CLINICAL THERAPEUTICS

Pulmonary Rehabilitation for Management of Chronic Obstructive Pulmonary Disease

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

A 61-year-old woman is referred for pulmonary consultation. She smoked one pack of cigarettes a day for 45 years but quit a year ago. For 2 years she has noted progressive exertional dyspnea, with breathlessness occurring when she is walking up one flight of stairs or hurrying on level ground. A diagnosis of chronic obstructive pulmonary disease (COPD) was made a year ago, and she was treated with inhaled medications. She is sedentary and recently gained 15 lb (6.8 kg); her only frequent social activity is playing cards. Her physical examination is normal except for a weight of 195 lb (88.5 kg) (body-mass index [the weight in kilograms divided by the square of the height in meters], 32) and for decreased breath sounds and prolonged expiration on chest auscultation. Spirometry reveals moderate airway obstruction; an echocardiogram is normal. The pulmonary consultant recommends enrollment in a pulmonary rehabilitation program.

THE CLINICAL PROBLEM

COPD currently ranks fourth as a cause of death in the United States[1] and is on course to be the third most common cause of death worldwide by 2020.[2] Whereas COPD was once principally a disease of men, it now kills roughly equal numbers of men and women in the United States. In 2000, COPD was responsible for 8 million physician office visits, 1.5 million emergency department visits, and 726,000 hospitalizations (about 13% of total hospitalizations)[3]; it is second only to coronary heart disease as a reason for payment of Social Security disability benefits.

Exercise intolerance resulting from dyspnea or fatigue is often the chief symptom reported by patients with COPD. The degree of exercise intolerance roughly parallels the severity of the disease, but exercise intolerance is also distinctly present in patients with only mild disease.[4] The extent to which quality of life is impaired is reflected in patients' symptoms, decreased functional status, and frequency of exacerbations.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Although COPD primarily affects lung function, it often has extrapulmonary manifestations.[5] Principal among these systemic manifestations is skeletal-muscle dysfunction,[6] especially in the leg muscles involved with ambulation. Examination of leg-muscle tissue has revealed distinct abnormalities: decreased aerobic enzyme activity,[7] a low fraction of type I (aerobic) fibers, decreased capillarity, the presence

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of inflammatory cells, and increased apoptosis.[8] These defects tend to reduce aerobic capacity, which is manifested in the early onset of lactic acidosis.[9] Muscle fatigue occurs at work rates that would not engender fatigue in healthy subjects. It has been shown that in an appreciable fraction of patients with COPD, muscle fatigue rather than dyspnea is the primary factor limiting exercise tolerance.[10] It is likely that the primary cause of these muscle abnormalities is deconditioning[11] (patients with COPD are often very sedentary), but other COPD-specific factors probably contribute as well.

Pulmonary rehabilitation does not directly improve lung mechanics or gas exchange.[12] Rather, it optimizes the function of other body systems so that the effect of lung dysfunction is minimized[13] (Fig. 1). High-intensity rehabilitative exercise programs improve muscle function by inducing changes in muscle biochemistry. As a result, higher work rates can be tolerated without appreciable lactic acidosis.[9] For patients in whom ambulatory muscle dysfunction is a primary limitation, delayed fatigue directly enhances exercise tolerance. For patients in whom ventilatory limitation is primary, decreased lactic acidosis at a given level of exercise decreases ventilatory demand, probably by means of decreased carotid-body stimulation.[9]

Dyspnea is also mitigated by reducing dynamic hyperinflation, which results when exercise leads to increased ventilatory demand and inadequate time is allowed for expiration, given the limitations on expiratory airflow. End-expiratory and, therefore, end-inspiratory lung volume is forced to increase progressively. When end-inspiratory lung volume approaches the limiting volume (total lung capacity), the elastic work of breathing and dyspnea increase markedly. Exercise training lowers ventilatory demand, resulting in a slowing of respiration at a given level of exercise. With a longer expiratory time there is less dynamic hyperinflation and, therefore, less dyspnea.[14]

Pulmonary rehabilitation also works through other, less well-defined mechanisms. Exercise programs often result in desensitization to dyspnea (a decrease in the perception of dyspnea for a given task).[15] Factors hypothesized to contribute to this desensitization include the antidepressant effect of exercise as well as the social interaction and distraction from dyspneic sensations that occur during exercise with a group of patients who have the same condition. In addition, rehabilitation programs typically incorporate education in the development of self-management strategies, an approach that involves a partnership between the patient and health professionals to system-

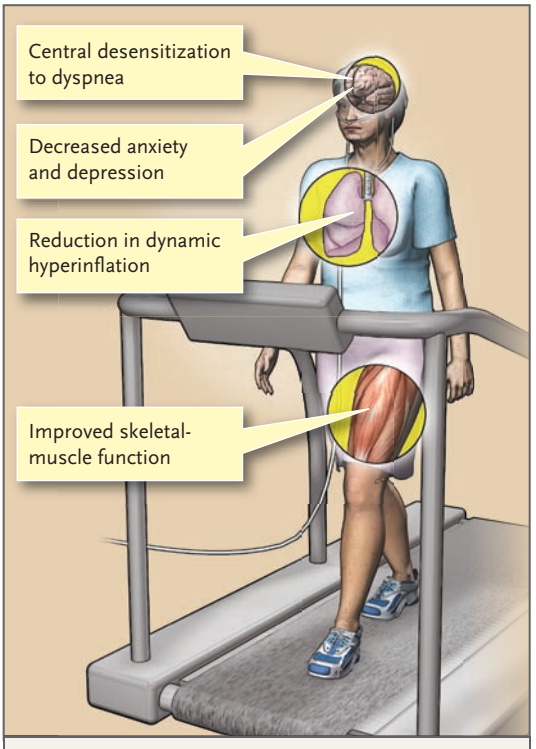

Figure 1. Targets of Exercise Training as Part of a Pulmonary Rehabilitation Program for Patients with COPD.

Exercise training does not improve lung function, but it does ease other manifestations of COPD, increasing exercise tolerance, reducing dyspnea, and improving quality of life. Improved skeletal-muscle function is related, in part, to a reversal of deconditioning. Exercise training improves aerobic function of the muscles of ambulation. Dyspnea is mitigated by the reduction in dynamic hyperinflation that occurs when exercise-induced increases in the rate and depth of breathing result in inadequate time for full expiration, given the high expiratory airflow resistance. End-expiratory lung volume rises, and exercise is terminated when end-inspiratory lung volume approaches levels at which the high elastic work of breathing causes severe dyspnea. Exercise training reduces the ventilatory requirement and respiratory rate during heavy exercise, prolonging the time allowed for expiration and reducing dynamic hyperinflation. Desensitization to dyspnea occurs centrally as a result of exercise training; the underlying mechanism is uncertain. Decreased anxiety and depression are thought to result from increased exercise capacity and consequent increases in activities of daily living, coupled with feelings of mastery.

atically manage the symptoms of the disease.[16] This approach promotes adaptive behaviors, such as abstinence from smoking, better adherence to pharmacologic and exercise therapy, and earlier recognition and treatment of COPD exacerbations. Self-management education has been shown to reduce the use of health care services and costs among patients with moderate-to-severe COPD and a history of hospitalizations.[16,17]

CLINICAL EVIDENCE

Many clinical trials have examined the benefits of pulmonary rehabilitation, although virtually all of them were single-center trials of modest size. Demonstrations of benefit are based on randomized, controlled (though unblinded) studies. For three outcomes, the benefit is unequivocal[18]: exercise capacity (in incremental, constant work rate, and timed walking tests), severity of dyspnea, and health-related quality of life. For these three outcomes, the magnitude of benefit is generally superior to any other COPD therapy.

A recent meta-analysis by Lacasse et al. summarized 31 randomized, controlled trials of pulmonary rehabilitation.[19] In 11 trials involving 618 participants, health-related quality of life was evaluated with the use of the Chronic Respiratory Disease Questionnaire (CRQ).[20] Improvements were demonstrated in the four domains evaluated by this instrument: dyspnea, fatigue, emotional function, and mastery (the patient's feeling of control over the disease). The average effect size was 1.5 to 2.1 times the estimated minimum clinically important difference between the treatment and control groups. In 16 trials involving 669 participants, the weighted mean improvement in functional exercise capacity, assessed on the basis of the distance walked in 6 minutes, was 48 m. This approximated the estimated minimum clinically important difference of 50 m.

Individual studies of the effects of pulmonary rehabilitation have shown reductions in hospitalization and other measures of health care use[21,22] and improvements in cost-effectiveness.[23] Reductions in depression and anxiety and improvements in cognitive function and self-efficacy have been reported in trials specifically investigating these outcomes.[24] A survival benefit has not been demonstrated with pulmonary rehabilitation, although the randomized trials that have examined survival were relatively small and were underpowered to detect this effect.[18]

CLINICAL USE

The most common model for pulmonary rehabilitation in the United States is a multidisciplinary, hospital-based outpatient program, as originally developed and implemented by Petty et al.[25] Pulmonary rehabilitation is also provided in home-based, community-based, and inpatient settings. Program staffing varies but generally centers on a coordinator, who is typically trained in nursing, respiratory therapy, or physical therapy. The successful coordinator has excellent interpersonal skills, since (at least initially) a primary task is to motivate people to do what they may find unpleasant. Generally, a pulmonologist oversees the program.

Forced expiratory volume in 1 second (FEV_1) is not the sole criterion for selecting patients for pulmonary rehabilitation,[24] but patients who are typically referred for rehabilitation in the United States have stage 3 (severe) disease according to the four-stage Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of severity (Table 1).[2] However, those with milder disease may have distinct exercise intolerance that can be remediated with pulmonary rehabilitation. Patients whose disease is classified as stage 4 (very severe) may also be appropriate candidates,[26] although special efforts may be required to provide them with activities that are commensurate with their reduced exercise tolerance. Selection for pulmonary rehabilitation may also focus on patients whose dyspnea is out of proportion to

Table 1. Spirometric Classification of COPD Severity on the Basis of Post-Bronchodilator FEV_1.*

Stage and Severity	Definition
I — mild	$FEV_1/FVC < 0.70$, $FEV_1 \geq 80\%$ of predicted
II — moderate	$FEV_1/FVC < 0.70$, $50\% \leq FEV_1 < 80\%$ of predicted
III — severe	$FEV_1/FVC < 0.70$, $30\% \leq FEV_1 < 50\%$ of predicted
IV — very severe	$FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ of predicted plus chronic respiratory failure

* Respiratory failure is defined as an arterial partial pressure of oxygen (PaO_2) that is less than 8.0 kPa (60 mm Hg), with or without an arterial partial pressure of carbon dioxide ($PaCO_2$) that is greater than 6.7 kPa (50 mm Hg), while the patient is breathing ambient air at sea level.[2] COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.

the severity of their disease and on those for whom leg fatigue is the symptom that limits exercise tolerance.[27]

In general, pulmonary rehabilitation is not recommended for patients who are unable to walk (because of orthopedic or neurologic disorders) or those with unstable cardiac disease (unstable angina or recent myocardial infarction). Other relative contraindications include cognitive or psychiatric problems that would prevent the patient from comprehending or cooperating with the treatment plan. Some programs exclude active smokers, although there are no convincing data that support this decision.[28]

Many rehabilitation programs feature three directly supervised sessions per week, each lasting 3 to 4 hours. The duration of most programs ranges from 6 to 12 weeks, although some studies suggest that longer programs may provide additional and more durable benefits.[24] Program participation begins with clinical assessments by the medical director and rehabilitation coordinator, with reevaluation at intervals to gauge the patient's progress toward individualized exercise and educational goals. An argument can be made for an initial formal cardiopulmonary exercise test,[29] which provides information on the mechanism and severity of exercise intolerance, helps identify any cardiovascular or other contraindications to a rigorous exercise program, indicates whether there is a need for supplemental oxygen, and provides a guide for the intensity of the exercises prescribed.

The exercise program is the centerpiece of pulmonary rehabilitation. Endurance exercise of the leg muscles is the main focus, with walking, stationary cycling, and treadmill exercise commonly performed. High-intensity regimens are generally preferred, with initial targets of at least 60% of the maximum exercise tolerance,[13] although lower-intensity exercise is also beneficial. Exercise intensity is increased as tolerated under the observation of rehabilitation staff. A resistance-exercise component is also often included[18]; improved leg strength aids in some activities of daily living and may lessen the risk of falls (although this benefit has yet to be demonstrated in clinical trials). Resistance training that involves the upper arms is also useful,[18] both because it facilitates the ability to carry out the activities of daily living and because some of the upper-arm muscles also serve as auxiliary muscles of respiration.[30] Respiratory-muscle training was once common, but it is now known that even with improvement of respiratory-muscle strength, functional capacity usually does not improve.[18]

Ancillary measures have been added to the training routine to increase the intensity of exercise. In this regard, optimal bronchodilation during exercise sessions seems prudent.[31] The use of supplemental oxygen during training sessions, even in patients without substantial exercise desaturation, reduces ventilatory demand.[32] Other interventions that are being studied include the use of noninvasive ventilatory support, heliox (an inhaled mixture of helium and oxygen), ventilatory-pattern feedback, and anabolic steroids.[33,34]

Education is included in pulmonary rehabilitation to improve the patient's understanding of the disease and its treatment and to promote collaborative self-management strategies.[16-18] Examples of the latter include cessation of smoking, incorporation of exercise and increased physical activity in the home setting, promotion of the importance of adherence to therapy, and development of an action plan for earlier detection and treatment of COPD exacerbations. Since anxiety and depression are common in patients with COPD who are referred for pulmonary rehabilitation, many programs include a psychosocial component based on the needs of the individual patient.

Patients with COPD cachexia, characterized by involuntary weight loss and depletion of lean body mass, have a very poor prognosis. Nutritional supplementation is often offered to such patients, but this approach has had only limited efficacy in clinical trials.[35] The appetite stimulant megestrol acetate has been shown to increase body weight, but the weight gain typically consists of fat mass only.[36] Furthermore, overweight patients, as compared with those of normal weight, tend to have ventilatory limitation at lower exercise intensities because of the increased metabolic cost of activity. Weight-loss strategies are often recommended as part of pulmonary rehabilitation, although evidence of efficacy is lacking.

The increased exercise tolerance — and attendant benefits — gained during rehabilitation will recede within months after the program's end if patients resume their formerly sedentary lifestyle. Maintenance programs have been devised to help combat this tendency[37]; these programs often include exercise classes that meet at regu-

lar intervals. Many patients who complete pulmonary rehabilitation programs highly value the improvement in their condition and are successful in altering their lifestyle to maintain it, but reliable estimates of the percentage of participants who achieve this lifestyle alteration are not available.

Currently, pulmonary rehabilitation programs are available for only a small fraction of patients with COPD who could potentially benefit from this approach; program availability is particularly problematic among lower-income, minority, and rural populations. A roadblock to achieving widespread availability in the United States has been the lack of a uniform funding policy. The cost of pulmonary rehabilitation has not been extensively documented; a recent report indicates that the average cost for a program with an average duration of 8 weeks in the National Emphysema Treatment Trial was about $2,200 per participant.[38] Reimbursement from third-party payers varies regionally. It is hoped that the recent passage of legislation designed to improve Medicare funding policy, to be implemented by January 2010, will increase access to pulmonary rehabilitation programs.[39]

ADVERSE EFFECTS

No data from a registry of serious adverse events occurring during pulmonary rehabilitation have been published, but the widespread clinical impression is that these events are relatively rare. The principal risks of pulmonary rehabilitation programs are related to the exercise component of such programs. Musculoskeletal injury is a risk, since patients with COPD tend to be elderly and are often debilitated. This risk is reduced when rehabilitation is supervised by trained personnel. Exercise-induced bronchospasm occurs in some patients with COPD, and judicious use of bronchodilators before or during exercise may be appropriate. Perhaps the most important risk is that of a cardiovascular event (e.g., myocardial ischemia or infarction, arrhythmia, or even sudden cardiac death). Patients with COPD have a substantially increased risk of cardiovascular death, as compared with healthy age-matched controls.[40,41] Before a patient starts an exercise program, evaluation for ischemic heart disease by means of a stress test is advisable.

AREAS OF UNCERTAINTY

Most patients with COPD can benefit from a pulmonary rehabilitation program. Although some reports suggest that one quarter to one third of patients do not have a response to such a program,[42,43] the criteria for defining nonresponse have not been firmly established. Studies that have attempted to define subgroups of patients who will benefit from pulmonary rehabilitation have not identified any important predictors of a response to treatment.[42,43]

In cross-sectional studies, patients with COPD who have better exercise tolerance, less dyspnea, and lower rates of hospitalization have higher survival rates.[44-46] Since pulmonary rehabilitation provides these benefits,[18] it would be reasonable to suppose that it might impart a survival advantage. However, a randomized, adequately powered trial required to detect a modest (but clinically important) survival advantage has yet to be performed.[18,47]

Patients with high levels of physical activity have been found to use fewer health care resources and to have a lower risk of death,[48] making this a desirable goal in pulmonary rehabilitation. However, although rehabilitation unequivocally increases exercise capacity, it is less clear whether this beneficial effect translates into increased daily physical activity at home. Studies using activity monitors to evaluate the extent of patients' physical activity outside the study environment have had mixed results.[49-51]

The benefits in exercise capacity and health status realized from pulmonary rehabilitation tend to decline in the months after the intervention.[18] Other than prolonging the formal program of pulmonary rehabilitation (which is not often feasible in the United States), it is unclear how best to maintain the benefits in the long term. Low-cost maintenance programs are a feature of many established rehabilitation programs. The self-management approach of incorporating exercise training in the home setting shows promise, but its benefits need to be confirmed.

GUIDELINES

Several documents summarize current knowledge regarding pulmonary rehabilitation practice: the American Thoracic Society–European

Respiratory Society Statement on Pulmonary Rehabilitation,[13] Pulmonary Rehabilitation: Joint American College of Chest Physicians–American Association of Cardiovascular and Pulmonary Rehabilitation Evidence-Based Clinical Practice Guidelines,[18] State of the Art: Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease,[24] and the British Thoracic Society Statement on Pulmonary Rehabilitation.[52] All these statements conclude that pulmonary rehabilitation has been proven beneficial in reducing dyspnea and improving functional capacity and quality of life for patients with COPD. Pulmonary rehabilitation is also recommended for patients with symptomatic COPD by the Global Initiative for Chronic Obstructive Lung Disease[2] and in the American Thoracic Society–European Respiratory Society Statement on Standards for Diagnosis and Treatment of Patients with COPD.[53]

RECOMMENDATIONS

The patient in the vignette is an appropriate candidate for pulmonary rehabilitation, and we would recommend that she be enrolled in an outpatient, hospital-based program. Before she begins treatment, a stress test for cardiovascular evaluation, perhaps in the form of a cardiopulmonary exercise test, should be performed. Useful, but not mandatory, preprogram assessments include initial measurements of functional capacity (e.g., by means of a 6-minute walk test) and health-related quality of life (e.g., with the CRQ). She should then begin an 8-week program consisting of 24 sessions held for 3 hours each 3 times a week. In the exercise component of the program, we would include relatively high-intensity treadmill and stationary-cycle ergometer training as well as lower-intensity calisthenics. A self-management strategy for future COPD exacerbations should also be formulated, focusing on early recognition and treatment of exacerbations. At the end of the program, the 6-minute walk test and CRQ might be readministered and reassessed. After the patient has completed the formal program, we would strongly advise her to attend maintenance exercise sessions and to participate in a support group for patients with COPD.

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REFERENCES

1. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. Natl Vital Stat Rep 2008;56(10):1-120.
2. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55.
3. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance — United States, 1971–2000. MMWR Surveill Summ 2002;51(SS-6):1-16.
4. Babb TG, Viggiano R, Hurley B, Staats B, Rodarte JR. Effect of mild-to-moderate airflow limitation on exercise capacity. J Appl Physiol 1991;70:223-30.
5. Decramer M, De Benedetto F, Del Ponte A, Marinari S. Systemic effects of COPD. Respir Med 2005;99:Suppl B:S3-S10.
6. Skeletal muscle dysfunction in chronic obstructive pulmonary disease: a statement of the American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med 1999;159:S1-S40.
7. Maltais F, LeBlanc P, Whittom F, et al. Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. Thorax 2000;55:848-53.
8. Agustí AG, Sauleda J, Miralles C, et al. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:485-9.
9. 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.
10. Pepin V, Saey D, Laviolette L, Maltais F. Exercise capacity in chronic obstructive pulmonary disease: mechanisms of limitation. COPD 2007;4:195-204.
11. Wagner PD. Skeletal muscles in chronic obstructive pulmonary disease: deconditioning, or myopathy? Respirology 2006;11:681-6.
12. Casaburi R. Exercise training in chronic obstructive lung disease. In: Casaburi R, Petty TL, eds. Principles and practice of pulmonary rehabilitation. Philadelphia: W.B. Saunders, 1993:204-24.
13. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173:1390-413.
14. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 2005;128:2025-34.
15. Haas F, Salazar-Schicchi J, Axen K. Desensitization to dyspnea in chronic obstructive pulmonary disease. In: Casaburi R, Petty TL, eds. Principles and practice of pulmonary rehabilitation. Philadelphia: W.B. Saunders, 1993:241-51.
16. Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med 2003;163:585-91.
17. Bourbeau J, Collet JP, Schwartzman K, Ducruet T, Nault D, Bradley C. Economic benefits of self-management education in COPD. Chest 2006;130:1704-11.
18. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest 2007;131:4S-42S.
19. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;4:CD003793.
20. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of

quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773-8.
21. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000;355:362-8. [Erratum, Lancet 2000; 355:1280.]
22. 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.
23. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax 2001;56:779-84.
24. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172:19-38.
25. Petty TL, Nett LM, Finigan MM, Brink GA, Corsello PR. A comprehensive care program for chronic airway obstruction: methods and preliminary evaluation of symptomatic and functional improvement. Ann Intern Med 1969;70:1109-20.
26. 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;155:1541-51.
27. Saey D, Debigare R, LeBlanc P, et al. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;168:425-30.
28. Lacasse Y, Maltais F, Goldstein RS. Smoking cessation in pulmonary rehabilitation: goal or prerequisite? J Cardiopulm Rehabil 2002;22:148-53.
29. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2004.
30. Celli BR, Rassulo J, Make BJ. Dyssynchronous breathing during arm but not leg exercise in patients with chronic airflow obstruction. N Engl J Med 1986;314:1485-90.
31. 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;127:809-17.
32. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med 2003;168:1034-42.
33. Casaburi R, Bhasin S, Cosentino L, et al. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:870-8.
34. Casaburi R. Boosting the effectiveness of rehabilitative exercise training. Am J Respir Crit Care Med 2008;177:805-6.
35. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS, White J. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;2:CD000998.
36. Weisberg J, Wanger J, Olson J, et al. Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. Chest 2002;121:1070-8.
37. 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;167:880-8.
38. Fan VS, Giardino ND, Blough DK, Kaplan RM, Ramsey SD. Costs of pulmonary rehabilitation and predictors of adherence in the National Emphysema Treatment Trial. COPD 2008;5:105-16.
39. Text of H.R. 6331 [110th]: Medicare Improvement for Patients and Providers Act of 2008. (Accessed March 4, 2009, at http://www.govtrack.us/congress/billtext.xpd?bill=h110-6331.)
40. van Eeden SF, Sin DD. Chronic obstructive pulmonary disease: a chronic systemic inflammatory disease. Respiration 2008;75:224-38.
41. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest 2005;128:2640-6.
42. Garrod R, Marshall J, Barley E, Jones PW. Predictors of success and failure in pulmonary rehabilitation. Eur Respir J 2006;27:788-94.
43. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopulm Rehabil 2001;21:10-7.
44. McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. Chest 2007;132:1748-55.
45. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121:1434-40.
46. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 2004;23:28-33.
47. 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;122:823-32.
48. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 2006;61:772-8.
49. Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD more active after pulmonary rehabilitation? Chest 2008;134:273-80.
50. Sewell L, Singh SJ, Williams JE, Collier R, Morgan MD. Can individualized rehabilitation improve functional independence in elderly patients with COPD? Chest 2005;128:1194-200.
51. Steele BG, Belza B, Cain KC, et al. A randomized clinical trial of an activity and exercise adherence intervention in chronic pulmonary disease. Arch Phys Med Rehabil 2008;89:404-12.
52. British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. Thorax 2001;56:827-34.
53. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46. [Erratum, Eur Respir J 2006;27:242.]