

Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease

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Summary

In patients with pulmonary disease, disease severity and prognosis are determined not only by lung function impairment (1, 2). In patients with mild, moderate, or severe disease, exercise capacity,

health-related quality of life, and participation in activities of daily living are often impaired out of proportion to lung function impairment (3–5). Hence, therapies that improve the patient's lung function may have relatively limited impact on the above-mentioned outcomes (6, 7). Optimal bronchodilatation can be seen as a first step in the treatment of patients with chronic obstructive pulmonary disease (COPD); greater treatment effects (e.g., improvements in exercise performance, symptoms, and health-related quality of life) are often achieved only after the addition of pulmonary rehabilitation (8). Comprehensive pulmonary rehabilitation programs aim at tackling the systemic consequences of COPD, as well as the behavioral and educational deficiencies observed in many patients (9).

Since the first controlled trials on pulmonary rehabilitation in the mid-1970s (10, 11) (for review *see* Casaburi and Petty [12]) and initial skepticism in the early 1980s (13), pulmonary rehabilitation has proven to result in clinically significant improvements in more than 20 methodologically well-designed randomized controlled trials (14). According to the World Health Organization's Global Initiative for Chronic Obstructive Lung Disease (GOLD) consensus document on the management of COPD (15), pulmonary rehabilitation should be considered in patients with an FEV₁ below 80% of the predicted value. In addition, most national and international guidelines consider pulmonary rehabilitation an important treatment option (9, 16–18). Hence, ideal candidates show, despite optimal medical treatment, significant abnormalities in their function and their participation in everyday life, leading to impaired health-related quality of life. In addition, candidates should be motivated to engage in a rehabilitation process that is often demanding both in terms of time and in physical and psychological investment (19). At the severe end of the disease spectrum, the results of the National Institutes of Health National Emphysema Treatment Trial (NETT), investigating the effects of lung volume reduction surgery, are strong encouragement for the implementation of pulmonary rehabilitation programs for patients with COPD.

The NETT, indeed, identified lung volume reduction surgery as an expensive (20), but effective treatment option in selected patients *after* they had undergone pulmonary rehabilitation (21). In patients screened for lung volume reduction surgery, pulmonary rehabilitation programs were thought to be an essential preparatory step before considering surgery. When, despite pulmonary rehabilitation, patients still have severely impaired exercise capacity, and have predominantly upper lobe emphysema, they are likely to benefit substantially from lung volume reduction surgery. Moreover, because the improved lung function seen after lung volume reduction surgery (22) facilitates exercise at higher intensity, rehabilitation programs after the surgery are beneficial as well. The results of the NETT study have triggered discussions on the reimbursement of pulmonary rehabilitation programs in the United States (23).

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Today the question is no longer “should patients with chronic obstructive lung disease receive pulmonary rehabilitation?” but rather “how should pulmonary rehabilitation be delivered to patients with COPD?” and “which components form the basis of the success of pulmonary rehabilitation programs?” The present review focuses on the present state of the art and science concerning the physiological rationale for exercise training; we also discuss the potential of the multidisciplinary approach generally adopted during rehabilitation programs.

EFFECTIVENESS IN TERMS OF CLINICALLY IMPORTANT OUTCOMES

The goals of pulmonary rehabilitation programs are to reduce symptoms, improve activity and daily function, and restore the highest level of independent function in patients with a respiratory disease (9, 16–19). The success of achieving these goals can be assessed by using both physiological and psychosocial outcome measures.

Rehabilitation programs are recommended to be set up as individualized and multidisciplinary interventions. The different components of the program aim at improving physical and psychological functioning of patients in interaction with his or her environment, enhancing knowledge of the disease, and improving self-management.

Exercise Performance

In a meta-analysis, the effects of pulmonary rehabilitation programs on exercise tolerance were systematically reviewed (14). Improvement of exercise tolerance has been estimated from incremental exercise tests, constant work rate tests, or free walking tests. In the following, pooled data are presented as a reasonable estimate of the anticipated effects of rehabilitation programs. Although clinically these programs differed in terms of duration, number of sessions, training intensity, and so on (factors that are discussed below), statistical heterogeneity was not significant (24): for maximal work rate $Q = 4.9, p = 0.55$; for peak oxygen uptake $Q = 11.8, p = 0.22$; for constant work rate tests $Q = 3.55, p = 0.47$; and for the 6-minute walking test $Q = 14.5, p = 0.2$.

In incremental tests, peak work rate improves on average by 18% compared with baseline (weighted mean of studies [14, 25–27], reporting maximal exercise tolerance in a parallel group design). The interquartile range of the improvement reported across studies was 13 to 24% improvement in the treatment groups, compared with the respective control groups. Peak oxygen uptake improved by 11% when the rehabilitation groups are compared with the respective controls (interquartiles of different studies, 4 to 18% improvement). The effect of pulmonary rehabil-

itation on whole body constant work rate exercise tolerance is much greater. As a weighted average of five randomized controlled studies (27–31), endurance exercise time improved by an average of 87%. One study showed a 14% increase in the theoretical maximal sustainable work rate, another outcome that may be relevant to everyday life (32). A combination of improved mechanical efficiency, improved muscle force (33) and oxidative capacity (34, 35), adaptations in the breathing pattern (36, 37), and consequently reduced dynamic hyperinflation (38) are likely to contribute to the improved exercise tolerance that is consistently reported.

Exertional dyspnea is consistently reported to be reduced after pulmonary rehabilitation (36). The reduction in dyspnea is partially mediated through the reduced ventilatory requirements at identical work rates and at identical oxygen consumption. In addition, patients have also reported reduced sensation of dyspnea at identical levels of ventilation (39). The latter may be the consequence of less dynamic hyperinflation at isoventilation and desensitization to dyspnea. In patients with inspiratory muscle weakness (40, 41), but not in patients with better preserved inspiratory muscle force (39, 42), improved sensation of dyspnea at isoventilation may be due to improved inspiratory muscle function after rehabilitation.

The clinical relevance of the benefit of pulmonary rehabilitation is illustrated by the improved functional capacity, as measured by the 6-minute walk test. The pooled effect size of all randomized controlled studies of the results of pulmonary rehabilitation is 49 m, with a 95% confidence interval of 26–72 m (14). The minimal clinically important difference of the 6-minute walking test has been estimated to be 54 m (43). In Figure 1 the effects of rehabilitation programs are displayed along with the program characteristics (25, 31, 33, 44–52). Although a formal test for statistical heterogeneity failed to be significant ($Q = 14.5, p = 0.2$), clinically relevant heterogeneity is observed across studies. From Figure 1 it is suggested that programs with more rehabilitation sessions (median across programs, 28 sessions) had somewhat more effect than programs with fewer sessions (34.5 m with 28 sessions or fewer, versus 50.3 m with more than 28 sessions). Other factors that may interfere with the overall effect of the program are the setting, the intensity, the duration of the training session, and the duration of the program. A meta-analysis attempting to investigate whether these factors would lead to statistically significant difference in results, however, revealed only a trend for longer programs (more than 6 months, 70 [41–93] m) to be superior to shorter programs (42 [10–72] m) and showed a strong trend for enhanced effects (60 [34–86] versus 18 [15–50] m) when close supervision of the patients was ensured (14).

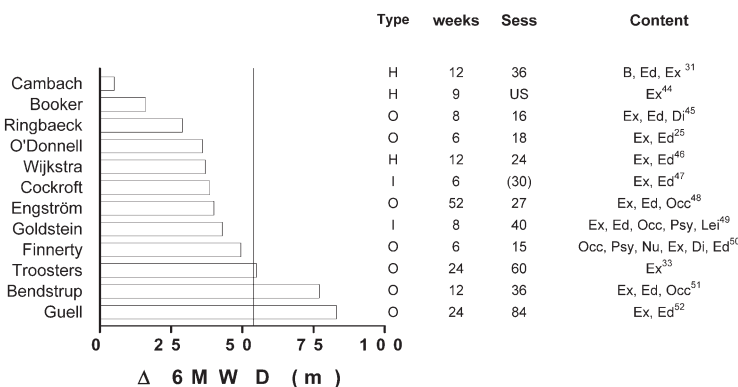


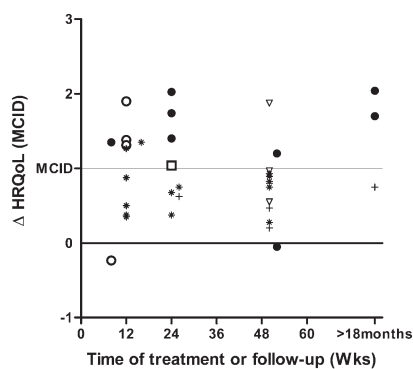
Figure 1. Left: Summary of published differences in the 6-minute walking distance (6MWD, expressed in meters) between groups of patients who underwent rehabilitation including exercise training and their respective control groups receiving usual care. The minimal clinically important difference is indicated by the thin vertical line. Right: The type of program (outpatient [O], inpatient [I], or home based [H]), the duration (in weeks), and the number of sessions (Sess). US = unsupervised sessions performed at home; the number within parentheses indicates that the exact number of sessions was not reported. In addition, the various components of the rehabilitation program are displayed (Ex = exercise; B = breathing exercises; Ed = education sessions; Di = dietary intervention; Occ = occupational therapy; Psy = psychotherapy; Lei = leisure activities; Nu = nurse specialist).

From a randomized controlled study conducted in the authors' center (33), we calculated that the number needed to treat, to have one patient with a clinically significant benefit, was three (95% confidence interval, 1.7–6.4). Others found similar results (52), even if sustained improvement over a 24-month follow-up period was used as a criterion. The addition of pulmonary rehabilitation to the treatment of patients with stable COPD, hence, seems to result in more significant improvements in exercise tolerance than adding an additional bronchodilator (53).

Health-related Quality of Life and Related Outcomes

A review of the published literature shows that the improvement in health-related quality of life after pulmonary rehabilitation clearly exceeds the minimal clinically important difference. When disease-specific instruments were used, the lower limit of the 95% confidence interval exceeded the minimal clinically important difference (14). Figure 2 summarizes the effects of various randomized controlled trials investigating the effect of outpatient rehabilitation (33, 48, 50–52, 54, 55), inpatient rehabilitation (49), and home rehabilitation (30, 31, 55, 56) on health-related quality of life. For comparison, the effects of several large trials of bronchodilator administration, inhaled corticosteroids, and combination products are also depicted. These pharmacologic trials have been reviewed in detail elsewhere (57). Because these studies used different health-related quality of life instruments, effects are displayed as a fraction of the minimal clinically important difference; therefore an effect size exceeding “1” is considered to be of clinical relevance. The two rehabilitation trials not showing improvement in health-related quality of life above the minimal clinically important difference are one trial of home rehabilitation in patients with severe dyspnea (55) and one trial of outpatient rehabilitation applying a low training frequency (27 training sessions over 1 year) (48). In the 11 remaining rehabilitation trials, the effects were both clinically relevant and statistically significant. In contrast, few trials with bronchodilators, inhaled steroids, or combination products yielded improvements in health-related quality of life exceeding the minimal clinically important difference.

Improved health-related quality of life is observed even in the absence of clinically significant improvements in exercise



in mild exacerbations may lead to a further, albeit more modest, reduction in use of health care resources. It is appealing to speculate that a reduction in mild and moderate acute exacerbations may lead in the long term to a modification of disease progression, as exacerbation frequency has been linked to decline in FEV₁ (79). No study has so far confirmed this hypothesis. Nevertheless, in the aforementioned study (52), during the 24 months of follow-up more patients from the control group became oxygen dependent. Oxygen dependency can perhaps be seen as a marker of disease progression.

Survival

So far no study has convincingly shown evidence of improved survival after pulmonary rehabilitation (27, 33, 48, 52, 54, 56, 60). None of these studies, however, has been powered to detect a reduction in mortality. When all these studies are pooled, 1-year to 18-month mortality risk was 7.8% in the rehabilitation group (23 of 315 randomized patients died) and 9.9% in the control group (28 of 283 patients died). The pooled odds of dying in the rehabilitation group, as compared with the control group, was 0.69 (relative risk, 0.38–1.25; $p = 0.395$ [heterogeneity $Q = 2.02$, $p = 0.91$]). This suggests that our current best estimate is that rehabilitation reduces the short-term risk of dying by 31%. This risk reduction is, however, not statistically significant at all because, even when pooled, the number of patients studied is insufficient to detect this magnitude of effect. Because patients who enroll in pulmonary rehabilitation are generally in a relatively stable state, their likelihood of dying in the short term is rather low. Hence the absolute reduction in mortality is likely to be relatively modest. Studies investigating patients with higher mortality risk (e.g., after discharge from the hospital for an acute exacerbation) may be more successful in finding effects on survival (80). Indeed, in these patients inactivity has been identified as a factor independently related to hospital readmission (81) and mortality (82). Because increasing the patient's activity level is a central goal of rehabilitation, rehabilitation programs initiated after severe exacerbations may show improved survival in smaller studies. Alternatively, a large-scale multicenter randomized trial employing a prolonged follow-up period (perhaps 3 years) is required to conclusively establish whether pulmonary rehabilitation impacts the progression of disease and survival. If one assumes, on the basis of the above-described analysis of the available literature, an absolute 2% mortality difference per year, and a durable effect of rehabilitation (i.e., with proper maintenance programs; *see below*), up to 750 to 1,000 patients would be required in both the treatment and control groups with 3 years of follow-up.

EXERCISE TRAINING

Exercise reconditioning is the key to a successful rehabilitation program (83). The challenge is to design a training program that stimulates the cardiovascular system and the skeletal muscle so that physiological adaptations in the skeletal muscle are induced that reverse the deleterious impact of deconditioning and other systemic manifestations of COPD that impact skeletal muscle. Training programs in lung disease must accommodate the limitations of the patient with COPD. These limitations include inability to increase oxygen delivery to the peripheral muscle because of gas exchange inefficiency in the lungs, constraints on lung mechanics (dynamic hyperinflation and flow limitation) (84), and the development of pulmonary hypertension during exercise (85). Beyond these limitations, muscle dysfunction is a factor limiting exercise tolerance in a substantial fraction of patients (4, 86, 87). Exercise training programs should be adapted to the individual limitations of the patient, taking cardiovascular, pulmonary, and skeletal muscle limitations into account.

Skeletal Muscle Dysfunction in COPD: An Update

Skeletal muscle dysfunction has now been widely accepted in COPD, and has been reviewed in several excellent reviews in the *Journal* (88–90). Skeletal muscle atrophy or weakness is clearly a negative prognostic factor (91–93) and requires appropriate action. The potential for at least partial reversibility of this dysfunction is believed to be an important determinant of the physiological gains achieved with pulmonary rehabilitation. Skeletal muscle dysfunction is typically characterized by reduced muscle strength, reduced muscle endurance, impaired muscle oxidative capacity (as shown by reduced activity of the enzymes citrate synthase and hydroxyacetyl-CoA dehydrogenase [94, 95]), and a shift toward a glycolytic fiber type distribution (low fraction of Type I fibers) (96–100). These changes result in reduced skeletal muscle endurance (100), increased fatigability (101, 102), a lowering of the lactate threshold (94), and increased ventilatory requirements during exercise.

Although several complementary mechanisms may be the basis of the observed skeletal muscle dysfunction, the exact factors that cause skeletal muscle dysfunction in individual patients remain largely unknown. Hence, wide variation in skeletal muscle weakness among subjects is observed, ranging from normal function in some patients to severe impairment in others (103).

A first mechanism potentially contributing to skeletal muscle dysfunction is the sedentary lifestyle of patients with COPD (104–107). The accompanying deconditioning leads to skeletal muscle atrophy. Atrophy can be observed at the whole muscle level (108) or at the myocyte level (109), but can also be indirectly assessed by the loss in (extremity) fat-free mass (110). The proportional reduction in muscle mass and muscle force (108) and the preserved *in vitro* contractile properties of the quadriceps give further support to the importance of inactivity-induced atrophy (111). Partial reversibility of low muscle oxidative capacity (35, 112), as well as increases in muscle cross-sectional area (113), are seen with exercise conditioning programs. In addition, skeletal muscle strength (33, 39, 114, 115) and skeletal muscle fatigability (116) have also been reported to be significantly improved after exercise training in COPD. These observations give support to the hypothesis that inactivity is an important driver of the observed abnormalities in the skeletal muscles of these patients.

There are several reasons, however, to posit that inactivity, albeit an important factor, is not the only factor responsible for the observed skeletal muscle dysfunction: (1) a study employing 6 months of high-intensity exercise training failed to normalize skeletal muscle force (33); (2) studies investigating healthy subjects with an activity level similar to that of patients with COPD observed reductions in myosin heavy chain Type I expression in the skeletal muscles of patients with COPD (96), or found that the muscles of patients with COPD adapted differently to strenuous exercise stimuli (117); (3) in a subset of patients with COPD, exercise training responses of the peripheral muscle are clearly abnormal, reducing rather than improving the scavenging potential for free radicals (118). Hence, other mechanisms have been suggested to exacerbate the observed skeletal muscle abnormalities in COPD. Acute or chronic treatment with high-dose oral corticosteroids has been directly associated with the development of muscle weakness (119, 120) and poor survival (121). Relatively modest doses of steroids administered over a period of 14 days, administered to stable patients (e.g., in the context of a reversibility trial), however, seem not to exert demonstrable adverse effects on quadriceps and respiratory muscle force in the average patient (122). More recent studies have underlined the importance of systemic inflammation as a mechanism for development of muscle weakness. Systemic inflamma-

tion has been suggested to contribute to excessive muscle weakness, especially during severe exacerbations of COPD (123). Circulating levels of interleukin-8 were significantly correlated with muscle weakness (123). Weight loss and especially loss of fat-free mass (a surrogate measure of muscle mass) have been associated with systemic inflammation (124). In addition, increased levels of skeletal muscle apoptosis were observed in patients presenting with weight loss (125). Another factor related to the process of muscle wasting in COPD is oxidative stress. Patients with COPD are exposed to increased levels of oxidative stress, both when stable and (more evidently) during acute exacerbations (126, 127). During exercise, larger amounts of free radicals are formed as a result of increased mitochondrial activity. When there is insufficient scavenging potential for these free radicals, oxidative damage to lipids and proteins may result. There is still debate on the oxidant-antioxidant balance in COPD. Several authors have reported impaired systemic or skeletal muscle antioxidant capacity in patients with COPD (117, 128) and lipid peroxidation was observed, even at rest (117, 129, 130). Others, however, do not confirm that skeletal muscle antioxidant capacity is reduced at rest (118). After local (117) or whole body (131) exercise, markers of oxidative stress damage were significantly increased. Hence, it seems likely that some patients are more susceptible to oxidative damage than others. Inflammatory status, nutritional status, and steroid treatment (132) as well as activity level (133) may interact to magnify the deleterious effects of oxidative damage. Although muscle antioxidant capacity was found to be improved after exercise training in patients with heart failure (134) and in healthy subjects, the response to exercise training in patients with COPD is highly variable (118, 135).

A last factor may be related to the angiotensin-converting enzyme genotype of patients with COPD. Hopkinson and coworkers reported that the deletion (*D*) allele of the angiotensin-converting enzyme gene polymorphism was associated with better preserved quadriceps force (136). Interestingly, the insertion (*I*) allele of the angiotensin-converting enzyme polymorphism may be related to enhanced endurance capacity in healthy subjects (137), athletes (138, 139), and patients with COPD (140). In addition, the insertion allele may result in somewhat greater training effects in terms of maximal exercise capacity (140). This is surely an exciting avenue for further research, and the integration of the genotype of patients with COPD may prove to be helpful in our understanding of the variability in muscle weakness seen across patients with COPD in future research.

Irrespective of the precise mechanism leading to skeletal muscle abnormalities, it is clear that reversing this dysfunction is an important, and clinically relevant, objective of exercise training programs in COPD.

Principles of Design for Exercise Training Programs

In healthy subjects, cardiorespiratory fitness is improved when the following guidelines for exercise training intensity are observed. Exercises should be performed 3 to 5 days per week at an intensity above 40 to 85% of the oxygen uptake reserve (difference between resting and peak oxygen uptake) for more than 20 minutes (or at lower intensity, preferably for 30 minutes), continuously or in intervals (141). These guidelines were established by rather painstaking studies (142) in which matrices of programs with various characteristics were studied, with the goal of establishing the minimal parameters of an effective program. Whether these guidelines are appropriate for patients with COPD has been debated. Systematic studies to determine the minimal program duration, session duration, or number of sessions per week have not been performed. Without evidence to the contrary, it has generally been conceded that these program parameters are unlikely to differ substantially between healthy

subjects and patients with COPD (9, 143). Nevertheless, controversy exists.

The duration (weeks of training) of the rehabilitative exercise training program is a much discussed but poorly investigated topic. There is substantial sentiment in the rehabilitation community that longer programs than absolutely required to elicit a physiologic training effect may be of benefit, taking into account that patients generally start off with severe muscle weakness and deconditioning. Clearly, shorter programs (6–8 weeks) are less expensive and allow more patients to experience rehabilitation. However, a key goal of pulmonary rehabilitation is to change the patient's behavior (e.g., from a sedentary toward a more active lifestyle). Although measurable physiological changes may occur within weeks, behavioral changes may require longer time periods (144). It is therefore not surprising that some pulmonary rehabilitation programs of longer duration (6 months or longer) have shown better long-term effects (33, 52) as compared with shorter interventions (27, 145, 146). On the other end of the spectrum, responses to short-term rehabilitation programs seem to be strongly influenced by the duration of the program (147–149) and the training intensity (34). Programs shorter than 6 weeks currently lack validation, as no randomized controlled trial has been performed. One trial compared 4 weeks with 7 weeks of rehabilitation (147) and concluded that 4 weeks of rehabilitation was less effective. Two other studies reported effects at 4 and 8 weeks (150) and at 6 and 12 weeks (51) and confirmed that longer rehabilitation programs yield significantly greater effects. In a large multicenter trial, greater effects were shown after 6 months compared with 3 months of rehabilitation (151).

At present, rehabilitation programs including high-intensity endurance training in which patients are engaged for a relatively long period of time have been demonstrated to reduce symptoms and increase exercise tolerance, skeletal muscle function, and health-related quality of life. A minimum of about 8 weeks seems necessary to achieve substantial effects, but longer programs generally achieve more favorable results. It is worth noting that neither patients nor health care providers are well served by programs that yield only modest benefits. The goal should be to induce as great a benefit as possible and these benefits should be long-lasting.

Can Training Intensity Be High Enough in Patients with COPD to Yield a Physiologic Training Effect?

During whole body exercise, at the peak exercise level tolerated significant metabolic reserve remains in the skeletal muscle of many patients with severe COPD due to a ventilatory limitation (152). In contrast, when small muscle groups are exercised in isolation, a higher metabolic rate can be achieved (153) because the ventilatory demand of exercising a small muscle mass is not great. It has been posited that in patients with severe COPD it may be difficult to achieve a level of training intensity high enough to result in physiological training effects due to the central ventilatory limitation (13). However, there is now a wealth of experience that indicates that physiological evidence of a training effect can be achieved, if high training targets are employed. As first pointed out by Punzal and coworkers, patients with COPD can exercise for prolonged periods at high fractions of their peak exercise tolerance (154). In patients with COPD with primarily moderate disease, exercise training conducted at about 75% of the peak work rate (60% of the difference between the lactate threshold and peak oxygen uptake) resulted in significant physiological effects (34). A similar training strategy was shown to be effective in patients with severe disease. (37) Others have confirmed that high training intensity is required to elicit physiologic training effects (155, 156). These findings probably partially explain the disappointing training effects in earlier studies (13),

in which exercise intensity may have been insufficient. Maltais and coworkers showed that training at 60% of the peak work rate achieved in an incremental exercise test resulted in significantly improved exercise tolerance (157), but that few subjects were able to achieve a target training intensity of 80% of the peak work rate, despite careful supervision and encouragement. A word of caution is warranted when a fraction of the peak work rate achieved in an incremental exercise test is used to specify a target training intensity. The rate of work rate increment used during the maximal incremental exercise test is a determinant of the peak work rate obtained (158). In the study by Maltais and coworkers (157), 10-W/minute increments were used. If a lower rate of work rate increment had been used, peak work rate would have been lower and the authors would probably have concluded that patients could tolerate a higher fraction of this revised peak work rate. Using the appropriate work rate increment, Neder and coworkers confirmed that the work rate that could be sustained by patients was about 80% of the peak work rate, on average (159). When walking is used as the primary form of exercise, even higher fractions of the peak work can be sustained (154, 160). Walking engages larger muscle groups and hence results in less stress on the skeletal muscle at isoventilation. Hence, during walking, patients may reach the limits of the ventilatory system before the skeletal muscle is fatigued during exercise (161). This is also reflected in the lower lactate levels at isoventilation and identical oxygen consumption (160, 162). As long as ventilation is just below peak ventilation, patients with COPD without significant respiratory muscle weakness are able to sustain the exercise for a relatively long time (159, 160). From the foregoing, it can be speculated that exercise intensity targets in the range of 60 to 80% of the peak work rate may be practical depending on the exercise type and the incremental exercise protocol applied. The lower limit of effective training intensities (i.e., the critical training intensity) has not been identified with any certainty, although it seems likely that the higher the intensity, the better the physiological training effect. It should be stressed that these considerations yield only an initial exercise target. Rehabilitation therapists need to be given the latitude to adjust these targets up or down depending on the patient's symptomatic response. Hence close supervision of the patients is needed. Further, as the rehabilitation program proceeds, therapists should be encouraged to adjust training intensity. Weekly increments of training intensity are possible in patients with COPD (33, 115, 157, 163). Symptom scores have been posited to be useful in establishing an exercise prescription and for subsequently adjusting it. One group has proposed that on the modified Borg Rating of Perceived Exertion Scale (with a range of 0 to 10 points) a score of 4–6 generally indicates adequate training intensity (164). Alternatively, the target dyspnea score can be obtained from incremental exercise testing. These targets remain stable for a relative work rate over the course of a rehabilitation program (165). At present it remains unclear whether symptom scores are a sufficiently reliable method for establishing an exercise prescription. Nevertheless, the Borg Scale has been used in many clinical studies to guide increments in training load (27, 33, 48, 54, 55, 166).

As indicated above, it is difficult to ensure that all patients with COPD achieve and tolerate a level of exercise intensity high enough that a physiologic training effect is achieved. Strategies have been investigated to allow the patient to tolerate higher exercise intensities with the aim of achieving a greater training effect, or a more comfortable training regimen. This is especially true for the patients with very severe disease: those with severe muscle weakness or profound ventilatory limitation to exercise (this has been a particular concern in patients awaiting lung volume reduction surgery and lung transplantation).

Specific Strategies to Increase Training Intensity

Reducing work of breathing during training. Many patients with COPD reach the boundaries of the ventilatory system during incremental exercise (167), and high-intensity constant work rate exercise (159). Hence interventions that allow higher levels of ventilation, or reduce the ventilation requirement at a given level of exercise, may allow patients to perform exercise training at higher intensities. This may lead to enhanced training results, typically in patients in GOLD Stages III and IV (FEV_1 less than 50% predicted).

OXYGEN SUPPLEMENTATION. Oxygen supplementation during exercise clearly reduces the ventilatory requirements for a given work rate and increases maximal exercise tolerance, even in patients without appreciable exercise desaturation (168). At high exercise levels, oxygen delivery to the exercising muscles is enhanced (169). At near maximal exercise levels, modest reductions in circulating lactate levels are correlated with the reduced ventilation during exercise (170, 171). These findings were confirmed in healthy subjects breathing hyperbaric, or hyperoxic, air (172, 173). At lower exercise levels, the major mechanism of benefit is reduction in carotid body drive to breathing (174). Acute administration of oxygen was also shown to reduce the exercise-induced pulmonary hypertension in moderate to severe COPD (175). Despite the consistent improvements found in exercise tolerance, most studies seeking to determine whether providing supplemental oxygen during training improved the gains in exercise tolerance elicited by rehabilitative training have failed to show an additional benefit (176–178). This led to the belief that oxygen supplementation during exercise training would be of limited benefit. In one study, however, Emtner and colleagues studied patients with COPD who did not experience clinically significant desaturation with exercise as they participated in a training program with high-intensity targets (179). Those patients randomized to respire supplemental oxygen during exercise training succeeded in training at higher training intensities than those respiring supplemental air. Consequently the improvement in exercise tolerance was greater in patients who trained with oxygen supplementation. The observation that the benefit was more pronounced in patients with a greater acute response to oxygen supplementation is of special interest to clinicians prescribing oxygen therapy. Despite the fact that this is a relatively small study, these data suggest that oxygen supplementation may be a useful tool with which to enhance training intensity in patients with COPD (180). This in turn may lead to greater physiological effects of the exercise training program. Although these results are promising, so far, no studies showed that use of oxygen supplements during training results in superior and clinically significant benefits in quality of life and activities of daily living. Neither have studies confirmed that providing oxygen during exercise training sessions results in more durable effects of the training programs. This is surely a point of interest for further research. These missing elements preclude making strong recommendations, at present, on the use of oxygen supplementation in rehabilitation practice. Nevertheless, if confirmed in longer term studies these findings may form the basis of a more rational prescription of oxygen during high-intensity exercise training programs.

NONINVASIVE MECHANICAL VENTILATION. Noninvasive mechanical ventilation, administered in the form of continuous positive pressure ventilation or pressure support ventilation (bilevel positive airway pressure or proportional assist ventilation), unloads the respiratory muscles (181). Noninvasive mechanical ventilation has therefore found use during severe exacerbations of COPD (182) and hypoxic respiratory failure (183). It also has been shown to improve dyspnea and exercise endurance in pa-

tients with COPD (184–186), healthy subjects (187), and even patients with chronic heart failure (188). Using inspiratory support, the load on the inspiratory muscles is reduced, with a consequent reduction in the work of breathing (184). Blood gases improve (189) and patients are able to sustain lactic acid accumulation for a longer period of time (190). Hence, the application of inspiratory support, through proportional assist ventilation, or continuous positive airway pressure ventilation may potentially lead to enhanced training intensity. Two trials indeed confirmed this hypothesis (191, 192), showing somewhat greater physiologic benefits of training with “proportionally assisted ventilation” in patients with severely impaired, hypercapnic COPD. In patients with less severe disease, however, others could not confirm these findings (193). Patient selection seems crucial when clinicians apply this intervention. The improvement obtained by noninvasive mechanical ventilation was more pronounced in patients with respiratory muscle weakness (186). Given the difficulties in adjusting the mask and ventilator settings, individual supervision of patients is necessary. In addition, two of the four studies investigating the effect of inspiratory pressure support during exercise training report that some patients do not support the ventilatory assist (192, 193). It should be noted, however, that the total dropout reported in the four groups treated with noninvasive mechanical ventilation (191–194) was not significantly different from the dropout among patients not receiving this intervention. The aforementioned factors may complicate the clinical application of assisted ventilation in exercise programs. As an alternative, noninvasive positive pressure ventilation at home in combination with an outpatient rehabilitation program resulted in an additional increase in the shuttle walking distance and health-related quality of life compared with exercise training alone (195).

HELIUM–OXYGEN BREATHING. Breathing gas mixtures with low density (e.g., 79% He, 21% O₂; heliox) lowers airflow resistance and therefore decreases exercise-induced hyperinflation (196). Exercise tolerance is improved (152, 197). So far, however, no trial has shown that heliox breathing during rehabilitative exercise training yields a superior increase in exercise tolerance outcomes (194). It should be mentioned that, with current technology, the cost of respiring heliox during an entire exercise program is appreciable.

BREATHING EXERCISES. The benefit of adding breathing exercises to pulmonary rehabilitation programs is yet unclear. Diaphragmatic breathing, long a technique taught in rehabilitation programs, seems on shaky ground, as it been shown to decrease breathing efficiency (198). The deterioration of breathing efficiency during diaphragmatic breathing may result from the recruitment of additional muscles or a deteriorated mechanical coupling of inspiratory muscles, rib cage, and abdomen, reducing the pleural pressure developed for a given muscle contraction (198). Pursed-lip breathing is often adopted by patients spontaneously (9, 199). With pursed-lip breathing, recruitment of the abdominal muscles during expiration is facilitated (200). During quiet pursed-lip breathing, pulmonary gas exchange is improved, as is illustrated by an increase in arterial oxygen saturation (200). Pursed-lip breathing has also been shown to have favorable effects on breathing pattern (201–203), increasing tidal volume, reducing the ratio of the inspiratory time to the total duration of the respiratory cycle (T_i/T_{tot}), and reducing dyspnea. Significant reductions in end-expiratory lung volumes, and hence hyperinflation, were observed with optoelectronic plethysmography, especially in patients with more severe airflow obstruction (201). In selected patients pursed-lip breathing was also shown to reduce the oxygen cost of breathing (202). The effect of pursed-lip breathing during exercise has not been thoroughly studied. Adding 5 cm H₂O of positive expiratory pressure (much like the

pressure achieved during pursed-lip breathing) did not alleviate dyspnea during exercise in patients with moderate COPD (204). According to the above-mentioned observations, however, these patients may not have been the best candidates. In clinical practice, patients with severe COPD can be readily trained to employ pursed-lip breathing and the effectiveness can be assessed both symptomatically and by oxygen saturation measurements. When effective, patients generally will adopt this breathing pattern spontaneously at rest, during exercise, or during recovery from exercise.

Adjustments to the training program to deal with central limitations. **INTERVAL TRAINING.** Some patients have significant problems with achieving the target training intensity for the 20- to 30-minute duration recommended by the American College of Sports Medicine (157). Other forms of whole body exercise training have therefore been developed in COPD. During interval training, the 30-minute exercise bout is divided into smaller exercise bouts with appropriate training intensity (e.g., 70–100% of the peak work rate in an incremental test). These bouts may be as long as 2 to 3 minutes (205, 206), or as short as 30 seconds (207, 208). Using 1-minute exercise bouts, Sabapathy and co-workers showed that ventilation was reduced by about 20%, compared with constant work at identical work rate. Consequently training time and total work performed were increased by 63% and 31%, respectively (209). With interval training higher work rates are achieved with lower symptom scores (207). The total exercise time of 30 minutes, however, is respected. Besides its effectiveness in patients with COPD, interval training was shown to be a suitable training modality in congestive heart failure (210) and in healthy elderly subjects (211). Although no randomized trial has shown that interval training is superior to continuous exercise training in rehabilitative exercise programs for patients with COPD (206, 207), these programs have been shown to elicit fewer symptoms during exercise training (207). The latter has been linked to less dynamic hyperinflation during this form of exercise (208, 209). Hence this form of training may be more comfortable in patients with more severe dynamic hyperinflation. It would be worthwhile to compare the effects of interval training in patients with severe airflow obstruction, who might benefit most from this training modality.

STRENGTH (RESISTANCE) TRAINING. Training small muscle groups alleviates the ventilatory burden of exercise training. Hence these muscles, not limited by the central cardiorespiratory limitations, can achieve significantly higher relative work rates (152, 153). Resistance training (weight lifting) is a way of training small muscle groups, and has been applied in several studies in COPD (29, 113, 114, 212–214). Training volume is expressed as the number of repetitions and the weight lifted (generally expressed as a fraction of the maximum weight that can be lifted once, the one-repetition maximum). A typical program might incorporate two or three sets of eight repetitions each at 70% of the one-repetition maximum (114, 115). Studies using resistance training as the only training modality consistently find improved skeletal muscle strength after at least 8 weeks of resistance training. Whether there is transfer toward improved endurance in patients suffering from muscle dysfunction is still controversial. Among healthy elderly subjects, studies showed that resistance training improved skeletal muscle oxidative capacity and endurance (215) and increased capillarization and oxygen flux through the skeletal muscle (216, 217). In COPD, increased whole body endurance, 6-minute walking distance, and $\dot{V}O_2$ peak were also reported after resistance training (29, 114, 115). However, other trials in COPD failed to show convincing effects on whole body endurance when resistance training was added to endurance training (113), or with resistance training as the only intervention (214). Studies looking more closely at muscular changes after

resistance training (muscle biopsy material, or magnetic resonance spectroscopy) are not yet available in COPD. Nevertheless, the enhanced muscle strength reported in all trials that included resistance training is in itself a clinically relevant improvement in these patients, who generally suffer from muscle weakness. Resistance training is currently often used in combination with endurance training. This combination was shown in two studies to have complementary effects (i.e., effect on strength and endurance) (113, 114). Therefore, the combination of resistance and endurance exercise is advised in clinical rehabilitation. It should be acknowledged, however, that the greater improvement in skeletal muscle strength after the addition of resistance training has not been shown to translate into superior benefits in terms of health-related quality of life, or symptomatology.

NEUROMUSCULAR ELECTRICAL STIMULATION. During neuromuscular electrical stimulation, specific muscle groups of interest (generally lower limb) are activated using low-intensity electrical currents. Two trials have evaluated the effectiveness of 6 weeks of neuromuscular electrical stimulation in COPD (218, 219). Both studies showed that in stable patients with severe muscle weakness, transcutaneous neuromuscular electrical stimulation of the lower limb muscles resulted in significant increases in skeletal muscle strength and functional exercise capacity. Peak oxygen uptake increased in one study (218). In this study increased endurance of a constant work rate task was also shown. In more debilitated patients with respiratory failure who were receiving mechanical ventilation and had a history of being bed bound for at least 30 days, Zanotti and coworkers showed a faster functional recovery of patients when neuromuscular electrical stimulation was applied (220). Although preliminary reports (in the literature a total of 24 patients have received the intervention so far) are in favor of using neuromuscular electrical stimulation as a modality of resistance training in the weakest patients, further study is needed to determine its place in conjunction with other interventions. Neuromuscular electrical stimulation, however, is apparently safe, can be conducted at home, has few reported side effects, and is relatively inexpensive.

Ergogenic drugs: growth hormone/insulin-like growth factors and anabolic steroids. A review of the literature reveals that five studies have investigated the effects of anabolic steroids in COPD. Most studies have included only men. Studied drugs are oxandrolone (221), nandrolone decanoate (222, 223), stanozolol (224), and testosterone (214). All studies report an increase in body weight. Anabolic steroids have the benefit over nutritional interventions (222) and appetite stimulants (225) that the increase in body weight is achieved mainly through a gain in lean body mass (221, 222, 224) (in fact, fat mass generally decreases). Gain in lean body mass may be beneficial because increase in lean mass has been associated with decrease in all-cause mortality in patients with severe COPD (226). Four studies were conducted in the context of a pulmonary rehabilitation program consisting of endurance training, strength training, and/or respiratory muscle training (214, 222–224). Anabolic steroids have been found to increase muscle strength (and to enhance the effects of strength training programs) (227), but not to improve exercise endurance (or to enhance the effects of endurance programs) (228, 229). This is not surprising, because anabolic steroids induce muscle hypertrophy and do not induce the capillary increases and increases in aerobic enzymes that would be expected to increase exercise endurance (230).

So far the clinical relevance of anabolic steroid use in unselected patients with COPD admitted to rehabilitation is not clear (231), as no systematic improvements in skeletal muscle force or exercise tolerance were observed (221, 224).

Some comments should be made regarding the limitation of these studies. First, the dose of anabolic steroids that appropri-

ately balances risks and benefits has not been established. This is made more difficult when testosterone analogs are used. These drugs yield decreased levels of circulating testosterone (through pituitary inhibition of gonadotropin secretion) so that blood assays are not generally helpful in assessing the adequacy of dosing. When testosterone is administered, levels within the physiologic range for young men or supraphysiologic levels can be targeted (232). It deserves mention that the dose–response relationship between testosterone dose and anabolic effects (muscle mass gain, strength increase) has been found to be linear well beyond the physiologic range (233). A second issue regards patient selection for this intervention. Hypogonadal men have been found to have substantial benefit of normalization of testosterone levels (234), so it has been proposed that candidates for testosterone supplementation have circulating levels in the low (or at least low normal) range. In fact, many men with severe COPD have testosterone levels in this range (214, 235, 236). Third, as many patients with COPD receive intermittent systemic corticosteroid courses and corticosteroids have been shown to induce muscle dysfunction (119) it has been proposed that anabolic steroids can be used to counteract the effects of corticosteroids (223). In fact, patients receiving oral corticosteroid treatment often have reduced testosterone levels (235). Administration of anabolic steroids may normalize androgen levels and “protect” patients from developing corticosteroid-induced myopathy (120). In a *post hoc* analysis, Creutzberg and coworkers showed that patients receiving oral corticosteroid treatment indeed derived more functional benefit from nandrolone treatment (223). Last, administration of anabolic steroids was shown to be more effective when combined with resistance training (237). In one study, Casaburi and coworkers indeed reported that quadriceps force and fatigability tended to improve more when hypogonadal patients undergoing resistance training received supplemental testosterone (strength, +27 versus +17% in resistance training only; fatigability, +81 versus +45%) (214). These results encourage further larger scale studies in this target population (hypogonadal COPD), to revisit the rather negative image of androgen replacement therapy. At present, however, data showing better preserved long-term results of resistance training in patients with COPD are lacking. It remains unclear whether patients should be maintained on testosterone treatment and/or resistance training to maintain the observed benefits. In healthy subjects testosterone administered for up to 20 weeks seemed to have an acceptable safety profile, but it remains unclear whether these data can be extrapolated to COPD. Ferreira and colleagues administered stanozolol for 6 months to patients with COPD without significant (short-term) side effects (224). Testosterone replacement therapy should not be administered to patients with prostate hypertrophy or a history of prostate cancer. Testosterone increases hematocrit (238), and therefore seems not a treatment option in patients with a hemoglobin concentration greater than $16 \text{ g} \cdot \text{dl}^{-1}$. Because testosterone can cause sodium and water retention, caution is also warranted in patients with renal disease and congestive heart failure.

Administration of recombinant human growth hormone is another pathway to stimulate anabolism in patients with muscle wasting. Although controversial in healthy elderly subjects (239), the rationale for the addition of growth hormone or insulin-like growth factor (the primary mediator of the anabolic action of growth hormone on muscle) to the therapy of patients with COPD can be found in the disturbed anabolic–catabolic balance (240). One study investigated the effectiveness of growth hormone replacement in the context of pulmonary rehabilitation but failed to show an effect on skeletal muscle force or exercise capacity (241). In heart failure, a trial confirmed that systemic growth hormone replacement therapy was safe, but it did not

improve cardiac function or exercise capacity (242). Whether specific groups of patients (e.g., those with blunted insulin-like growth factor-I [IGF-I] response to exercise) may benefit from growth hormone administration or from more advanced strategies to stimulate the growth hormone axis (e.g., locally administered IGF-I [243], recombinant human IGF-I in combination with one of its binding proteins [IGF-binding protein-3 complex; 244], or administration of a growth hormone-releasing factor [245]) should be further investigated. For the present, however, the high cost of growth hormone, the requirement that it be administered by injection, and the lack of evidence of substantial functional benefits do not make it an attractive intervention in the context of a rehabilitation program.

Respiratory muscle training. The respiratory muscles have been specifically targeted for training in COPD. Inspiratory muscle training programs can be conducted at home, using resistive breathing with target inspiratory pressures or target inspiratory flows or with threshold loading devices. Normocapnic hyperpnea has also been applied, albeit less frequently, in COPD (246). When training load is appropriate (controlled and more than 30–40% of maximal inspiratory pressure [$P_{i\max}$]), inspiratory muscle training leads consistently to reductions in dyspnea and improved measures of inspiratory muscle performance (247). Programs are relatively inexpensive, but require regular supervision. Whether inspiratory muscle training translates to increased exercise tolerance and quality of life is much less clear (247). Therefore there has been some debate as to whether inspiratory muscle training should be part of rehabilitation programs in COPD, with evidence-based guidelines concluding that it should not be a routine component (16, 18, 83). Its rationale has been questioned. Although measures of inspiratory muscle strength (indirectly assessed through the pressure these muscles can generate) are clearly reduced in the average patient with COPD, this is in part because the respiratory muscles act at a mechanical disadvantage because of hyperinflation. The respiratory muscles adapt to the chronically imposed increased work of breathing and, unlike the peripheral muscles, the diaphragm of patients with severe COPD has a greater oxidative capacity than is seen in healthy subjects (248–252). In addition, it has been shown that patients with COPD are able to sustain a level of ventilation close to the maximal voluntary ventilation during exercise (159), and contractile fatigue is rarely observed after exercise in stable COPD (253, 254). Hence respiratory muscles, unlike the peripheral muscles, seem not to suffer from “deconditioning” and a training intervention may not be warranted. On the other hand, diaphragm work is increased in COPD, especially during exercise (255, 256). The increased relative work of breathing is illustrated by the high $P_i/P_{i\max}$ ratio at which patients breathe during exercise. $P_i/P_{i\max}$ is related to the perceived dyspnea sensation, especially when the tidal volume/vital capacity ratio is also taken into account (257). It leads to the perception of “unrewarded inspiration,” “inspiratory difficulty,” and “shallow breathing” (257), which is clearly distinct from the complaints seen in healthy subjects during exercise. Hyperinflation places a further burden on the respiratory muscles. Therefore the mechanisms of adaptation of the respiratory muscles may still be insufficient in some patients with COPD (258); if respiratory muscle training increases $P_{i\max}$, it seems reasonable to expect that dyspnea on exertion will be reduced. It is clear that well-designed inspiratory muscle training does improve $P_{i\max}$ and leads to hypertrophy of the Type II fibers in the intercostal muscles, and an increase in the proportion of Type I fibers (259). In patients with inspiratory muscle weakness it can be speculated that this may transform into functional benefits. This has indeed been confirmed, to some extent, by a systematic literature review (247). Therefore, in patients with inspiratory muscle weakness, the prescription of

strictly standardized inspiratory muscle training may be justified as an adjunct to exercise training (64, 246, 260), with the aim of improving exercise-induced symptoms of dyspnea. It should be noted, however, that whole body exercise training, by itself, has improved inspiratory muscle force in some studies (33, 39). Inspiratory muscle training as a stand-alone treatment is clearly inferior to general exercise training in COPD if the goal is to improve function or health-related quality of life. As to the latter outcome, no study has shown that the addition of inspiratory muscle training to a whole body exercise training program yielded significant benefits. In addition, one study investigating the long-term effects of inspiratory muscle training suggested that the effects obtained from the inspiratory muscle training may—as would be expected from the responses to exercise training—wear off rapidly when the inspiratory muscle training is discontinued (261).

Should Exercise Training Be Prescribed for All Patients with COPD?

As a group, patients with COPD clearly benefit from exercise training programs. For a long time, patients with severe lung disease were believed not to be good candidates for exercise training programs (13). Later, lactic acid production was seen as a prerequisite to achieve an appropriate training response (34), as reductions in lactic acid were coupled to significant reductions of minute ventilation for a given work rate and oxygen consumption. However, more recent studies in which high-intensity training stimuli were applied clearly showed that patients with FEV_1 below 40% of the predicted values or those with hypercapnia (GOLD Stage IV) should not be excluded from exercise training (37, 37, 157, 262, 263). In a large study by Berry and coworkers (166), patients with mild, moderate, and severe COPD showed the same proportional improvement in exercise tolerance after pulmonary rehabilitation. Further, in patients not manifesting significant lactic acid accumulation during heavy exercise, significant physiologic training effects were confirmed (37, 154). Despite the overall success of pulmonary rehabilitation across disease severity stages, a significant number of patients (roughly 30%) have no significant improvement in exercise capacity (264). When increases in peak oxygen consumption are used as the only measure to define response to exercise training, as many as 50% of the patients may be nonresponders (165). This is clearly more than is observed after carefully monitored endurance training in healthy subjects (265). The question concerning why a minority of patients is not responding adequately to an exercise training stimulus is intriguing, and no final answer can yet be given.

Clinical data suggest that patients with more pronounced muscle weakness and somewhat less impaired ventilatory reserve may be better candidates for exercise training programs (264). These data concur with others showing that patients with a poor walking distance—which is correlated with muscle weakness in COPD—and greater breathing reserve are the best candidates for exercise training (266). The variance explained by the proposed model, however, is too low to allow for appropriate patient selection. Older age (267), severe lung function impairment (166), the presence of hypercapnia (262), and current smoking (268) seem not to be valid exclusion criteria for pulmonary rehabilitation.

It should be acknowledged, however, that failure to respond to an exercise program, in terms of physiological benefits, does not mean that the rehabilitation of the patient should be regarded as unsuccessful. In one of the above-mentioned studies the so-called nonresponders showed a clinically relevant improvement in health-related quality of life (264). Identifying patients nonresponsive to exercise training should therefore not necessarily lead to a reduction of patients referred to comprehen-

sive pulmonary rehabilitation. It may, however, lead to a better program design. Other interventions that are integral parts of rehabilitation (described below) improve individual patients in important respects outside of the context of exercise physiology.

OTHER COMPONENTS OF PULMONARY REHABILITATION PROGRAMS

A European Respiratory Society task force on pulmonary rehabilitation recommended that rehabilitation programs should be flexible, patient tailored, and include a variety of components besides exercise, depending on resources available and taking into account patient preferences and available evidence (19). The American Thoracic Society in its 1999 guideline on pulmonary rehabilitation (9) and the British Thoracic Society guidelines (18) also advocate the multidisciplinary nature of pulmonary rehabilitation programs with attention to educational, psychosocial, and behavioral interventions.

Improving Education and Self-management

When delivered outside of the context of a comprehensive rehabilitation program, the benefit of educational sessions is considered only minimal (27, 63, 83, 269, 270). Education aiming only to improve patient knowledge about the disease does not improve health status (269, 271). Educational programs improving “self-management” of patients may be more successful. Self-management is a form of education aiming at teaching skills to optimally control the disease, achieve behavioral change, and improve coping with the disease. Although a meta-analysis (272) and a trial in “low-risk” patients (273) showed no significant effects of these interventions, another trial including patients with more severe disease at risk for readmission after hospitalization was successful (78). Because the number of sessions is generally limited, these interventions were also shown to be cost-effective (274) and can be incorporated relatively easily in rehabilitation programs.

Several points can be addressed in educational interventions. Because up to 75% of patients may have difficulties in understanding how and when to take their inhalation medication (275), this may be a particularly useful target for educational sessions. In the context of a pulmonary rehabilitation program, education was shown to improve adherence to medication (276). Another important aspect in education programs concerns teaching patients to deal with exacerbations, using so-called action plans. These may be of particular benefit to patients with a history of being admitted to the hospital (78). With specific training, patients may adopt these action plans rapidly, and deal more appropriately with acute exacerbations (277). Education sessions may be offered to individual patients or small groups of patients by all members of the rehabilitation team.

Psychosocial Support: Rationale and Practical Implication

The incidence of depression in patients with COPD is about 2.5-fold higher compared with the general population (278). Pulmonary rehabilitation programs including psychological interventions improve these mood disturbances more than those consisting of exercise training only (279). Hence psychological counseling may be of benefit to those patients selected for pulmonary rehabilitation and presenting with symptoms of anxiety and depression (some 20–40% of patients [65–67]). In addition, spouses of patients with COPD were reported to suffer from depressive symptoms and stress (280–282), and may require the attention of the rehabilitation team. Psychologists are the best placed health care providers to provide treatment of patients with significant anxiety or depressive symptoms and also to optimize and discuss smoking cessation strategies with patients con-

tinuing to smoke. Smoking cessation counseling, education, and nicotine replacement therapy (or treatment with antidepressants such as bupropion and nortriptyline) maximize the chances for sustained smoking cessation (57). Some studies of rehabilitative therapy have excluded current smokers (49), but the rationale to do so is lacking. Smokers, however, are more likely to decline invitations to take part in rehabilitation programs (66, 283). Indeed, smokers are generally less adherent than ex-smokers (284). Nevertheless, a significant number of patients are current smokers at inclusion in pulmonary rehabilitation programs (27, 66, 285) that do not explicitly exclude smokers.

Improving Activities of Daily Living: Role for Occupational Therapy

Transforming the achieved physiological improvements into benefits that are relevant to patients is critical to the success of pulmonary rehabilitation. This integration may be facilitated by occupational therapists. Programs including specific occupational therapy interventions showed significant benefits on reported activities of daily living (51). The intervention by the occupational therapist may consist of functional training in activities of daily living, energy-conserving strategies, and the use of wheeled walking aids. The latter have been shown to result in increased functional autonomy in patients with COPD, especially in the patients with more severe disease (286, 287), through an increase in ventilatory capacity and walking efficiency (288). The prescription of rollators adds to the incremental cost of pulmonary rehabilitation (289). The latter authors report that the prescription of assistive devices (mainly rollators) led to an incremental cost of 133 U.S. dollars (1989 U.S. dollars). Only one, relatively small study has addressed this aspect to some extent in a prospective study (290). This study suggests that independence in activities of daily living is improved only when patients receive occupational therapy as part of their rehabilitation program. Although promising, the design of this single study (nonrandomized) and the fact that the results pertain to a short inpatient rehabilitation program do not allow us to draw firm conclusions.

Nutritional Interventions

Patients with COPD are often underweight (291). The loss of fat-free mass is most closely related to morbidity (291, 292) and mortality (293). Nutritional interventions as a treatment of weight loss are, in general, not effective in outpatients (294). However, one study showed that when patients gain more than 2 kg of body weight, survival is significantly improved (226). In addition, an increase of 1 body mass index unit was also associated with improved survival in underweight patients (293). It should be noted that the use of body mass index as an indicator of “underweight” may be misleading, as many patients with a normal body mass index have a low fat-free mass (295). The latter factor is related to muscle wasting (110), which is even more closely related to mortality risk (93). Nutritional specialists involved in pulmonary rehabilitation should balance the calorie intake of patients with the energy requirements of patients, taking into account that patients with COPD have increased resting energy expenditure compared with age-matched subjects (296). Patients nonresponsive to nutritional interventions are characterized by more systemic inflammation, older age, and low dietary intake (297). Exercise training or a more active lifestyle (106) may induce a negative protein balance because of the increased energy expenditure. In these patients, nutritional supplements may be beneficial and may even lead to a somewhat greater training effect in terms of functional status (298, 299) and body composition and health-related quality of life (299),

but the data currently available remain insufficient to make strong recommendations regarding the use of nutritional supplements. At present prospective randomized trials supporting the use of nutritional interventions unequivocally are missing. Nevertheless, in selected patients with insufficient calorie (in particular, protein) intake, nutritional supplements may be helpful to meet prescribed calorie intake. Further research could focus on the long-term nutritional advice that should be given to patients. There is currently no evidence that nutritional supplements further increase the duration of benefits of exercise training. In addition, it should be recognized that nutritional supplementation may deter patients from consuming their regular meals, hence resulting in less rather than more calorie intake, jeopardizing any positive effect of nutritional supplements (300). Another new avenue for future research is the potential impact of supplementing specific nutrients and amino acids that may play a role in the oxidant–antioxidant balance, or are specific building blocks of key proteins (128, 301, 302). The clinical implications and precise prescription regimens of these so-called nutraceuticals in COPD are, however, currently unknown.

Obviously, in obese patients (some 14% of the patients admitted to the rehabilitation program in Leuven, Belgium), the focus of the dietary intervention may be weight loss rather than weight gain. The challenge here is to not lose fat-free mass.

EVALUATION BEFORE, DURING, AND AFTER PULMONARY REHABILITATION

It is outside the scope of the present state of the art review to give an exhaustive summary of all available measurements that can be performed before a patient can be enrolled in a rehabilitation program (*see* Table E1 in the online supplement for a summary of available tests). Strong evidence promoting tests as essential to pulmonary rehabilitation is not available. Hence the choice of tests before starting rehabilitation and at follow-up visits should be driven by ensuring program safety (e.g., maximal ergometry with gas exchange and ECG monitoring before starting the program [299]), and availability. Patients selected to be screened for pulmonary rehabilitation should be motivated to be enrolled in a rehabilitation program, and the participants should understand the engagement (19). To individually tailor the program it is important to have a multidisciplinary assessment of the patients. On the basis of this assessment, the program and its components can be established for each candidate. Assessment of disease severity is generally obtained from lung function measurement (303), and can be accompanied by a measure of symptoms, body mass index, and functional exercise tolerance (1). To assess the indication for participation in a pulmonary rehabilitation program reduced health-related quality of life and impaired exercise tolerance may identify potential candidates. A maximal exercise test is recommended to assess safety of exercise and the factors contributing to exercise limitation (304) and to design the exercise program. To further optimize the exercise training programs in patients with severe ventilatory limitation other assessments may be helpful. These include skeletal muscle strength tests (i.e., quadriceps and/or upper limb) to investigate the indication for resistance training (115). In patients with impaired inspiratory muscle force, clinicians could consider inspiratory muscle training. Hence assessment of the inspiratory muscles may be helpful to guide this decision (247).

To complement the exercise training program with other interventions such as specific education, psychological counseling, occupational therapy, or nutritional counseling specific and validated questionnaires (Table E1) can be applied. It is important to mention that questionnaires are generally validated at a “group” level, but they may lack precision in individual patients.

At the individual patient level, however, the use of questionnaires may standardize a first contact with a patient and may highlight problems in the psychosocial field or in activities of daily living. Although assessment of body composition can be done by dual energy X-ray absorptiometry scanning (305), data on body composition and fat-free mass are currently often obtained from bioelectrical impedance. The latter technique is valid only if it is properly standardized. Guidelines for the standardization have been developed (306) and the technique has been validated in stable COPD (307).

Depending on its complexity, the evaluation of the program outcome should be chosen. As a minimum, the effects should be assessed in terms of exercise tolerance. As mentioned above, field exercise tests, such as the 6-minute walking distance or the shuttle walking test, as well as submaximal constant work rate tests are appropriate outcome measures. Besides these tests measures of health-related quality of life may be useful to evaluate and compare the overall effectiveness of the program. The effects of a rehabilitation program should on average exceed the minimally clinically important difference (0.5 point per question for the Chronic Respiratory Disease Questionnaire [308] and 4 points for the St. George’s Respiratory Questionnaire [309]). The relatively large confidence intervals around these minimally clinically important differences (e.g., for the total score on the Chronic Respiratory Disease Questionnaire, 0.4 to 0.7 point per question; and for the St. George’s Respiratory Questionnaire, 1.6 to 6.4 points per question [309]) preclude judgment of clinically relevant changes in individual patients from these questionnaires. When other disciplines are involved in the rehabilitation process of individual patients, more specific evaluations may be required. Evaluation after the program also helps clinicians to design the appropriate follow-up strategy for individual patients.

ORGANIZING PULMONARY REHABILITATION PROGRAMS

Where to Organize Rehabilitation Programs

Rehabilitation programs can be organized as inpatient programs, outpatient programs (in rehabilitation centers, or in the community), or as home-based programs. The choice of a program for an individual patient will be based on availability, reimbursement, patient preference, and expected efficacy. When several options are available in the proximity of a patient, cost-effectiveness may drive the clinician’s choice. Programs involving highly trained general practitioners, primary care nurses, and physical therapists (56, 60) or hospital-directed home care or community-based programs may be less expensive compared with inpatient programs or outpatient hospital-based programs (60). However, home-based or community-based programs may be less successful, especially among patients with more severe COPD (31, 55). It seems likely that compliance will not be as good and that the benefits of group exercise are lost (310). In addition, home care settings reported in clinical trials may not be representative of the average home care setting program. Some “home care” programs reported in the literature have featured frequent home visits by rehabilitation professionals, which may not be realistically achieved in many health care settings or regions.

Inpatient programs are generally much more expensive compared with other settings (289). Hence, this treatment option seems justified only for a small subgroup of patients with very severe disease, not able to leave the house. Among these patients, the alternative of home-based rehabilitation was shown to be ineffective (31, 55). In one small study of patients hospitalized with acute exacerbations (311), a combination of a short inpatient program and home-based exercises (312) showed long-term improved functional exercise performance. In many countries, however, incentives are given to keep hospital stay as short

as possible. Discharge should be quick and well planned. Studies have transferred part of the acute hospitalization to the home setting (313, 314). Inpatient programs may therefore not be the preferred setting of rehabilitation.

With the present state of knowledge, multidisciplinary outpatient rehabilitation may offer rehabilitation with relatively secure improvements in clinically relevant end points such as functionality, health-related quality of life, and use of health care resources at an acceptable cost. These programs can be offered to patients able to be transported to the center and living within a reasonable distance from the center. It is important that the effects seen in the context of a clinical trial were reproduced in other rehabilitation centers in a larger region (151, 315), suggesting that results obtained in clinical trials can be extrapolated to clinical practice. For patients living farther away from the center, inpatient rehabilitation can be provided, at a much higher cost. Alternatively, home rehabilitation can be offered, at a higher risk of poor effectiveness (31, 55), unless a thoroughly prepared team of primary health care providers is available to provide regular home visits (46, 316).

Strategies to Maintain the Effects of Pulmonary Rehabilitation

There is currently debate concerning the follow-up care that should be provided to patients with COPD after graduation from pulmonary rehabilitation programs. After a 6-month program, two groups of investigators showed prolonged (more than 1 year after stopping the program) benefits without rigorous maintenance programs (33, 52). After shorter programs, more intensive follow-up care seems important. Usual care (27), regular telephone support, and once-monthly follow-up visits (145, 317) were insufficient to maintain benefits of an 8-week outpatient or 6-week inpatient rehabilitation program. One study showed that compliance with maintenance home exercise therapy was relatively low (317). Continued three-times weekly outpatient rehabilitation up to 15 months after graduation was superior to exercise advice during the follow-up (149). Repetition of short programs were found to be an ineffective treatment option, although in patients with frequent exacerbations there is a further reduction in exacerbation rate when the program is repeated (75). We currently advise once-weekly high-intensity maintenance exercise training sessions, preferably supervised by a qualified physiotherapist (318).

SUGGESTIONS FOR FURTHER RESEARCH

Optimal Combination of Program Length and Proper Maintenance in COPD

In the literature, programs vary from as short as few weeks to as long as 1 year. Despite the lack of a clear dose-response relation in the immediate outcomes, there is consensus that programs shorter than 6 to 8 weeks are less effective (16, 18). More research is clearly needed to investigate how long programs should be and how frequently sessions should be held to result in maximal (rather than merely statistically significant) effects. In addition, the somewhat disappointing results of "remote" (i.e., home programs, with distant telephone support of the rehabilitation team) maintenance programs (145) should prompt further research to investigate more appropriate strategies to maintain training effects as long as possible. The potential of programs supervised through telemedicine is an interesting field of research, especially because many Medicaid organizations in the United States seem in favor of reimbursing telemedicine-oriented programs (319).

New Strategies to Improve Rehabilitation Outcome in COPD

Selection of the optimal candidate for exercise training and the other interventions that are part of the pulmonary rehabilitation process is clearly a focal point for further research. The decision to enroll all patients in interventions other than exercise training currently lacks solid evidence. It is, however, clear that several interventions may be of benefit to carefully selected patients and progress has been made in defining these interventions. Studies suggest that supplemental oxygen and anabolic steroids may become potentially useful adjuncts in selected patients. Previous studies investigating the effects of these supplements had been largely negative, but perhaps targeted the wrong population, were too general in their inclusion criteria, or did not apply an optimal rehabilitation strategy. Consistent with these thoughts, it might be speculated that nutritional interventions or appetite stimulants will be beneficial in specific subgroups of patients. Similarly, erythropoietin might be offered to the minority of patients that are anemic. Surprisingly, on this last topic, few data are currently available on the prevalence of anemia in COPD. Preliminary reports suggest, however, that up to 16% of patients with COPD may have hemoglobin levels below 12 g/dl (320). Increasing hemoglobin improves oxygen delivery to the exercising muscle and enhances exercise capacity in patients with renal disease (321) and also in patients with congestive heart failure (322). Schönhofer and coworkers showed that blood transfusion, which normalized hemoglobin levels in anemic patients with COPD, significantly reduced resting ventilation and work of breathing (323). An intriguing observation in one of the above-mentioned studies (223) was the positive association of increase in hematocrit and increase in peak work rate after training. In the latter study, nandrolone decanoate induced small but significant increases in hemoglobin content. Increased hemoglobin content was also reported in another trial investigating the effect of testosterone administration (324). Although speculative, there is a rationale to study the effect of erythropoietin treatment in anemic patients during pulmonary rehabilitation. The latter is even more interesting because erythropoietin has been shown to act as a protective cytokine to hypoxia-induced damage (325), and was shown to exert antiinflammatory properties (326).

Some patients, responding to exercise with an inappropriate downregulation of free radical scavengers (118), may benefit from antioxidant therapy (e.g., vitamin E or *N*-acetylcysteine). As in animal models (327), pretreatment of patients with *N*-acetylcysteine indeed increased endurance time, and avoided disturbances of the oxidant balance (328). Whether these findings may be applied in exercise training programs remains speculative. Alternatively, training programs should be further modified to avoid exhaustive muscle contractions that lead to oxidative damage (117).

The effect of the combination of bronchodilating drugs with pulmonary rehabilitation programs also merits further study. Bronchodilators have been shown to increase ventilatory capacity and exercise capacity (329, 330). A study identified that a subgroup of patients improving exercise capacity after optimal bronchodilatation had less contractile quadriceps fatigue when exercise was performed without bronchodilators (86). In contrast, those not improving exercise capacity after successful bronchodilatation were shown to have more contractile fatigue. Another study showed that the benefits of rehabilitative exercise were amplified when participants received the long-acting anticholinergic agent tiotropium (324). It seems plausible that the relatively modest improvements in health-related quality of life and exercise tolerance seen when bronchodilators are adminis-

tered will be amplified when combined with pulmonary rehabilitation.

It is clear that all the above-mentioned interventions may not be of benefit to the “average patient.” In carefully selected subpopulations, greater benefits of rehabilitation programs are to be expected; perhaps other interventions may be dropped as valid treatment options. This should lead to further individualization of rehabilitation programs. Costs and benefits of these specific interventions should be carefully considered.

Last, the current state of the art could address only the short-term effects of these “new strategies” to enhance the outcome of rehabilitation in COPD. However, long-term improvement of patients is obviously the ultimate goal. It remains unclear which of the above-mentioned interventions could play a role in the long-term management of patients with COPD. Studies building on the short-term success of some of the interventions, looking at long-term outcome and safety (e.g., for testosterone replacement therapy), are needed.

SUMMARY

Careful review of the currently available literature clearly shows the benefit of pulmonary rehabilitation in COPD. More evidence has become available concerning the magnitude and mechanisms of the obtained benefits. In addition, it has become clearer that patients at both ends of the disease spectrum can be good candidates for properly designed rehabilitation programs. We attempted to summarize the available evidence and added some clinical practice advice in our attempt to define the present state of the art.

Rehabilitation programs should be part of a larger decision tree including optimal medical therapy and nonpharmacologic treatment options, such as surgery, not discussed in the present review. Future research in rehabilitation should focus on further fine-tuning the rehabilitation programs for individual patients. However, the overwhelming evidence currently available is clearly sufficient for regulatory authorities to conclude that there is an evidence base for reimbursement for pulmonary rehabilitation. The current programs improve health-related quality of life and exercise tolerance to a greater extent than any other intervention currently available for patients with COPD. Pulmonary rehabilitation reduces health care use in patients with excessive use of health care resources. Tailoring programs to make these benefits as large and as long-lasting as possible remains a major challenge.

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References

- 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.
- Oga T, Nishimura K, Tsukino M, Sato S, Hagiuro 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* 2003;167:544–549.
- Hamilton AL, Killian KJ, Summers E, Jones NL. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. *Chest* 1996;110:1255–1263.
- 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.
- Mahler DA, Harver A. A factor analysis of dyspnea ratings, respiratory muscle strength, and lung function in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;145:467–470.
- Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, Cornelissen PJ. Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002;19:209–216.
- Ikeda A, Nishimura K, Koyama H, Tsukino M, Mishima M, Izumi T. Dose response study of ipratropium bromide aerosol on maximum exercise performance in stable patients with chronic obstructive pulmonary disease. *Thorax* 1996;51:48–53.
- Weiner P, Magadle R, Berar-Yanay N, Davidovich A, Weiner M. The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD. *Chest* 2000;118:672–678.
- American Thoracic Society. Pulmonary rehabilitation: 1999. *Am J Respir Crit Care Med* 1999;159:1666–1682.
- McGavin CR, Gupta SP, Lloyd EL, McHardy GJ. Physical rehabilitation for the chronic bronchitic: results of a controlled trial of exercises in the home. *Thorax* 1977;32:307–311.
- Degre S, Sergysels R, Messin R, Vandermoten P, Salhadin P, Denolin H, De Coster A. Hemodynamic responses to physical training in patients with chronic lung disease. *Am Rev Respir Dis* 1974;110:395–402.
- Casaburi R, Petty TL. Principles and practice of pulmonary rehabilitation. Philadelphia, PA: W.B. Saunders; 1993.
- Belman MJ, Kendregan BA. Exercise training fails to increase skeletal muscle enzymes in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1981;123:256–261.
- 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.
- Fabbri LM, Hurd SS. Global strategy for the diagnosis, management and prevention of COPD: 2003 update. *Eur Respir J* 2003;22:1–2.
- Pulmonary Rehabilitation Guidelines Panel, American College of Chest Physicians and American Association of Cardiovascular and Pulmonary Rehabilitation. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. *Chest* 1997;112:1363–1396.
- Donner CF, Decramer M. Pulmonary rehabilitation. *Eur Respir Monogr* 2000;13:1–200.
- British Thoracic Society, Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. *Thorax* 2001;56:827–834.
- 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.
- National Emphysema Treatment Trial Research Group. Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med* 2003;348:2092–2102.
- 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.
- Gelb AF, McKenna RJ Jr, Brenner M, Epstein JD, Zamel N. Lung function 5 years after lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 2001;163:1562–1566.
- Fahy BF. Pulmonary rehabilitation for chronic obstructive pulmonary disease: a scientific and political agenda. *Respir Care* 2004;49:28–38.
- Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. *BMJ* 1994;309:1351–1355.
- 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.
- Reardon J, Awad E, Normandin E, Vale F, Clark B, ZuWallack RL. The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. *Chest* 1994;105:1046–1052.
- 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.
- Weiner P, Azgad Y, Ganam R. Inspiratory muscle training combined with general exercise reconditioning in patients with COPD. *Chest* 1992;102:1351–1356.
- Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. *Thorax* 1992;47:70–75.
- 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.
31. Cambach W, Chadwick-Straver RV, Wagenaar RC, van Keimpema AR, Kemper HC. The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. *Eur Respir J* 1997;10:104–113.
 32. Puente-Maestu L, SantaCruz A, Vargas T, Martinez-Abad Y, Whipp BJ. Effects of training on the tolerance to high-intensity exercise in patients with severe COPD. *Respiration (Herrlisheim)* 2003;70:367–370.
 33. 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.
 34. 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.
 35. 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.
 36. Gigliotti F, Coli C, Bianchi R, Romagnoli I, Lanini B, Binazzi B, Scano G. Exercise training improves exertional dyspnea in patients with COPD: evidence of the role of mechanical factors. *Chest* 2003;123:1794–1802.
 37. 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.
 38. Porszasz J, Emtner M, Whipp BJ, Goto S, Somfay A, Casaburi R. Endurance training decreases exercise-induced dynamic hyperinflation in patients with COPD. *Eur Respir J* 2003;22:205s.
 39. 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.
 40. Harver A, Mahler DA, Daubenspeck JA. Targeted inspiratory muscle training improves respiratory muscle function and reduces dyspnea in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1989;111:117–124.
 41. Lisboa C, Munoz V, Beroiza T, Leiva A, Cruz E. Inspiratory muscle training in chronic airflow limitation: comparison of two different training loads with a threshold device. *Eur Respir J* 1994;7:1266–1274.
 42. 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.
 43. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;155:1278–1282.
 44. Booker HA. Exercise training and breathing control in patients with chronic airflow limitation. *Physiotherapy* 1984;70:258–260.
 45. 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.
 46. Wijkstra PJ, van Altena R, Kraan J, Otten V, Postma DS, Koeter GH. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. *Eur Respir J* 1994;7:269–273.
 47. Cockcroft AE, Saunders MJ, Berry G. Randomised controlled trial of rehabilitation in chronic respiratory disability. *Thorax* 1981;36:200–203.
 48. Engström 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.
 49. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994;344:1394–1397.
 50. 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.
 51. Bendstrup KE, Ingemann JJ, Holm S, Bengtsson B. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2801–2806.
 52. 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.
 53. Oga T, Nishimura K, Tsukino M, Hajiro T, Ikeda A, Izumi T. The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease: a comparison of three different exercise tests. *Am J Respir Crit Care Med* 2000;161:1897–1901.
 54. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Ionescu AA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362–368.
 55. 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.
 56. Wijkstra PJ, Ten Vergert EM, van Altena R, Otten V, Kraan J, Postma DS, Koeter GH. Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50:824–828.
 57. Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA* 2003;290:2301–2312.
 58. 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.
 59. Puente-Maestu L, Sanz ML, Sanz P, Cubillo JM, Mayol J, Casaburi R. Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2000;15:517–525.
 60. 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.
 61. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1185–1189.
 62. Kozora E, Tran ZV, Make B. Neurobehavioral improvement after brief rehabilitation in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2002;22:426–430.
 63. 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.
 64. Dekhuijzen PN, Beek MML, Folgering HT, van Herwaarden CL. Psychological changes during pulmonary rehabilitation and target-flow inspiratory muscle training in COPD patients with a ventilatory limitation during exercise. *Int J Rehabil Res* 1990;13:109–117.
 65. Withers NJ, Rudkin ST, White RJ. Anxiety and depression in severe chronic obstructive pulmonary disease: the effects of pulmonary rehabilitation. *J Cardiopulm Rehabil* 1999;19:362–365.
 66. 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.
 67. Trappenburg J, Vandenbrouck N, Spruit M, Coosemans I, Stans L, Delva D, Troosters T, Gosselink R, Decramer M. Psychosocial determinants of effectiveness of pulmonary rehabilitation in COPD patients. *Eur Respir J* 2002;20:183s.
 68. Light RW, Merrill EJ, Despars JA, Gordon GH, Mutalipassi LR. Prevalence of depression and anxiety in patients with COPD: relationship to functional capacity. *Chest* 1985;87:35–38.
 69. Blumenthal JA, Babyak MA, Moore KA, Craighead WE, Herman S, Khatri P, Waugh R, Napolitano MA, Forman LM, Appelbaum M, et al. Effects of exercise training on older patients with major depression. *Arch Intern Med* 1999;159:2349–2356.
 70. Engström CP, Persson LO, Larsson S, Sullivan M. Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *Eur Respir J* 2001;18:69–76.
 71. 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.
 72. Young P, Dewse M, Fergusson W, Kolbe J. Improvements in outcomes for chronic obstructive pulmonary disease (COPD) attributable to a hospital-based respiratory rehabilitation programme. *Aust N Z J Med* 1999;29:59–65.
 73. Stewart DG, Drake DF, Robertson C, Marwitz JH, Kreutzer JS, Cifu

- DX. Benefits of an inpatient pulmonary rehabilitation program: a prospective analysis. *Arch Phys Med Rehabil* 2001;82:347–352.
74. Bowen JB, Thrall RS, ZuWallack RL, Votto JJ. Long-term benefits of short-stay inpatient pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis* 1999;54:189–192.
 75. 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.
 76. Croxton TL, Weinmann GG, Senior RM, Wise RA, Crapo JD, Buist AS. Clinical research in chronic obstructive pulmonary disease: needs and opportunities. *Am J Respir Crit Care Med* 2003;167:1142–1149.
 77. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779–784.
 78. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, Renzi P, Nault D, Borycki E, Schwartzman K, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003;163:585–591.
 79. Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–852.
 80. Troosters T, Gosselink R, De Paepe C, Decramer M. Pulmonary rehabilitation improves survival in COPD patients with a recent severe acute exacerbation. *Am J Respir Crit Care Med* 2002;165:A16.
 81. Garcia-Aymerich J, Ferrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;58:100–105.
 82. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Felez M, Khalaf A, Marrades RM, Monso E, Serra-Batlles J, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:680–685.
 83. Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview. *Chest* 1997;111:1077–1088.
 84. O'Donnell DE, D'Arsigny C, Fitzpatrick M, Webb KA. Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. *Am J Respir Crit Care Med* 2002;166:663–668.
 85. Barbera JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* 2003;21:892–905.
 86. 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.
 87. Casaburi R. Limitation to exercise tolerance in chronic obstructive pulmonary disease: look to the muscles of ambulation. *Am J Respir Crit Care Med* 2003;168:409–410.
 88. Debigare R, Cote CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease: clinical relevance and mechanisms. *Am J Respir Crit Care Med* 2001;164:1712–1717.
 89. 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:S1–40.
 90. Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;168:10–48.
 91. Decramer M, Gosselink R, Troosters T, Verschuere M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur Respir J* 1997;10:417–423.
 92. Decramer M, Gosselink R, Troosters T, Schepers R. Peripheral muscle force is a determinant of survival in COPD. *Eur Respir J* 1998;12:261S.
 93. Marquis K, Debigare R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, Maltais F. 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.
 94. Maltais F, Simard AA, Simard C, Jobin J, Desgagnés 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.
 95. Maltais F, LeBlanc P, Whittom F, Simard C, Marquis K, Belanger M, Breton MJ, Jobin J. Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. *Thorax* 2000;55:848–853.
 96. 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.
 97. 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.
 98. 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.
 99. Gosker HR, van Mameren H, van Dijk PJ, Engelen MP, van der Vusse GJ, Wouters EF, Schols AM. Skeletal muscle fibre-type shifting and metabolic profile in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:617–625.
 100. Allaire J, Maltais F, Doyon JF, Noel M, LeBlanc P, Carrier G, Simard C, Jobin J. Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* 2004;59:673–678.
 101. Mador MJ, Deniz O, Aggarwal A, Kufel TJ. Quadriceps fatigability after single muscle exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;168:102–108.
 102. Saey D, Michaud A, Couillard A, Cote CH, Mador MJ, LeBlanc P, Jobin J, Maltais F. Contractile fatigue, muscle morphometry, and blood lactate in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;171:1109–1115.
 103. Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardio-pulm Rehabil* 2000;20:353–360.
 104. Pita F, Troosters T, Spruit M, Wyffels B, Schuffelers K, Decramer M, Gosselink R. Characteristics and determinants of activities of daily living in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;171:972–977.
 105. Schönhofer B, Ardes P, Geibel M, Kohler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. *Eur Respir J* 1997;10:2814–2819.
 106. 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.
 107. Casaburi R. Deconditioning. In: Fishman AP, editor. Pulmonary rehabilitation. New York: Marcel Dekker; 1996. pp. 213–230.
 108. 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.
 109. 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.
 110. Engelen MP, Schols AM, Does JD, Wouters EF. Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2000;71:733–738.
 111. Debigare R, Cote CH, Hould FS, LeBlanc P, Maltais F. *In vitro* and *in vivo* contractile properties of the vastus lateralis muscle in males with COPD. *Eur Respir J* 2003;21:273–278.
 112. 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.
 113. 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.
 114. 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.
 115. 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.
 116. Mador MJ, Kufel TJ, Pineda LA, Steinwald A, Aggarwal A, Upadhyay AM, Khan MA. Effect of pulmonary rehabilitation on quadriceps fatigability during exercise. *Am J Respir Crit Care Med* 2001;163:930–935.
 117. 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.
118. 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.
 119. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994;150:11-16.
 120. Decramer M, de Bock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153:1958-1964.
 121. Schols AM, Wesseling G, Kester AD, de Vries G, Mostert R, Slangen J, Wouters EF. Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. *Eur Respir J* 2001;17:337-342.
 122. Hopkinson NS, Man WD, Dayer MJ, Ross ET, Nickol AH, Hart N, Moxham J, Polkey MI. Acute effect of oral steroids on muscle function in chronic obstructive pulmonary disease. *Eur Respir J* 2004;24:137-142.
 123. Spruit M, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, Bouillon R, Decramer M. Muscle force during an acute exacerbation in hospitalised COPD patients and its relationship with CXCL8 and IGF-1. *Thorax* 2003;58:752-756.
 124. 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.
 125. 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.
 126. Sahin U, Unlu M, Ozguner F, Sutcu R, Akkaya A, Delibas N. Lipid peroxidation and glutathione peroxidase activity in chronic obstructive pulmonary disease exacerbation: prognostic value of malondialdehyde. *J Basic Clin Physiol Pharmacol* 2001;12:59-68.
 127. Rahman I, Skwarska E, MacNee W. Attenuation of oxidant/antioxidant imbalance during treatment of exacerbations of chronic obstructive pulmonary disease. *Thorax* 1997;52:565-568.
 128. 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.
 129. Barreiro E, Gea J, Corominas JM, Hussain SN. Nitric oxide synthases and protein oxidation in the quadriceps femoris of patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2003;29:771-778.
 130. Allaire J, Maltais F, LeBlanc P, Simard PM, Whittom F, Doyon JF, Simard C, Jobin J. Lipofuscin accumulation in the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Muscle Nerve* 2002;25:383-389.
 131. Heunks LM, Vina J, van Herwaarden CL, Folgering HT, Gimeno A, Dekhuijzen PN. Xanthine oxidase is involved in exercise-induced oxidative stress in chronic obstructive pulmonary disease. *Am J Physiol* 1999;277:R1697-R1704.
 132. Mitsui T, Azuma H, Nagasawa M, Iuchi T, Akaike M, Odomi M, Matsumoto T. Chronic corticosteroid administration causes mitochondrial dysfunction in skeletal muscle. *J Neurol* 2002;249:1004-1009.
 133. Lawler JM, Song W, Demaree SR. Hindlimb unloading increases oxidative stress and disrupts antioxidant capacity in skeletal muscle. *Free Radic Biol Med* 2003;35:9-16.
 134. Ennezat PV, Malendowicz SL, Testa M, Colombo PC, Cohen-Solal A, Evans T, LeJemtel TH. Physical training in patients with chronic heart failure enhances the expression of genes encoding antioxidative enzymes. *J Am Coll Cardiol* 2001;38:194-198.
 135. Rabinovich RA, Mayer AM, Ardite E, Vilaro J, Barbera JA, Rodriguez-Roisin R, Fernandez-Checa JC, Roca J. Skeletal muscle redox capacity is reduced in COPD patients with low BMI [abstract]. *Am J Respir Crit Care Med* 2003;167:A73.
 136. Hopkinson NS, Nickol AH, Payne J, Hawe E, Man WD, Moxham J, Montgomery H, Polkey MI. Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:395-399.
 137. Zhang B, Tanaka H, Shono N, Miura S, Kiyonaga A, Shindo M, Saku K. The I allele of the angiotensin-converting enzyme gene is associated with an increased percentage of slow-twitch Type I fibers in human skeletal muscle. *Clin Genet* 2003;63:139-144.
 138. Collins M, Xenophontos SL, Cariolou MA, Mokone GG, Hudson DE, Anastasiades L, Noakes TD. The ACE gene and endurance performance during the South African Ironman Triathlons. *Med Sci Sports Exerc* 2004;36:1314-1320.
 139. MacArthur D, North KN. Genes and human elite athletic performance. *Hum Genet* 2005;116:331-339.
 140. Gosker HR, Pennings HJ, Schols AM. ACE gene polymorphism in COPD. *Am J Respir Crit Care Med* 2004;170:572-573.
 141. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults [position stand]. *Med Sci Sports Exerc* 1998;30:975-991.
 142. Pollock M, Ayres J, Ward A. Cardiorespiratory fitness: response to differing intensities and duration of training. *Arch Phys Med Rehabil* 1977;58:467-473.
 143. Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: the basic questions. *Eur Respir J* 1997;10:2884-2891.
 144. Sneed NV, Paul SC. Readiness for behavioral changes in patients with heart failure. *Am J Crit Care* 2003;12:444-453.
 145. Ries AL, Kaplan RM, Myers R, Prewitt LM. Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. *Am J Respir Crit Care Med* 2003;167:880-888.
 146. Swerts PM, Kretzers LM, Terpstra-Lindeman E, Verstappen FT, Wouters EF. Exercise reconditioning in the rehabilitation of patients with chronic obstructive pulmonary disease: a short and long-term analysis. *Arch Phys Med Rehabil* 1990;71:570-573.
 147. 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.
 148. Salman GF, Mosier MC, Beasley BW, Calkins DR. Rehabilitation for patients with chronic obstructive pulmonary disease. *J Gen Intern Med* 2003;18:213-221.
 149. Berry MJ, Rejeski WJ, Adair NE, Ettinger WH, Zaccaro D, 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.
 150. 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.
 151. Troosters T, Gosselink R, Van Hove P, Derom E, Barch P, Pirnay F, Debruycker F, Smeets F, Neirincx L, Decramer M, REVALIS Study Group. Effects of pulmonary rehabilitation in a clinical setting [abstract]. *Am J Respir Crit Care Med* 2002;165:A735.
 152. Richardson RS, Sheldon J, Poole DC, Hopkins SR, Ries AL, Wagner PD. Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:881-885.
 153. Richardson RS, Leek BT, Gavin TP, Haseler LJ, Mudaliar SR, Henry R, Mathieu-Costello O, Wagner PD. Reduced mechanical efficiency in COPD, but normal peak $\dot{V}O_2$ with small muscle exercise. *Am J Respir Crit Care Med* 2004;169:89-96.
 154. Punzal PA, Ries AL, Kaplan RW, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. *Chest* 1991;100:618-623.
 155. 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.
 156. Gimenez M, Servera E, Vergara P, Bach JR, Polu JM. Endurance training in patients with chronic obstructive pulmonary disease: a comparison of high versus moderate intensity. *Arch Phys Med Rehabil* 2000;81:102-109.
 157. 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.
 158. Debigare R, Maltais F, Mallet M, Casaburi R, LeBlanc P. Influence of work rate incremental rate on the exercise responses in patients with COPD. *Med Sci Sports Exerc* 2000;32:1365-1368.
 159. Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease: the power-duration relationship. *Am J Respir Crit Care Med* 2000;162:497-504.
 160. Troosters T, Vilaro J, Rabinovich RA, Casas A, Barbera JA, Rodriguez-Roisin R, Roca J. Physiological responses to six minute walking test in COPD patients. *Eur Respir J* 2002;20:564-569.

161. Man WD, Soliman MG, Gearing J, Radford SG, Rafferty GF, Gray BJ, Polkey MI, Moxham J. Symptoms and quadriceps fatigability following walking and cycling in COPD. *Am J Respir Crit Care Med* 2003;168:562–567.
162. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. *J Appl Physiol* 2000;88:1715–1720.
163. Maltais F, LeBlanc P, Jobin J, Berube C, Bruneau J, Carrier L, Breton MJ, Falardeau G, Belleau R. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:555–561.
164. Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. *Chest* 1996;109:1169–1175.
165. 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.
166. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248–1253.
167. Bauerle O, Chrusch CA, Younes M. Mechanisms by which COPD affects exercise tolerance. *Am J Respir Crit Care Med* 1998;157:57–68.
168. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose–response effect of oxygen on hyperinflation and exercise endurance in nonhypoxemic COPD patients. *Eur Respir J* 2001;18:77–84.
169. 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.
170. O'Donnell DE, Bain DJ, Webb KA. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *Am J Respir Crit Care Med* 1997;155:530–535.
171. Stein DA, Bradley BL, Miller WC. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. *Chest* 1982;81:6–10.
172. Neubauer B, Tetzlaff K, Buslaps C, Schwarzkopf J, Bettinghausen E, Rieckert H. Blood lactate changes in men during graded workloads at normal atmospheric pressure (100 kPa) and under simulated caisson conditions (400 kPa). *Int Arch Occup Environ Health* 1999;72:178–181.
173. Hogan MC, Cox RH, Welch HG. Lactate accumulation during incremental exercise with varied inspired oxygen fractions. *J Appl Physiol* 1983;55:1134–1140.
174. 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.
175. 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.
176. Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax* 2000;55:539–543.
177. 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.
178. 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.
179. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in non-hypoxemic COPD patients. *Am J Respir Crit Care Med* 2003;168:1034–1042.
180. Brusasco V, Pellegrino R. Oxygen in the rehabilitation of patients with chronic obstructive pulmonary disease: an old tool revisited. *Am J Respir Crit Care Med* 2003;168:1021–1022.
181. Mehta S, Hill N. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001;163:540–577.
182. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003;326:185.
183. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003;168:1438–1444.
184. 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.
185. 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.
186. van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Acute effects of inspiratory pressure support during exercise in patients with COPD. *Eur Respir J* 2004;23:34–40.
187. Babcock MA, Pegelow DF, Harms CA, Dempsey JA. Effects of respiratory muscle unloading on exercise-induced diaphragm fatigue. *J Appl Physiol* 2002;93:201–206.
188. O'Donnell DE, D'Arsigny C, Raj S, Abdollah H, Webb KA. Ventilatory assistance improves exercise endurance in stable congestive heart failure. *Am J Respir Crit Care Med* 1999;160:1804–1811.
189. Hernandez P, Maltais F, Gursahaney A, LeBlanc P, Gottfried SB. Proportional assist ventilation may improve exercise performance in severe chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2001;21:135–142.
190. Polkey MI, Hawkins P, Kyroussis D, Ellum SG, Sherwood R, Moxham J. Inspiratory pressure support prolongs exercise induced lactataemia in severe COPD. *Thorax* 2000;55:547–549.
191. Hawkins P, Johnson LC, Nikolettou 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.
192. Costes F, Agresti A, Court-Fortune I, Roche F, Vergnon JM, Barthelémy JC. Noninvasive ventilation during exercise training improves exercise tolerance in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2003;23:307–313.
193. 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.
194. 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.
195. 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.
196. Goto S, Porszasz J, Sakurai S, Whipp BJ, Casaburi R. Effect of helium breathing on dynamic hyperinflation, minute ventilation and exercise intolerance in severe COPD patients. *Am J Respir Crit Care Med* 2004;169:A467.
197. Oelberg DA, Kacmarek RM, Pappagianopoulos PP, Ginns LC, System DM. Ventilatory and cardiovascular responses to inspired He–O₂ during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1876–1882.
198. Gosselink RA, Wagenaar RC, Rijswijk H, Sargeant AJ, 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.
199. American Thoracic Society. Dyspnea: mechanisms, assessment, and management [consensus statement]. *Am J Respir Crit Care Med* 1999;159:321–340.
200. Breslin EH. The pattern of respiratory muscle recruitment during pursed-lip breathing. *Chest* 1992;101:75–78.
201. 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.
202. Jones AY, Dean E, Chow CC. Comparison of the oxygen cost of breathing exercises and spontaneous breathing in patients with stable chronic obstructive pulmonary disease. *Phys Ther* 2003;83:424–431.
203. Sharp JT, Drutz 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.
204. van der Schans CP, de Jong W, de Vries G, Kaan WA, Postma DS, Koeter GH, van der Mark TW. Effects of positive expiratory pressure breathing during exercise in patients with COPD. *Chest* 1994;105:782–789.
205. Gosselink R, Troosters T, Decramer M. Effects of exercise training in COPD patients: interval versus endurance training. *Eur Respir J* 1998;12:2S.
206. 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.
207. 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.
208. Vogiatzis I, Nanas S, Kastanakis E, Georgiadou O, Papazahou O, Roussos C. Dynamic hyperinflation and tolerance to interval exercise in patients with advanced COPD. *Eur Respir J* 2004;24:385–390.
 209. Sabapathy S, Kingsley RA, Schneider DA, Adams L, Morris NR. Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. *Thorax* 2004;59:1026–1031.
 210. Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Beneke R, Lehmann M, Roskamm H. Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med Sci Sports Exerc* 1997;29:306–312.
 211. Ahmaidi S, Masse-Biron J, Adam B, Choquet D, Freville M, Libert JP, Prefaut C. Effects of interval training at the ventilatory threshold on clinical and cardiorespiratory responses in elderly humans. *Eur J Appl Physiol Occup Physiol* 1998;78:170–176.
 212. 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.
 213. Pantou LB, Golden J, Broeder CE, Browder KD, Cestaro-Seifer DJ, Seifer FD. The effects of resistance training on functional outcomes in patients with chronic obstructive pulmonary disease. *Eur J Appl Physiol* 2004;91:443–449.
 214. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis M, Fournier M, Storer T. Anabolic effects of testosterone replacement and strength training in men with COPD. *Am J Respir Crit Care Med* 2004;170:870–878.
 215. Jubrias SA, Esselman PC, Price LB, Cress ME, Conley KE. Large energetic adaptations of elderly muscle to resistance and endurance training. *J Appl Physiol* 2001;90:1663–1670.
 216. Hepple RT, Mackinnon SL, Goodman JM, Thomas SG, Plyley MJ. Resistance and aerobic training in older men: effects on \dot{V}_{O_2} peak and the capillary supply to skeletal muscle. *J Appl Physiol* 1997;82:1305–1310.
 217. McGuigan MR, Bronks R, Newton RU, Sharman MJ, Graham JC, Cody DV, Kraemer WJ. Resistance training in patients with peripheral arterial disease: effects on myosin isoforms, fiber type distribution, and capillary supply to skeletal muscle. *J Gerontol A Biol Sci Med Sci* 2001;56:B302–B310.
 218. 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.
 219. 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.
 220. Zanutti E, Felicetti G, Maimi 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.
 221. Yeh SS, DeGuzman B, Kramer T. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest* 2002;122:421–428.
 222. 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.
 223. 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.
 224. Ferreira IM, Verreschi IT, Nery LE, Goldstein RS, Zamel N, Brooks D, Jardim JR. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. *Chest* 1998;114:19–28.
 225. Weisberg J, Wanger J, Olson J, Streit B, Fogarty C, Martin T, Casaburi R. Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. *Chest* 2002;121:1070–1078.
 226. 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.
 227. Casaburi R. Rationale for anabolic therapy to facilitate rehabilitation in chronic obstructive pulmonary disease. *Baillieres Clin Endocrinol Metab* 1998;12:407–418.
 228. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004;34:513–554.
 229. Casaburi R, Storer T, Bhasin D. Testosterone effects on body composition and muscle performance. In: Bhasin D, Gabelnick H, Spieler J, Swerdloff RD, Wang C, editors. *Biology, pharmacology and clinical applications of androgens*. New York: Wiley Liss; 1996. p. 283–288.
 230. Sinha-Hikim I, Artaza J, Woodhouse L, Gonzalez-Cadavid N, Singh AB, Lee MI, Storer TW, Casaburi R, Shen R, Bhasin S. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *Am J Physiol Endocrinol Metab* 2002;283:E154–E164.
 231. Creutzberg EC, Casaburi R. Endocrinological disturbances in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;46:76s–80s.
 232. Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, Casaburi R, Bhasin S. Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *J Clin Endocrinol Metab* 2003;88:1478–1485.
 233. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, et al. Testosterone dose–response relationships in healthy young men. *Am J Physiol Endocrinol Metab* 2001;281:E1172–E1181.
 234. Bhasin S, Storer TW, Berman N, Yarasheski KE, Clevenger B, Phillips J, Lee WP, Bunnell TJ, Casaburi R. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J Clin Endocrinol Metab* 1997;82:407–413.
 235. Kamischke A, Kemper DE, Castel MA, Luthke M, Rolf C, Behre HM, Magnusen H, Nieschlag E. Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. *Eur Respir J* 1998;11:41–45.
 236. Laghi F, Antonescu-Turcu A, Collins E, Segal J, Tobin DE, Jubran A, Tobin MJ. Hypogonadism in men with chronic obstructive pulmonary disease: prevalence and quality of life. *Am J Respir Crit Care Med* 2005;171:728–733.
 237. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, Dike M, Sinha-Hikim I, Shen R, Hays RD, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000;283:763–770.
 238. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc* 2003;51:101–115.
 239. Greenlund LJ, Nair KS. Sarcopenia: consequences, mechanisms, and potential therapies. *Mech Ageing Dev* 2003;124:287–299.
 240. Debigare R, Marquis K, Cote CH, Tremblay RR, Michaud A, LeBlanc P, Maltais F. Catabolic/anabolic balance and muscle wasting in patients with COPD. *Chest* 2003;124:83–89.
 241. 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.
 242. Acevedo M, Corbalan R, Chamorro G, Jalil J, Nazzari C, Campusano C, Castro P. Administration of growth hormone to patients with advanced cardiac heart failure: effects upon left ventricular function, exercise capacity, and neurohormonal status. *Int J Cardiol* 2003;87:185–191.
 243. Adams GR, McCue SA. Localized infusion of IGF-I results in skeletal muscle hypertrophy in rats. *J Appl Physiol* 1998;84:1716–1722.
 244. Boonen S, Rosen C, Bouillon R, Sommer A, McKay M, Rosen D, Adams S, Broos P, Lenaerts J, Raus J, et al. Musculoskeletal effects of the recombinant human IGF-I/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double-blind, placebo-controlled pilot study. *J Clin Endocrinol Metab* 2002;87:1593–1599.
 245. Koutkia P, Canavan B, Breu J, Torriani M, Kissko J, Grinspoon S. Growth hormone-releasing hormone in HIV-infected men with lipodystrophy: a randomized controlled trial. *JAMA* 2004;292:210–218.
 246. 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.
 247. 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.
 248. 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.
 249. 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.
 250. 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.

251. Ribera F, N'Guessan B, Zoll J, Fortin D, Serrurier B, Mettauer B, Bigard X, Ventura-Clapier R, Lampert E. Mitochondrial electron transport chain function is enhanced in inspiratory muscles of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003;167:873–879.
252. Levine S, Nguyen T, Kaiser LR, Rubinstein N, Maislin G, Gregory C, Rome LC, Dudley G, Sieck GC, Shrager J. Human diaphragm remodeling associated with chronic obstructive pulmonary disease: clinical implications. *Am J Respir Crit Care Med* 2003;168:706–713.
253. Mador MJ, Kufel TJ, Pineda LA, Sharma GK. Diaphragmatic fatigue and high-intensity exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:118–123.
254. Polkey MI, Kyroussis D, Keilty SE, Hamnegard CH, Mills GH, Green M, Moxham J. Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. *Am J Respir Crit Care Med* 1995;152:959–964.
255. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, Sliwinski P. Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1637–1641.
256. 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.
257. 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.
258. Rochester DF. The diaphragm in COPD: better than expected, but not good enough. *N Engl J Med* 1991;325:961–962.
259. Ramirez-Sarmiento A, Orozco-Levi M, Guell R, Barreiro E, Hernandez N, Mota S, Sengenis M, Broquetas JM, Casan P, Gea J. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes. *Am J Respir Crit Care Med* 2002;166:1491–1497.
260. 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.
261. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Maintenance of inspiratory muscle training in COPD patients: one year follow-up. *Eur Respir J* 2004;23:61–65.
262. Foster S, Lopez D, Thomas HM III. Pulmonary rehabilitation in COPD patients with elevated Pco₂. *Am Rev Respir Dis* 1988;138:1519–1523.
263. 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.
264. Troosters T, Gosselink R, Decramer M. Exercise training in COPD; how to distinguish responders from nonresponders. *J Cardiopulm Rehabil* 2001;21:10–17.
265. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc* 2001;33:S446–S451.
266. ZuWallack RL, Patel K, Reardon JZ, Clark BA, Normandin EA. Predictors of improvement in the 12 minute walking distance following a six week out-patient pulmonary rehabilitation program. *Chest* 1991;99:805–808.
267. Couser JJ, Guthmann R, Hamadeh MA, Kane CS. Pulmonary rehabilitation improves exercise capacity in elderly. *Chest* 1995;107:730–734.
268. Sinclair DJ, Ingram CG. Controlled trial of supervised exercise training in chronic bronchitis. *BMJ* 1980;280:519–521.
269. Gallefoss F, Bakke PS, Rsgaard PK. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159:812–817.
270. Stulberg MS, Carrieri-Kohlman V, Demir-Deviren S, Nguyen HQ, Adams L, Tsang AH, Duda J, Gold WM, Paul S. Exercise training improves outcomes of a dyspnea self-management program. *J Cardiopulm Rehabil* 2002;22:109–121.
271. Sassi-Dambron DE, Eakin EG, Ries AL, Kaplan RM. Treatment of dyspnea in COPD: a controlled clinical trial of dyspnea management strategies. *Chest* 1995;107:724–729.
272. Monnikhof E, van der Valk P, van der Palen J, van Herwaarden C, Partridge MR, Zielhuis G. Self-management education for patients with chronic obstructive pulmonary disease: a systematic review. *Thorax* 2003;58:394–398.
273. Monnikhof 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 pulmonary disease. *Eur Respir J* 2003;22:815–820.
274. Gallefoss F, Bakke PS. Cost-benefit and cost-effectiveness analysis of self-management in patients with COPD: a 1-year follow-up randomized, controlled trial. *Respir Med* 2002;96:424–431.
275. Goodman DE, Israel E, Rosenberg M, Johnston R, Weiss ST, Drazen JM. The influence of age, diagnosis, and gender on proper use of metered-dose inhalers. *Am J Respir Crit Care Med* 1994;150:1256–1261.
276. Devine EC, Percy J. Meta-analysis of the effects of psychoeducational care in adults with chronic obstructive pulmonary disease. *Patient Educ Couns* 1996;29:167–178.
277. Watson PB, Town GI, Holbrook N, Dwan C, Toop LJ, Drennan CJ. Evaluation of a self-management plan for chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:1267–1271.
278. van Manen JG, Bindels PJ, Dekker FW, Jzermans CJI, van der Zee JS, Schade E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. *Thorax* 2002;57:412–416.
279. de Godoy DV, de Godoy RF. A randomized controlled trial of the effect of psychotherapy on anxiety and depression in chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2003;84:1154–1157.
280. Unger DG, Jacobs SB. Couples and chronic obstructive airway diseases: the role of gender in coping and depression. *Womens Health* 1995;1:237–255.
281. Keele-Card G, Foxall MJ, Barron CR. Loneliness, depression, and social support of patients with COPD and their spouses. *Public Health Nurs* 1993;10:245–251.
282. Bergs D. “The hidden client”—women caring for husbands with COPD: their experience of quality of life. *J Clin Nurs* 2002;11:613–621.
283. Vallet G, Ahmaidi S, Serres I, Fabre C, Bourgoignie 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.
284. Turner J, Wright E, Mendella L, Anthonisen N, IPPB Study Group. Predictors of patient adherence to long-term home nebulizer therapy for COPD: intermittent positive pressure breathing. *Chest* 1995;108:394–400.
285. Troosters T, Gosselink R, Scholier D, Spruit M, Pitta F, Probst V, Decramer M. Pulmonary rehabilitation in smokers with COPD. *Eur Respir J* 2004;24:667s.
286. 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.
287. Honeyman P, Barr P, Stubbing DG. Effect of a walking aid on disability, oxygenation, and breathlessness in patients with chronic airflow limitation. *J Cardiopulm Rehabil* 1996;16:63–67.
288. Probst V, Troosters T, Coosemans I, Spruit M, Pitta F, Decramer M, Gosselink R. Mechanisms of improvement in exercise capacity using a rollator in COPD. *Chest* 2004;126:1102–1107.
289. Goldstein RS, Gort EH, Guyatt GH, Feeny D. Economic analysis of respiratory rehabilitation. *Chest* 1997;112:370–379.
290. Lorenzi CM, Cilione C, Rizzardi R, Furino V, Bellantone T, Lugli D, Cini E. Occupational therapy and pulmonary rehabilitation of disabled COPD patients. *Respiration (Herrlisheim)* 2004;71:246–251.
291. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994;7:1793–1797.
292. Shoup R, Dalsky G, Warner S, Davies M, Connors M, Khan M, Khan F, ZuWallack R. Body composition and health-related quality of life in patients with obstructive airways disease. *Eur Respir J* 1997;10:1576–1580.
293. 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.
294. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional supplementation in stable chronic obstructive pulmonary disease [Cochrane review]. *Cochrane Database Syst Rev* 2000;3:CD000998.
295. 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.
296. Baarends EM, Schols AM, Pannemans DL, Westerterp KR, Wouters EF. Total free living energy expenditure in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:549–554.

297. 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.
298. 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.
299. 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.
300. Schols AM. Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. *Eur Respir J Suppl* 2003;46:81s-86s.
301. Engelen MP, Schols AM. Altered amino acid metabolism in chronic obstructive pulmonary disease: new therapeutic perspective? *Curr Opin Clin Nutr Metab Care* 2003;6:73-78.
302. Pouw EM, Schols AM, Deutz NE, Wouters EF. Plasma and muscle amino acid levels in relation to resting energy expenditure and inflammation in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:797-801.
303. World Health Organization. Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2003. Available at www.goldcopd.com (accessed March 2005).
304. 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.
305. 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.
306. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, et al. Bioelectrical impedance analysis. I. Preview of principles and methods. *Clin Nutr* 2004;23:1226-1243.
307. Schols AM, Wouters EF, Soeters PB, Westerterp KR. Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1991;53:421-424.
308. Redelmeier DA, Guyatt GH, Goldstein RS. Assessing the minimal important difference in symptoms: a comparison of two techniques. *J Clin Epidemiol* 1996;49:1215-1219.
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. Haas F, Salazar-Schicchi J, Axen R. Desensitization to dyspnea in chronic obstructive pulmonary disease. In: Casaburi R, Petty TL, editors. Principles and practice of pulmonary rehabilitation. Philadelphia, PA: W.B. Saunders; 1993. pp. 241.
311. Kirsten DK, Taube C, Lehnigk B, Jorres RA, Magnussen H. Exercise training improves recovery in patients with COPD after an acute exacerbation. *Respir Med* 1998;92:1191-1198.
312. 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.
313. Hernandez C, Casas A, Escarrabill J, Alonso J, Puig-Junoy J, Farrero E, Vilagut G, Collvinent B, Rodriguez-Roisin R, Roca J. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. *Eur Respir J* 2003;21:58-67.
314. Davies L, Wilkinson M, Bonner S, Calverley PM, Angus RM. "Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial. *BMJ* 2000;321:1265-1268.
315. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. *J Cardiopulm Rehabil* 2004;24:52-62.
316. Wijkstra PJ, van der Mark TW, Kraan J, van Altena R, Koeter GH, Postma DS. Long-term effects of home rehabilitation on physical performance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153:1234-1241.
317. Brooks D, Krip B, Mangovski-Alzamora S, Goldstein RS. The effect of postrehabilitation programmes on individuals with chronic obstructive pulmonary disease. *Eur Respir J* 2002;20:20-29.
318. Spruit MA, Troosters T, Trappenburg JC, Decramer M, Gosselink R. Exercise training during rehabilitation of patients with COPD: a current perspective. *Patient Educ Couns* 2004;52:243-248.
319. Palsbo SE. Medicaid payment for telerehabilitation. *Arch Phys Med Rehabil* 2004;85:1188-1191.
320. Hoernig S, Lange A, Witt C, Anker SD, John M. Anemia in chronic obstructive pulmonary disease: frequency and clinical characteristics [abstract]. *Am J Respir Crit Care Med* 2004;169:A843.
321. Marrades RM, Roca J, Campistol JM, Diaz O, Barbera JA, Torregrosa JV, Masclans JR, Cobos A, Rodriguez-Roisin R, Wagner PD. Effects of erythropoietin on muscle O₂ transport during exercise in patients with chronic renal failure. *J Clin Invest* 1996;97:2092-2100.
322. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;107:294-299.
323. Schönhofer B, Wenzel M, Geibel M, Kohler D. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. *Crit Care Med* 1998;26:1824-1828.
324. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005;127:809-817.
325. Tramontano AF, Muniyappa R, Black AD, Blendea MC, Cohen I, Deng L, Sowers JR, Cutaia MV, El Sherif N. Erythropoietin protects cardiac myocytes from hypoxia-induced apoptosis through an Akt-dependent pathway. *Biochem Biophys Res Commun* 2003;308:990-994.
326. Digicaylioglu M, Lipton SA. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF- κ B signalling cascades. *Nature* 2001;412:641-647.
327. Sastre J, Asensi M, Gasco E, Pallardo FV, Ferrero JA, Furukawa T, Vina J. Exhaustive physical exercise causes oxidation of glutathione status in blood: prevention by antioxidant administration. *Am J Physiol* 1992;263:R992-R995.
328. Koechlin C, Couillard A, Simar D, Cristol JP, Bellet H, 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.
329. 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.
330. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832-840.