nici, M.D., Claudio Donner, M.D., Emiel Wouters, M.D., Ph.D., Richard Zuwallack, M.D. (co-chairs)
Nicolino Ambrosino, M.D.
Jean Bourbeau, M.D.
Mauro Carone, M.D.
Bartolome Celli, M.D.
Marielle Engelen, Ph.D.
Bonnie Fahy, R.N., M.S.N.
Chris Garvey, R.N.
Roger Goldstein, M.D.
Rik Gosselink, P.T., Ph.D
Suzanne Lareau, R.N.
Neil MacIntyre, M.D.
Francois Maltais, M.D.
Mike Morgan, M.D.
Denis O'Donnell, M.D.
Christian Prefault, M.D.
Jane Reardon, R.N., M.S.N.
Carolyn Rochester, M.D.
Annemie Schols, Ph.D.
Sally Singh, Ph.D.
Thierry Troosters, P.T., Ph.D.

Conflict of Interest Statement: N.A. received €500 in 2003 and €1,000 in 2004 for speaking at conferences sponsored by Simesa, €500 in 2003 and €1,200 in 2004 for speaking at conferences sponsored by AstraZeneca, €500 in 2004 for speaking at conferences sponsored by Boheringer Ingelheim; €500 in 2004 for speaking at conferences sponsored by Novartis, $2000 in 2005 for consultancies for Pfizer; his institution has received unrestricted educational grants by Vivisol and Boheringer/Pfizer, as well as research grants for participating in a multi-center clinical trial by Boheringer Ingelheim. J.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.F. received $1,000 from Boehringer/Pfizer for attending speaker training in 2005. C.G. received $1,500 in 2006 for speaking at a conferences sponsored by Boehringer Ingelheim and $500 in 2006 for speaking at a conference sponsored by Pfizer, and has received $700 in 2004, $1200 in 2005, and $700 in 2006 for consulting on patient education material from Krames Staywell. R.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.M. received honoraria for speaking at conferences sponsored by Boehringer Ingelheim, Pfizer and GlaxoSmithKline ($12,000 each year from 2004-2005). He also received honoraria for serving on an advisory board for Boehringer Ingelheim, GlaxoSmithKline, and Altana Pharma ($6,000 in 2004, $4,000 in 2005); he received research grants for participating in multicenter trials from Boehringer Ingelheim, GlaxoSmithKline, Altana Pharma, and Merck ($300,000 for 2004-2006); he has been reimbursed by AstraZeneca for attending one conference and has received unrestricted research grants by Boehringer Ingelheim and GlaxoSmithKline. M.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.M. served as a consultant to SensorMedics regarding PFT equipment. L.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.O. has served on the advisory boards of GlaxoSmithKline, Altana, Pfizer, and AstraZeneca, and received industry-sponsored grants from GlaxoSmithkline, Altana, Pfizer, and AstraZeneca. C.P. received a total of $15,000 as a speaker at conferences sponsored by GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, and has been reimbursed by Boehringer Ingelheim for attending several conferences in the same period. C.R. received $3,000 in 2005 for serving on an advisory board for Novartis Pharmaceuticals, Inc., and receives financial support for participating in, and conducting clinical trials on, COPD from Boehringer Ingelheim Pharmaceuticals Inc. and from GlaxoSmithKline Pharmaceuticals. S.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.R. received $1,500 in 2004–2005 for speaking at meetings sponsored by GlaxoSmithKline and $2,000 in 2005 for lecture and consultation fees by Boehringer Ingelheim. A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of the manuscript. T.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.W. received research grants between 2003 and 2005 from GlaxoSmithKline (€385,000), AstraZeneca (€146,000), Boehringer Ingelheim (€183,000), Centocor (€120,000), and Numico (€120,000). R.Z. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Solicited Reviewers: Andrew Ries, M.D., M.P.H.; Richard Casaburi, Ph.D., M.D.; and Barry Make, M.D.

References

1. Grone O, Garcia-Barbero M. Integrated care: a position paper of the WHO European office for integrated health care services. *Int J Integr Care* 2001;1:1–15.
2. American Thoracic Society. Pulmonary rehabilitation—1999. *Am J Respir Crit Care Med* 1999;159:1666–1682.
3. Donner CF, Muir JF. Selection criteria and programmes for pulmonary rehabilitation in COPD patients. Rehabilitation and Chronic Care Scientific Group of the European Respiratory Society. *Eur Respir J* 1997;10:744–757.
4. American College of Chest Physicians, American Association of Cardiovascular and Pulmonary Rehabilitation. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. *Chest* 1997;112:1363–1396.
5. ZuWallack RZ, Crouch R, editors. American Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for pulmonary rehabilitation programs, 3rd ed. Champaign, IL: Human Kinetics; 2004.
6. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:19–38.
7. Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med* 1994;149:930–934.
8. Parekh PI, Blumenthal JA, Babyak MA, Merrill K, Carney RM, Davis RD, Palmer SM. Psychiatric disorder and quality of life in patients awaiting lung transplantation. *Chest* 2003;124:1682–1688.
9. Borak J, Chodosowska E, Matuszewski A, Zielinski J. Emotional status does not alter exercise tolerance in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1998;12:370–373.
10. Weisman IM, Zeballos RJ. An integrative approach to cardiopulmonary exercise testing. In: Weisman IM, Zebellos RJ, editors. Clinical exercise testing. *Prog Respir Res* Basil, Switzerland: Karger; 2002;32:300–322.
11. Hyatt RE. Expiratory flow limitation. *J Appl Physiol* 1983;55:1–7.
12. Pride NB, Macklem PT. Lung mechanics in disease. In: Fishman AP, editor. Handbook of physiology. Bethesda, MD: Oxford University Press. American Physiological Society. pp. 659–692.
13. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation to exercise: the exercise tidal volume loop. *Chest* 1999;116:488–503.
14. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:770–777.
15. Aliverti A, Stevenson N, Dellaca RL, Lo MA, Pedotti A, Calverley PM. Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. *Thorax* 2004;59:210–216.
16. Diaz O, Villafranca C, Ghezzo H, Borzone G, Leiva A, Milic-Emil J, Lisboa C. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Respir J* 2000;16:269–275.

17. Somfay A, Porszasz J, Lee SM, Casaburi R. Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest* 2002;121:393–400.
18. O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation in advanced COPD. *Am J Resp Crit Care Med* 2001; 163:892–898.
19. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic COPD patients. *Am J Respir Crit Care Med* 2003;168:1034–1042.
20. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose–response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. *Eur Respir J* 2001;18:77–84.
21. Fujimoto K, Matsuzawa Y, Yamaguchi S, Koizumi T, Kubo K. Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia. *Chest* 2002;122:457–463.
22. Maltais F, Simon M, Jobin J, Desmeules M, Sullivan MJ, Belanger M, LeBlanc P. Effects of oxygen on lower limb blood flow and O2 uptake during exercise in COPD. *Med Sci Sports Exerc* 2001;33:916–922.
23. World Health Organization. Definition of chronic cor pulmonale. *Circulation* 1963;27:594–615.
24. Santos S, Peinado VI, Ramirez J, Melgosa T, Roca J, Rodriguez-Roisin R, Barbera JA. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 2002;19:632–638.
25. Voelkel NF, Tuder RM. Hypoxia-induced pulmonary vascular remodeling: a model for what human disease? *J Clin Invest* 2000;106:733–738.
26. Chetty KG, Brown SE, Light RW. Improved exercise tolerance of the polycythemic lung patient following phlebotomy. *Am J Med* 1983;74: 415–420.
27. Sietsema K. Cardiovascular limitations in chronic pulmonary disease. *Med Sci Sports Exerc* 2001;33:S656–S661.
28. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease: part one. *Am J Respir Crit Care Med* 1994;150: 833–852.
29. Butler J, Schrijen F, Henriquez A, Polu JM, Albert RK. Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;138:350–354.
30. Chabot F, Schrijen F, Poincelot F, Polu JM. Interpretation of high wedge pressure on exercise in patients with chronic obstructive pulmonary disease. *Cardiology* 2001;95:139–145.
31. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:9–18.
32. Puente-Maestu L, Sanz ML, Sanz P, Ruiz de Ona JM, Rodriguez-Hermosa JL, Whipp BJ. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *Eur Respir J* 2000;15:1026–1032.
33. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:1541–1551.
34. Maltais F, LeBlanc P, Jobin J. Intensity of training and physiological adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:555–561.
35. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151–1156.
36. American Thoracic Society/European Respiratory Society. Skeletal muscle dysfunction in chronic obstructive pulmonary disease: a statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999;159:S1–S40.
37. Bernard S, LeBlanc P, Whittom F, Carrier G, Jobin J, Belleau R, Maltais F. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:629–634.
38. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;153:976–980.
39. Franssen FM, Wouters EF, Baarends EM, Akkermans MA, Schols AM. Arm mechanical efficiency and arm exercise capacity are relatively preserved in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2002;34:1570–1576.
40. Gea JG, Pasto M, Carmona MA, Orozco-Levi M, Palomeque J, Broquetas J. Metabolic characteristics of the deltoid muscle in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2001;17:939–945.
41. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, LeBlanc P. 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* 1996;153:288–293.
42. Maltais F, Jobin J, Sullivan MJ, Bernard S, Whittom F, Killian KJ, Desmeules M, Belanger M, LeBlanc P. Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD. *J Appl Physiol* 1998;84:1573–1580.
43. Killian KJ, LeBlanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;146:935–940.
44. Jeffery MM, Kufel TJ, Pineda L. Quadriceps fatigue after cycle exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:447–453.
45. Saey D, Debigare R, LeBlanc P, Mador MJ, Cote CG, Jobin J, Maltais F. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with COPD. *Am J Respir Crit Care Med* 2003;168:425–430.
46. Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. *N Engl J Med* 1997;337:1799–1806.
47. Levine S, Gregory C, Nguyen T, Shrager J, Kaiser L, Rubinstein N, Dudley G. Bioenergetic adaptation of individual human diaphragmatic myofibers to severe COPD. *J Appl Physiol* 2002;92:1205–1213.
48. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med* 1991;325:917–923.
49. Orozco-Levi M, Gea J, Lloreta JL, Felez M, Minguella J, Serrano S, Broquetas JM. Subcellular adaptation of the human diaphragm in chronic obstructive pulmonary disease. *Eur Respir J* 1999;13:371–378.
50. Doucet M, Debigare R, Joanisse DR, Cote C, Leblanc P, Gregoire J, Deslauriers J, Vaillancourt R, Maltais F. Adaptation of the diaphragm and the vastus lateralis in mild-to-moderate COPD. *Eur Respir J* 2004;24:971–979.
51. Decramer M, Demedts M, Rochette F, Billiet L. Maximal transrespiratory pressures in obstructive lung disease. *Bull Eur Physiopathol Respir* 1980;16:479–490.
52. Rochester DF, Braun NM. Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985;132:42–47.
53. Perez T, Becquart LA, Stach B, Wallaert B, Tonnel AB. Inspiratory muscle strength and endurance in steroid-dependent asthma. *Am J Respir Crit Care Med* 1996;153:610–615.
54. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154:1310–1317.
55. Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;143:905–912.
56. Killian KJ, Jones NL. Respiratory muscles and dyspnea. *Clin Chest Med* 1988;9:237–248.
57. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;152:2021–2031.
58. Heijdra YF, Dekhuijzen PN, van Herwaarden CL, Folgering HT. Nocturnal saturation improves by target-flow inspiratory muscle training in patients with COPD. *Am J Respir Crit Care Med* 1996;153:260–265.
59. O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997;155:109–115.
60. Sheel AW, Derchak PA, Pegelow DF, Dempsey JA. Threshold effects of respiratory muscle work on limb vascular resistance. *Am J Physiol Heart Circ Physiol* 2002;282:H1732–H1738.
61. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez De Suso JM, Moreno A, Barbera JA, Nadal J, de Jover L, Rodriguez-Roisin R, *et al.* Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159: 1726–1734.
62. Bernard S, Whittom F, LeBlanc P, Jobin J, Belleau R, Berube C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159: 896–900.
63. Maltais F, LeBlanc P, Simard C, Jobin J, Berube C, Bruneau J, Carrier L, Belleau R. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154:442–447.

64. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality: a systematic review. *Respir Res* 2005;6:54.
65. Emery CF, Leatherman NE, Burker EJ, MacIntyre NR. Psychological outcomes of a pulmonary rehabilitation program. *Chest* 1991;100:613–617.
66. Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. *Health Psychol* 1998;17:232–240.
67. O'Donnell DE, McGuire M, Samis L, Webb KA. The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. *Am J Respir Crit Care Med* 1995;152:2005–2013.
68. Whittom F, Jobin J, Simard PM, LeBlanc P, Simard C, Bernard S, Belleau R, Maltais F. Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1998;30:1467–1474.
69. American Thoracic Society/American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.
70. Green RH, Singh SJ, Williams J, Morgan MD. A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax* 2001;56:143–145.
71. Plankeel JF, McMullen B, MacIntyre NR. Exercise outcomes after pulmonary rehabilitation depend on the initial mechanisms of exercise limitation among non-oxygen-dependent COPD patients. *Chest* 2005;127:110–116.
72. Rossi G, Florini F, Romagnoli M, Bellatone T, Lucic S, Lugli D, Clini E. Length and clinical effectiveness of pulmonary rehabilitation in outpatients with chronic airway obstruction. *Chest* 2005;127:105–109.
73. Fuchs-Climent D, Le Gallais D, Varray A, Desplan J, Cadopi M, Prefaut C. Quality of life and exercise tolerance in chronic obstructive pulmonary disease: effects of a short and intensive inpatient rehabilitation program. *Am J Phys Med Rehabil* 1999;78:330–335.
74. Salman GF, Mosier MC, Beasley BW, Calkins DR. Rehabilitation for patients with chronic obstructive pulmonary disease. *J Gen Intern Med* 2003;18:213–221.
75. World Health Organization. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Geneva, Switzerland: World Health Organization; 2003.
76. Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, Goldstein RS. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002;3:CD003793.
77. Ringbaek TJ, Broendum E, Hemmingsen L, Lybeck K, Nielsen D, Andersen C, Lange P. Rehabilitation of patients with chronic obstructive pulmonary disease: exercise twice a week is not sufficient! *Respir Med* 2000;94:150–154.
78. Puente-Maestu L, Sanz ML, Sanz P, Cubillo JM, Mayol J, Casaburi R. Comparison of effects of supervised versus self-monitored training programs in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2000;15:517–525.
79. Vogiatzis I, Nanas S, Roussos C. Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J* 2002;20:12–19.
80. Engstrom CP, Persson LO, Larsson S, Sullivan M. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: a randomized controlled study. *Scand J Rehabil Med* 1999;31:207–213.
81. Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *Eur Respir J* 1996;9:2590–2596.
82. Normandin EA, McCusker C, Connors M, Vale F, Gerardi D, ZuWallack RL. An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. *Chest* 2002;121:1085–1091.
83. Vallet G, Ahmaidi S, Serres I, Fabre C, Bourgouin D, Desplan J, Varray A, Prefaut C. Comparison of two training programmes in chronic airway limitation patients: standardized versus individualized protocols. *Eur Respir J* 1997;10:114–122.
84. Punzal PA, Ries AL, Kaplan RW, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. *Chest* 1991;100:618–623.
85. Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. *Chest* 1996;109:1169–1175.
86. Chida M, Inase N, Ichioka M, Miyazato I, Marumo F. Ratings of perceived exertion in chronic obstructive pulmonary disease: a possible indicator for exercise training in patients with this disease. *Eur J Appl Physiol Occup Physiol* 1991;62:390–393.
87. Mahler DA, Ward J, Mejia-Alfaro R. Stability of dyspnea ratings after exercise training in patients with COPD. *Med Sci Sports Exerc* 2003;35:1083–1087.
88. Lake FR, Henderson K, Briffa T, Openshaw J, Musk AW. Upper-limb and lower-limb exercise training in patients with chronic airflow obstruction. *Chest* 1990;97:1077–1082.
89. Couser JI Jr, Martinez FJ, Celli BR. Pulmonary rehabilitation that includes arm exercise reduces metabolic and ventilatory requirements for simple arm elevation. *Chest* 1993;103:37–41.
90. Epstein SK, Celli BR, Martinez FJ, Couser JI, Roa J, Pollock M, Benditt JO. Arm training reduces the VO2 and VE cost of unsupported arm exercise and elevation in chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 1997;17:171–177.
91. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:1541–1551.
92. O'Donnell DE, McGuire M, Samis L, Webb KA. General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *Am J Respir Crit Care Med* 1998;157:1489–1497.
93. American College of Sports Medicine Position Stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc* 1998;30:992–1008.
94. Coppoolse R, Schols AM, Baarends EM, Mostert R, Akkermans MA, Janssen PP, Wouters EF. Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J* 1999;14:258–263.
95. Gosselink R, Troosters T, Decramer M. Effects of exercise training in COPD patients: interval versus endurance training. *Eur Respir J* 1998;12:2S.
96. Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. *Thorax* 1992;47:70–77.
97. Bernard S, Whittom F, LeBlanc P, Jobin J, Belleau R, Berube C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:896–901.
98. Spruit MA, Gosselink R, Troosters T, De Paepe C, Decramer M. Resistance versus endurance training in patients with COPD and skeletal muscle weakness. *Eur Respir J* 2002;19:1072–1078.
99. Ortega F, Toral J, Cejudo P, Villagomez R, Sanchez H, Castillo J, Montemayor T. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:669–674.
100. Clark CJ, Cochrane LM, Mackay E, Paton B. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. *Eur Respir J* 2000;15:92–97.
101. O'Shea SD, Taylor NF, Paratz J. Peripheral muscle strength training in COPD: a systematic review. *Chest* 2004;126:903–914.
102. Crapo RO, Casaburi R, Coates AL, Enright PL, Hawkinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, *et al.* Guidelines for methacholine and exercise challenge. Official Statement of the American Thoracic Society. *Am J Respir Crit Care Med* 2000;161:309–329.
103. Moorcroft AJ, Dodd ME, Webb AK. Exercise limitations and training for patients with cystic fibrosis. *Disabil Rehabil* 1998;20:247–253.
104. Gulmans VAM, de Meer K, Brackel HJL, Faber JAJ, Berger R, Helders PJM. Outpatient exercise training in children with cystic fibrosis: physiological effects, perceived competence and acceptability. *Pediatr Pulmonol* 1999;28:39–46.
105. Heijerman HGM. Chronic obstructive lung disease and respiratory muscle function: the role of nutrition and exercise training in cystic fibrosis. *Respir Med* 1993;87:49–51.
106. Orenstein DM, Noyes BE. Cystic fibrosis: In: Casaburi R, Petty T, editors. Principles and practice of pulmonary rehabilitation. Philadelphia: WB Saunders; 1993. pp. 439–458.
107. Murphy S. Cystic fibrosis in adults: diagnosis and management. *Clin Chest Med* 1987;8:695–710.
108. Boas SR. Exercise recommendations for individuals with cystic fibrosis. *Sports Med* 1997;1:17–37.
109. Newall C, Stockley RA, Hill SL. Exercise training and inspiratory muscle training in patients with bronchiectasis. *Thorax* 2005;60:943–948.
110. Bach JR. Pulmonary rehabilitation in neuromuscular disorders. *Neurology* 1993;14:515–529.

111. Casaburi R, Kukafka D, Cooper DB, Kesten S. Improvement in exercise endurance with the combination of tiotropium and rehabilitative exercise training in COPD patients [abstract]. *Am J Respir Crit Care Med* 2004;169:A756.
112. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153: 967–975.
113. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1557–1565.
114. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160: 542–549.
115. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in COPD. *Eur Respir J* 2004; 24:86–94.
116. Gandevia SC. The perception of motor commands or effort during muscular paralysis. *Brain* 1982;105:151–159.
117. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;127:809–817.
118. Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax* 2000;55:539–543.
119. Rooyackers JM, Dekhuijzen PN, van Herwaarden CL, Folgering HT. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur Respir J* 1997;10:1278–1284.
120. Wadell K, Henriksson-Larsen K, Lundgren R. Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia. *J Rehabil Med* 2001;33: 200–205.
121. McDonald CF, Blyth CM, Lazarus MD, Marschner I, Barter CE. Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. *Am J Respir Crit Care Med* 1995;152:1616–1619.
122. Jolly EC, Di B. V, Aguirre L, Luna CM, Berensztein S, Gene RJ. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. *Chest* 2001;120:437–443.
123. Ambrosino N, Strambi S. New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J* 2004;24:313–322.
124. O'Donnell DE, Sanii R, Giesbrecht G, Younes M. Effect of continuous positive airway pressure on respiratory sensation in patients with chronic obstructive pulmonary disease during submaximal exercise. *Am Rev Respir Dis* 1988;138:1185–1191.
125. O'Donnell DE, Sanii R, Younes M. Improvement in exercise endurance in patients with chronic airflow limitation using continuous positive airway pressure. *Am Rev Respir Dis* 1988;138:1510–1514.
126. Petrof BJ, Calderini E, Gottfried SB. Effect of CPAP on respiratory effort and dyspnea during exercise in severe COPD. *J Appl Physiol* 1990;69:179–188.
127. Keilty SE, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. *Thorax* 1994; 49:990–994.
128. Maltais F, Reissmann H, Gottfried SB. Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction. *Am J Respir Crit Care Med* 1995;151:1027–1033.
129. Polkey MI, Kyroussis D, Mills GH, Hamnegard CH, Keilty SE, Green M, Moxham J. Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD. *Am J Respir Crit Care Med* 1996;154:1146–1150.
130. Hawkins P, Johnson LC, Nikoletou D, Hamnegard CH, Sherwood R, Polkey MI, Moxham J. Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. *Thorax* 2002;57:853–859.
131. Bianchi L, Foglio K, Porta R, Baiardi R, Vitacca M, Ambrosino N. Lack of additional effect of adjunct of assisted ventilation to pulmonary rehabilitation in mild COPD patients. *Respir Med* 2002;96:359–367.
132. Johnson JE, Gavin DJ, Adams-Dramiga S. Effect of training with Heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. *Chest* 2002;122:464–472.
133. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:1335–1341.
134. Larson JL, Kim MJ, Sharp JT, Larson DA. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;138:689–696.
135. Lisboa C, Villafranca C, Leiva A, Cruz E, Pertuze J, Borzone G. Inspiratory muscle training in chronic airflow limitation: effect on exercise performance. *Eur Respir J* 1997;10:537–542.
136. Dekhuijzen PN, Folgering HT, van Herwaarden CL. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. *Chest* 1991;99:128–133.
137. Wanke T, Formanek D, Lahrmann H, Brath H, Wild M, Wagner C, Zwick H. Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. *Eur Respir J* 1994;7:2205–2211.
138. Lotters F, Van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J* 2002;20:570–576.
139. Belman MJ, Shadmehr R. Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease. *J Appl Physiol* 1988;65: 2726–2735.
140. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. *J Appl Physiol* 1982;52: 768–772.
141. Gosselink R, Wagenaar RC, Decramer M. Reliability of a commercially available threshold loading device in healthy subjects and in patients with chronic obstructive pulmonary disease. *Thorax* 1996;51:601–605.
142. Leith DE, Bradley M. Ventilatory muscle strength and endurance training. *J Appl Physiol* 1976;41:508–516.
143. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease: impact on exercise capacity, dyspnea, and quality of life. *Am J Respir Crit Care Med* 2000;162:1709–1714.
144. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol Occup Physiol* 1992;64:145–152.
145. Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clark CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2002;57:333–337.
146. Bourjeily-Habr G, Rochester C, Palermo F, Snyder P, Mohsenin V. Randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. *Thorax* 2002;57:1045–1049.
147. Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest* 2003;124:292–296.
148. Engelen MPKJ, Schols AMWJ, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in outpatients with COPD. *Eur Respir J* 1994;7:1793–1797.
149. De Benedetto F, Del Ponte A, Marinari S, Spacone A. In COPD patients, body weight excess can mask lean tissue depletion: a simple method of estimation. *Monaldi Arch Chest Dis* 2000;55:273–278.
150. Openbrier DR, Irwin MM, Rogers RM, Gottlieb GP, Dauber JH, Van Thiel DH, Pennock BE. Nutritional status and lung function in patients with emphysema and chronic bronchitis. *Chest* 1983;83:17–22.
151. Braun SR, Keim NL, Dixon RM, Clagnaz P, Anderegg A, Shrago ES. The prevalence and determinants of nutritional changes in chronic obstructive pulmonary disease. *Chest* 1984;86:558–563.
152. Fiaccadori E, Del Canale S, Coffrini E, Vitali P, Antonucci C, Cacciani G, Mazzola I, Guariglia A. Hypercapnic-hypoxemic chronic obstructive pulmonary disease (COPD): influence of severity of COPD on nutritional status. *Am J Clin Nutr* 1988;48:680–685.
153. Schols AMWJ, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151–1156.
154. Baarends EM, Schols AM, Mostert R, Wouters EF. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2807–2813.
155. Schols AMWJ, Fredrix EW, Soeters PB, Westerterp KR, Wouters EFM. Resting energy expenditure in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1991;5:983–987.
156. Engelen MPKJ, Schols AMWJ, Heidendal GAK, Wouters EFM. 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* 1998;68:1298–1303.
157. Hughes RL, Katz H, Sahgal V, Campbell JA, Hartz R, Shields TW. Fiber size and energy metabolites in five separate muscles from patients with chronic obstructive lung diseases. *Respiration (Herrlisheim)* 1983;44: 321–328.
158. Gosker HR, Engelen MP, van Mameren H, van Dijk PJ, van der Vusse GJ, Wouters EF, Schols AM. Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2002;76:113–119.
159. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. *Am J Clin Nutr* 1990;52:953–959.
160. Schols AM, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151–1156.
161. Steiner MC, Barton RL, Singh SJ, Morgan MD. Bedside methods versus dual energy X-ray absorptiometry for body composition measurement in COPD. *Eur Respir J* 2002;19:626–631.
162. Engelen MPKJ, Schols AMWJ, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in outpatients with COPD. *Eur Respir J* 1994;7:1793–1797.
163. Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000;94:859–867.
164. Baarends EM, Schols AM, Mostert R, Wouters EF. Peak exercise response in relation to tissue depletion in patients with chronic obstructive lung disease. *Eur Respir J* 1997;10:2807–2813.
165. Kobayashi A, Yoneda T, Yoshikawa M, Ikuno M, Takenaka H, Fukuoka A, *et al.* The relation of fat-free mass to maximum exercise performance in patients with chronic obstructive pulmonary disease. *Lung* 2000;178:119–127.
166. Engelen MP, Deutz NE, Wouters EF, Schols AM. Enhanced levels of whole-body protein turnover in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:1488–1492.
167. Nishimura Y, Tsutsumi M, Nakata H, Tsunenari T, Maeda H, Yokoyama M. Relationship between respiratory muscle strength and lean body mass in men with COPD. *Chest* 1995;107:1232–1236.
168. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. 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* 1995;152:1268–1274.
169. Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2000;20:353–360.
170. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;154:1310–1317.
171. Shoup R, Dalsky G, Warner S, Davies M, Connors M, Khan M, *et al.* Body composition and health-related quality of life in patients with obstructive airways disease. *Eur Respir J* 1997;10:1576–1580.
172. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791–1797.
173. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. *Am Rev Respir Dis* 1989;139:1435–1438.
174. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1856–1861.
175. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. *Eur Respir J* 2002;20:539–544.
176. Marquis K, Debigare R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, *et al.* 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* 2002;166:809–813.
177. Schols AM, Buurman WA. Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51:819–824.
178. Nguyen LT, Bedu M, Caillaud D, Beaufrere B, Beaujon G, Vasson M, *et al.* Increased resting energy expenditure is related to plasma TNF-alpha concentration in stable COPD patients. *Clin Nutr* 1999;18:269–274.
179. Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FC, Wouters EF. 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* 1998;52:396–401.
180. Steiner MC, Barton RL, Singh SJ, Morgan MD. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* 2003;58:745–751.
181. Efthimiou J, Fleming J, Gomes C, Spiro SG. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;137:1075–1082.
182. Whittaker JS, Ryan CF, Buckley PA, Road JD. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *Am Rev Respir Dis* 1990;142: 283–288.
183. Rogers RM, Donahoe M, Costantino J. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease: a randomized control study. *Am Rev Respir Dis* 1992;146:1511–1517.
184. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. *Chest* 2000;117:672–678.
185. Goris AH, Vermeeren MA, Wouters EF, Schols AM, Westerterp KR. Energy balance in depleted ambulatory patients with chronic obstructive pulmonary disease: the effect of physical activity and oral nutritional supplementation. *Br J Nutr* 2003;89:725–731.
186. Creutzberg EC, Schols AM, Weling Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:745–752.
187. Vermeeren MA, Wouters EF, Nelissen LH, van Lier A, Hofman Z, Schols AM. Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2001;73:295–301.
188. Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 2003;19: 120–127.
189. Franssen FM, Broekhuizen R, Janssen PP, Wouters EF, Schols AM. Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. *Chest* 2004; 125:2021–2028.
190. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Berube C, *et al.* Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:896–901.
191. Meredith CN, Frontera WR, O'Reilly KP, Evans WJ. Body composition in elderly men: effect of dietary modification during strength training. *J Am Geriatr Soc* 1992;40:155–162.
192. Yeh SS, DeGuzman B, Kramer T. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest* 2002;122:421–428.
193. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. 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* 1995;152:1268–1274.
194. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, *et al.* Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:870–878.
195. Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting JW. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease: a prospective, randomized, controlled study. *Am J Respir Crit Care Med* 1997;156:1800–1806.
196. Weisberg J, Wanger J, Olson J, Streit B, Fogarty C, Martin T, *et al.* Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. *Chest* 2002;121:1070–1078.
197. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci* 2001; 321:249–279.
198. Fontaine KR, Barofsky I. Obesity and health-related quality of life. *Obes Rev* 2001;2:173–182.
199. Larsson UE, Mattsson E. Perceived disability and observed functional limitations in obese women. *Int J Obes Rel Metab Disord* 2001;259: 1705–1712.
200. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. *Arch Intern Med* 1999;159:837–843.

201. Mohsenin V, Gee JBL. Effect of obesity on the respiratory system and pathophysiology of sleep apnea. *Curr Pulm* 1993;14:179–197.
202. Strollo PJ, Rogers RM. Obstructive sleep apnea. *N Engl J Med* 1996; 334:99–104.
203. Whittaker LA, Brodeur LE, Rochester CL. Functional outcome of inpatient pulmonary rehabilitation for patients with morbid obesity [abstract]. *Am J Respir Crit Care Med* 2000;161:A495
204. Guernelli J, Wainapel SF, Pack S, Miranda Lama E. Morbidly obese patients with pulmonary disease: a retrospective study of four cases. *Am J Phys Med Rehabil* 1999;78:60–65.
205. Ravens-Sieberer U, Redegeld ZM, Bullinger M. Quality of life after inpatient rehabilitation in children with obesity. *Int J Obes Rel Metab Disord* 2001;25:S63–S65.
206. Global Initiative for Chronic Obstructive Lung Disease. Global Initiative for Chronic Obstructive Pulmonary Disease workshop report: updated 2003. Available from: http://www.goldcopd.com (accessed July 2003).
207. American Thoracic Society/European Respiratory Society. Standards for the diagnosis and management of patients with COPD. Available from: http://www.thoracic.org/copd (accessed 2004).
208. Lareau SC, Insel KC. Patient and family education. In: Hodgkin JR, Celli BR, Connors GL. Pulmonary rehabilitation, 3rd ed. St. Louis: Elsevier; 2000.
209. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *JAMA* 2002;288:2469–2475.
210. Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. *Patient Educ Couns* 2004;53:271–277.
211. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev* 1977;84:191–215.
212. National Institute for Health and Clinical Excellence Guideline No 12. Chronic obstructive pulmonary disease. *Thorax* 2004;59:131.
213. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–852.
214. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, Bouillon R, Decramer M. Muscle force during an acute exacerbation in hospitalized patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003;59:741–742.
215. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jefferies DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1418–1422.
216. Andersson F, Borg S, Jansson SA, Jonsson AC, Ericsson A, Prutz C, *et al.* The costs of exacerbations in chronic obstructive pulmonary disease. *Respir Med* 2002;96:700–708.
217. Price MJ, Hurrell C, Efthimiou J, Medley HV. Health care costs of treating exacerbations of COPD. *Eur Respir J* 1999;14:380s.
218. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, Kussin P, Bellamy P, Goldman L, Knaus WA. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;154:959–967.
219. Wilkinson T, Donaldson G, Hurst J, Seemungal T, Wedzicha J. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;169:1298–1303.
220. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, Renzi P, Nault D, Borycki E, Schwartzman K, *et al.*; 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 Intern Med* 2003;163:585–591.
221. Hefner JE, Fahy B, Hilling L, Barbieri C. Attitudes regarding advance directives among patients in pulmonary rehabilitation. *Am J Respir Crit Care Med* 1996;154:1735–1740.
222. Heffner JE. Role of pulmonary rehabilitation in palliative care. *Respir Care* 2000;45:1371–1375.
223. Gosselink R. Controlled breathing and dyspnea in patients with chronic obstructive pulmonary disease. *J Rehabil Res Dev* 2003;40:25–34.
224. Bianchi R, Gigliotti F, Romagnoli I, Lanini B, Castellani C, Grazzini M, Scano G. Chest wall kinematics and breathlessness during pursed-lip breathing in patients with COPD. *Chest* 2004;125:459–465.
225. Gosselink R, Wagenaar H, Rijswijk A, Sargeant J, Decramer ML. Diaphragmatic breathing reduces efficiency of breathing in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:1136–1142.
226. Vitacca M, Clini E, Bianchi L, Ambrosino N. Acute effects of deep diaphragmatic breathing in COPD patients with chronic respiratory insufficiency. *Eur Respir J* 1998;11:408–415.
227. Sharp JT, Druz WS, Moisan T, Foster J, Machnach W. Postural relief of dyspnea in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1980;122:201–211.
228. Solway S, Brooks D, Lau L, Goldstein R. The short-term effect of a rollator on functional exercise capacity among individuals with severe COPD. *Chest* 2002;122:56–65.
229. Probst VS, Troosters T, Coosemans I, Spruit MA, Pitta FO, Decramer M, Gosselink R. Mechanisms of improvement in exercise capacity using a rollator in patients with COPD. Chest 2004126:1102–1107.
230. Lareau S, Larson JL. Ineffective breathing pattern related to airflow limitation. *Nursing Clin North Am* 1987;22:179–191.
231. Jones AP, Rowe BH. Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis. *Cochrane Database Syst Rev* 2000;2:CD000045.
232. Bellone A, Spagnolatti L, Massobrio M, Bellei E, Vinciguerra R, Barbieri A. Short-term effects of expiration under positive pressure in patients with acute exacerbation of chronic obstructive pulmonary disease and mild acidosis requiring non-invasive positive pressure ventilation. *Intensive Care Med* 2002;28:581–585.
233. van der Shans C, Prasad A, Main C. Chest physiotherapy compared to no chest physiotherapy in cystic fibrosis. *Cochrane Database Syst Rev* 2000;2:CD001401.
234. Monninkhof E, van der Valk P, van der Palen J, van Herwaarden C, Zielhuis G. Effects of a comprehensive self-management programme in patients with chronic obstructive lung disease. *Eur Respir J* 2003; 22:815–820.
235. World Health Organization. Adherence to long-term therapies: evidence for action. *Annex* 2003;1:143.
236. McAuley E, Lox C, Duncan TE. Long-term maintenance of exercise, self-efficacy, and physiological change in older adults. *J Gerontol Psych Sci* 1993;48:218–224.
237. Brassington GS, Atienza AA, Perczek RE, DiLorenzo TN, King AC. Intervention-related cognitive versus social mediators of exercise adherence in the elderly. *Am J Prev Med* 2002;23:80–86.
238. Jette AM, Rooks D, Lachman M, Lin TH, Levenson C, Heislen D, Giorgetti MM, Harris BA. Home-based resistance training: predictors of participation and adherence. *Gerontologist* 1998;38:412–421.
239. Rhodes RE, Martin AD, Tawnton JE, Rhodes EC, Donnelly M, Elliot J. Factors associated with exercise adherence among older adults: an individual perpective. *Sports Med* 1999;28:397–411.
240. Nault D, Dagenais J, Perreault V, Pépin J, Labrecque S, Séguin M, *et al.* Qualitative evaluation of a disease specific self-management program "Living Well with COPD." *Eur Respir J* 2000;16:317S.
241. Brooks D, Krip B, Mangovski-Alzamora S, Goldstein RS. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. *Eur Respir J* 2002;20:20–29.
242. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med* 2000;109:207–212.
243. Singer HK, Ruchinskas RA, Riley KC. The psychological impact of end-stage lung disease. *Chest* 2001;120:1246–1252.
244. Dowson CA, Cuijer RG, Mulder RT. Anxiety and self management behavior in chronic pulmonary disease: what has been learned? *Chron Respir Dis* 2004;1:213–220.
245. Heim E, Blaser A, Waidelich E. Dyspnea: psychophysiologic relationships. *Psychosom Med* 1972;34:405–423.
246. McCathie HC, Spence SH, Tate RL. Adjustment to chronic obstructive pulmonary disease: the importance of psychological factors. *Eur Respir J* 2002;19:47–53.
247. Mills TL. Comorbid depressive symptomatology: isolating the effects of chronic medical conditions on self-reported depressive symptoms among community-dwelling older adults. *Soc Sci Med* 2001;53:569–578.
248. Yohannes AM, Baldwin RC, Connolly MJ. Prevalence of sub-threshold depression in elderly patients with chronic obstructive pulmonary disease. *Int J Geriatr Psychiatry* 2003;18:412–416.
249. Lacasse Y, Rousseau L, Maltais F. Prevalence of depressive symptoms and depression in patients with severe oxygen-dependent chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2001;21:80–86.
250. Yohannes AM, Baldwin RC, Connolly MJ. Mood disorders in elderly patients with Chronic Obstructive Pulmonary Disease. *Rev Clin Gerontol* 2000;10:193–202.
251. Emery CF, Hauck ER, MacIntyre NR, Leatherman NE. Psychological functioning among middle-aged and older adult pulmonary patients in exercise rehabilitation. *Phys Occup Ther Geriatr* 1994;12:13–26.
252. Emery CF, Schein RL, Hauck ER, MacIntyre NR. Psychological and cognitive outcomes of a randomized trial of exercise among patients

with chronic obstructive pulmonary disease. *Health Psychol* 1998;17: 232–240.
253. Farkas SW. Impact of chronic illness on the patient's spouse. *Health Soc Work* 1980;5:39–46.
254. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361–370.
255. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–571.
256. Emery CF. Psychosocial considerations among pulmonary patients. In: Hodgkin JE, Connors GL, Bell CW, editors. Pulmonary rehabilitation: guidelines to success, 2nd ed. Philadelphia: Lippincott; 1993. pp. 279–292.
257. Kim HF, Kunik ME, Molinari VA, Hillman SL, Lalani S, Orengo CA, Petersen NJ, Nahas Z, Goodnight-White S. Functional impairment in COPD patients: the impact of anxiety and depression. *Psychosomatics* 2000;41:465–471.
258. Stockdale-Woolley R. Sex and COPD. East Hartford, CT: American Lung Association of Connecticut; 2002.
259. McKone EF, Bary SC, Fitzgerald MX, Gallagher CG. The role of supplemental oxygen during submaximal exercise in patients with cystic fibrosis. *Eur Respir J* 2002;20:134–142.
260. Emter M, Herala M, Stalenheim G. High-intensity physical training in adults with asthma: a 10-week rehabilitation program. *Chest* 1996;109: 323–330.
261. Cochrane LM, Clark CJ. Benefits and problems of a physical training program for asthmatic patients. *Thorax* 1990;45:345–351.
262. Cambach W, Wagenaar RC, Koelman TW, Ton van Keimpema AR, Kemper HC. The long-term effects of pulmonary rehabilitation in patients with asthma and chronic obstructive pulmonary disease: a research synthesis. *Arch Phys Med Rehabil* 1999;80:103–111.
263. Emter M, Finne M, Stalenheim G. High-intensity physical training in adults with asthma. A comparison between training on land and in water. *Scand J Rehabil Med* 1998;30:201–209.
264. Bradley J, Moran F, Greenstone M. Physical training for bronchiectasis. *Cochrane Database Syst Rev* 2002;3:CD002166.
265. Foster S, Thomas HM. Pulmonary rehabilitation in lung disease other than chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990; 141:601–604.
266. Novitch RS, Thomas HM. Pulmonary rehabilitation in chronic pulmonary interstitial disease. In: Fishman AP, editor. Pulmonary rehabilitation: lung biology in health and disease. Vol. 91. New York: Marcel Dekker; 1996. pp. 683–700.
267. Siegler EL, Stineman MG, Maislin G. Development of complications during rehabilitation. *Arch Intern Med* 1994;145:2185–2190.
268. Hill NS, Lynch JP. Pulmonary complications of neuromuscular diseases. *Semin Respir Crit Care Med* 2002;23:189–314.
269. Martinez TY, Pereira CA, dos Santos ML, Ciconelli RM, Guimaraes SM, Martinez JA. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with idiopathic pulmonary fibrosis. *Chest* 2000;17:1627–1632.
270. Strauss GD, Osher A, Wang CI. GoodrichE, Gold F, Colman W, Stabile M, Bobrenchuk A, Keens TG. Variable weight training in cystic fibrosis. *Chest* 1987;92:273–276.
271. Kinsman RA, Fernandez E, Schocket M, Dirks JF, Covino NA. Multidimensional analysis of the symptoms of chronic bronchitis and emphysema. *J Behav Med* 1983;6:339–357.
272. Guyatt GH, Townsend M, Berman LB, Pugsley SO. Quality of life in patients with chronic air-flow limitation. *Br J Dis Chest* 1987;81:45–54.
273. Breslin E, van der Schans C, Breukink S, Meek P, Mercer K, Volz W, Louie S. Perception of fatigue and quality of life in patients with COPD. *Chest* 1998;114:958–964.
274. Meek PM, Lareau SC, Anderson D. Memory for symptoms in COPD patients: how accurate are their reports? *Heart Lung* 2001;18:474–481.
275. Meek PM, Lareau SC. Critical outcomes in pulmonary rehabilitation: assessment and evaluation of dyspnea and fatigue. *J Rehabil Res Dev* 2003;40:13–24.
276. American Thoracic Society. Dyspnea: mechanisms, assessment and management: a consensus statement. *Am J Respir Crit Care Med* 1999; 159:321–340.
277. Mahler D, editor. Lung biology in health and disease: dyspnea. Vol. 111. New York: Marcel Decker; 1998.
278. ZuWallack R, Lareau S, Meek P. The effect of pulmonary rehabilitation on dyspnea. In: Mahler D, editor. Lung biology in health and disease: dyspnea. New York: Marcel Decker; 2004.
279. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377–381.
280. Hayes M, Patterson D. Experimental development of the graphic rating method. *Psychol Bull* 1921;18:98–99.
281. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58:339–343.
282. French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a cough-specific quality of life questionnaire. *Chest* 2002;121:1123–1131.
283. Lareau SC, Meek PM, Roos PJ. Development and testing of a modified version of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M). *Heart Lung* 1998;27:159–168.
284. Steele BG, Belza B, Cain K, Warms C, Coppersmith J, Howard J. Bodies in motion: monitoring daily activity and exercise with motion sensors in people with chronic pulmonary disease. *J Rehabil Res Dev* 2003;40:45–58.
285. Steele BG, Holt L, Belza B, Ferris S, Lakshminaryan S, Bucher DM. Quantitating physical activity in COPD using a triaxial accelerometer. *Chest* 2000;117:1359–1367.
286. Pitta F, Troosters T, Spruit MA, Decramer M, Gosselink R. Validation of a triaxial accelerometer to assess various activities in COPD patients [abstract]. *Am J Respir Crit Care Med* 2004;169:A594.
287. McGavin CR, Gupta SP, McHardy GJ. Twelve-minute walking test for assessing disability in chronic bronchitis. *BMJ* 1976;1:822–823.
288. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12 minute walking tests in respiratory disease. *BMJ* 1982;284: 1607–1608.
289. Larson JL, Covey MK, Vitalo CA, Alex CG, Patel M, Kim MJ. Reliability and validity of the 12-minute distance walk in patients with chronic obstructive pulmonary disease. *Nurs Res* 1996;45:203–210.
290. American Thoracic Society Statement. Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
291. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47:1019–1024.
292. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test chronic airflow obstruction. *Eur Respir J* 1994; 7:2016–2020.
293. Elpern EH, Stevens D, Kesten S. Variability in performance of timed walk tests in pulmonary rehabilitation programs. *Chest* 2000;118:98–105.
294. Steele B. Timed walking tests of exercise capacity in chronic cardiopulmonary illness. *J Cardiopulm Rehabil* 1996;16:25–33.
295. Sciurba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, Wise RA, for the National Emphysema Treatment Trial Research Group. Six-minute walk distance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:1522–1527.
296. Guyatt GH, Puglsey SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, Fallen EL, Taylor DW. Effect of encouragement on walking test performance. *Thorax* 1984;39:818–822.
297. Carr AJ, Gibson B, Robinson PG. Measuring quality of life: is quality of life determined by expectations or experience? *BMJ* 2001;322: 1240–1243.
298. Curtis JR, Deyo R, Hudson LD. Health-related quality of life among patients with chronic obstructive pulmonary disease. *Thorax* 1994;49: 162–170.
299. Aaron SD, Vandemheen KL, Clinch JJ, Ahuja J, Brison RJ, Dickinson G, Hebert PC. Measurement of short-term changes in dyspnea and disease-specific quality of life following an acute COPD exacerbation. *Chest* 2002;121:688–696.
300. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981;19:787–805.
301. Ware JE, Snow KK, Kosinski MA. SF-36 health survey manual and interpretation guide. Boston, MA: New England Medical Center; 1993.
302. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773–778.
303. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–1327.
304. Guyatt GH, King DR, Feeny DH, Stubbing D, Goldstein RS. Generic and specific measurement of health-related quality of life in a clinical trial of respiratory rehabilitation. *J Clin Epidemiol* 1999;52:187–192.

305. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994; 344:1394–1397.
306. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. *Eur Respir J* 1998;12:363–369.
307. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Lonescu AA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362–368.
308. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. *Control Clin Trials* 1989;10:407–415.
309. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002;19:398–404.
310. Williams JEA, Singh SJ, Sewell L, Guyatt GH, Morgan MDL. Development of a self-reported Chronic Respiratory Questionnaire (CRW-SR). *Thorax* 2001;56:954–959.
311. Schünemann HJ, Goldstein R, Mador J, McKim D, Stahl E, Griffith L, Puhan M, Grant BJB, Austin P, Collins R, *et al.* A randomized controlled trial to evaluate the self-administered standardized CRQ. *Eur Respir J* 2005;25:31–40.
312. Jones PW, Baveystock CM, Littlejohns P. 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* 1989;140:1538–1543.
313. Jones PW. Quality of life measurement for patients with diseases of the airways. *Thorax* 1991;46:676–682.
314. Make B, Gilmartin M, Brody JS, Snider GL. Rehabilitation of ventilatory dependent subjects with lung disease: the concept and the initial experience. *Chest* 1984;86:358–365.
315. Foster S, Lopez D, Thomas HM III. Pulmonary rehabilitation in COPD patients with elevated PaCO2. *Am Rev Respir Dis* 1988;138:1519–1523.
316. Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. *Arch Phys Med Rehabil* 1998;79:849–854.
317. Randal CJ, Martin DP, Martin TR. Patient-assessed health outcomes in chronic lung disease: what are they, how do they help us, and where do we go from here? *Am J Respir Crit Care Med* 1997;156:1032–1039.
318. Crockett AJ, Cranston JM, Moss JR, Alpers JH. The MOS SF-36 health survey questionnaire in severe chronic airflow limitation: comparison with the Nottingham Health Profile. *Qual Life Res* 1996;5:330–338.
319. Simonds AK, Elliot MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax* 1995;50:604–609.
320. Smith IE, Shneerson JM. A progressive care programme for prolonged ventilatory failure: analysis of outcome. *Br J Anaesth* 1995;75:399–404.
321. Wegner RE, Jorres RA, Kirsten DK, Magnussen H. Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD. *Eur Respir J* 1994;7:725–729.
322. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 1995;152:538–544.
323. Okubadejo AA, Jones PW, Wedzicha JA. Quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia. *Thorax* 1996;51:44–47.
324. Perrin C, El Far Y, Vandenbos F, Tamisier R, Dumon MC, Lemoigne F, Mouroux J, Blaive B. Domiciliary nasal intermittent positive pressure ventilation in severe COPD: effects on lung function and quality of life. *Eur Respir J* 1997;10:2835–2839.
325. Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW. Analysis of factors that characterize health impairment in patients with chronic respiratory failure. Quality of Life in Chronic Respiratory Failure Group. *Eur Respir J* 1999;13:1293–1300.
326. Carone M, Bertolotti G, Zotti AM, *et al.* Do oxygen therapy and mechanical ventilation have different effects on perceived health in chronic respiratory failure? *Eur Respir J* 1996;9:111s.
327. Carone M, Jones PW, for the QuESS Group. Quality of Life Evaluation and Survival Study: a 3-year prospective multinational study on patients with chronic respiratory failure. *Monaldi Arch Chest Dis* 2001; 56:17–22.
328. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
329. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. *J Cardiopulm Rehabil* 2001;21:10–17.
330. Steiner MC, Barton RL, Singh SJ, Morgan MD. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* 2003;58:745–751.
331. Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2000;20:353–360.
332. British Thoracic Society. Statement on pulmonary rehabilitation. *Thorax* 2001;56:827–834.
333. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
334. Young P, Dewse M, Fergusson W, Kolbe J. Respiratory rehabilitation in chronic obstructive pulmonary disease: predictors of nonadherence. *Eur Respir J* 1999;13:855–859.
335. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004;329:1209.
336. Behnke M, Jorres RA, Kirsten D, Magnussen H. Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. *Monaldi Arch Chest Dis* 2003;59:44–51.
337. Behnke M, Taube C, Kirsten D, Lehnigk B, Jorres RA, Magnussen H. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. *Respir Med* 2000;94:1184–1191.
338. Hernandez MT, Rubio TM, Ruiz FO, Riera HS, Gil RS, Gomez JC. Results of a home-based training program for patients with COPD. *Chest* 2000;118:106–114.
339. Strijbos JH, Postma DS, van Altena R, Gimeno F, Koeter GH. 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* 1996;109:366–372.
340. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnoea, quality of life, and healthcare costs in California. *J Cardiopulm Rehabil* 2004;24:52–62.
341. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122: 823–832.
342. Bestall JC, Paul EA, Garrod R, Garnham R, Jones RW, Wedzicha AJ. Longitudinal trends in exercise capacity and health status after pulmonary rehabilitation in patients with COPD. *Respir Med* 2003; 97:173–180.
343. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–586.
344. Finnerty JP, Keeping I, Bullough I, Jones J. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. *Chest* 2001;119:1705–1710.
345. Hui KP, Hewitt AB. A simple pulmonary rehabilitation program improves health outcomes and reduces hospital utilization in patients with COPD. *Chest* 2003;124:94–97.
346. Cambach W, Wagenaar RC, Koelman TW, van Keimpema AR, Kemper HC. The long-term effects of pulmonary rehabilitation in patients with asthma and chronic obstructive pulmonary disease: a research synthesis. *Arch Phys Med Rehabil* 1999;80:103–111.
347. Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, Sanchis J. Long-term effects of outpatient rehabilitation of COPD: a randomized trial. *Chest* 2000;117:976–983.
348. Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J* 1999;13:125–132.
349. Clini E, Foglio K, Bianchi L, Porta R, Vitacca M, Ambrosino N. Inhospital short-term training program for patients with chronic airway obstruction. *Chest* 2001;120:1500–1505.
350. Criner GJ, Cordova FC, Furukawa S, Kuzma AM, Travaline JM, Leyenson V, O'Brien GM. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe

chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:2018–2027.
351. Berry MJ, Rejeski WJ, Adair NE, Ettinger WH Jr, Zaccaro DJ, Sevick MA. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2003;23:60–68.
352. Ries AL, Kaplan RM, Myers R, Prewitt LM. Maintenance after pulmonary rehabilitation in chronic lung disease. *Am J Respir Crit Care Med* 2003;167:880–888.
353. Foglio K, Bianchi L, Ambrosino N. Is it really useful to repeat outpatient pulmonary rehabilitation programs in patients with chronic airway obstruction? A 2-year controlled study. *Chest* 2001;119:1696–1704.
354. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779–784.
355. Golmohammadi K, Jacobs P, Sin DD. Economic evaluation of a community-based pulmonary rehabilitation program for COPD. *Lung* 2004; 182:187–196.
356. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;121:1434–1440.
357. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. 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* 2002;167:544–549.
358. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-minute walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;1:28–33.
359. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
360. Bernard S, Whittom F, LeBlanc P, Jobin J, Belleau R, Berube C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159: 896–901.
361. Creutzberg EC, Wouters EF, Mostert R, Pluymers RJ, Schols AM. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest* 2003;124: 1733–1742.
362. Whittom F, Jobin J, Simard PM, LeBlanc P, Simard C, Bernard S, Belleau R, Maltais F. Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1998;30:1467–1474.
363. Couillard A, Maltais F, Saey D, Debigare R, Michaud A, Koechlin C, LeBlanc P, Prefaut C. Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:1664–1669.
364. Richardson RS, Leek BT, Gavin TP, Haseler LJ, Mudaliar SR, Henry R, Ries AL, Mathieu-Costello OD, Wagner PD. Reduced mechanical efficiency in COPD, but normal peak VO2 with small muscle exercise. *Am J Respir Crit Care Med* 2003;169:89–96.
365. Jakobsson P, Jorfeldt L, Brundin A. Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. *Eur Respir J* 1990;3:192–196.
366. Maltais F, Sullivan MJ, LeBlanc P, Duscha BD, Schachat FH, Simard C, Blank JM, Jobin J. Altered expression of myosin heavy chain in the vastus lateralis muscle in patients with COPD. *Eur Respir J* 1999; 13:850–854.
367. Gosker HR, Kubat B, Schaart G, van der Vusse GJ, Wouters EF, Schols AM. Myopathological features in skeletal muscle of patients with chronic obstructive pulmonary disease. *Eur Respir J* 2003;22:280–285.
368. Jakobsson P, Jorfeldt L, Henriksson J. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:374–377.
369. Sauleda J, Garcia-Palmer F, Wiesner RJ, Tarraga S, Harting I, Tomas P, Gomez C, Saus C, Palou A, Agusti AG. Cytochrome oxidase activity and mitochondrial gene expression in skeletal muscle of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1413–1417.
370. Jakobsson P, Jorfeldt L, Henriksson J. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:374–377.
371. Russell AP, Somm E, Debigare R, Hartley O, Richard D, Gastaldi G, Melotti A, Michaud A, Giacobino JP, Muzzin P, *et al.* COPD results in a reduction in UCP3 long mRNA and UCP3 protein content in types I and IIa skeletal muscle fibers. *J Cardiopulm Rehabil* 2004; 24:332–339.
372. Gosker HR, Schrauwen P, Hesselink MK, Schaart G, van der Vusse GJ, Wouters EF, Schols AM. Uncoupling protein-3 content is decreased in peripheral skeletal muscle of patients with COPD. *Eur Respir J* 2003;22:88–93.
373. Payen JF, Wuyam B, Levy P, Reutenauer H, Stieglitz P, Paramelle B, Le Bas JF. Muscular metabolism during oxygen supplementation in patients with chronic hypoxemia. *Am Rev Respir Dis* 1993;147:592–598.
374. Rabinovich RA, Figueras M, Ardite E, Carbó N, Troosters T, Filella X, Barbera JA, Fernandez-Checa JC, Argiles JM, Roca J. Increased TNFalfa plasma levels during moderate intensity exercise in COPD patients. *Eur Respir J* 2003;21:789–794.
375. Agusti AG, Sauleda J, Miralles C, Gomez C, Togores B, Sala E, Batle S, Busquets X. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166: 485–489.
376. Rabinovich RA, Ardite E, Troosters T, Carbo N, Alonso J, De Suso JM, Vilaro J, Barbera JA, Polo MF, Argiles JM, *et al.* Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164: 1114–1118.
377. Engelen MP, Schols AM, Does JD, Deutz NE, Wouters EF. Altered glutamate metabolism is associated with reduced muscle glutathione levels in patients with emphysema. *Am J Respir Crit Care Med* 2000; 161:98–103.
378. Koechlin C, Couillard A, Simar D, Christol JP, Bellet M, Hayot M, Prefaut C. Does oxidative stress alter quadriceps endurance in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2004;169: 1022–1027.
379. Rabinovich RA, Ardite E, Troosters T, Carbo N, Alonso J, De Suso JM, Vilaro J, Barbera JA, Polo MF, Argiles JM, *et al.* Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164: 1114–1118.