# 20. Chronic obstructive pulmonary disease (COPD)

## Author

Margareta Emtner, PT, PhD, Associate Professor, Uppsala University and Uppsala University Hospital, Uppsala, Sweden

## Summary

Reduced physical performance capacity is common in people with chronic obstructive pulmonary disease. Destruction of the small airways and alveoli, inflammation of the bronchi and deterioration of skeletal muscle strength contribute to the reduced performance capacity. Exercise training improves physical capacity and reduces dyspnoea (shortness of breath). Everyone should be recommended to engage in 30 minutes of physical activity in daily life, 5–7 days per week. Participation in exercise training should also be encouraged. The training should comprise aerobic exercise (fitness training), dynamic strength training and flexibility training (see table below). Suitable activities include cycling, walking, and fitness training on land or in the water. No training should occur at saturation levels (oxygen saturation) below 88–90 per cent.

Type of training	Intensity	Frequency (times/week)	Duration
Aerobic fitness training	Low intensity: 55–70% of max HR* 40–60% of VO <sub>2</sub> max**	2–5	≥ 30 min.
	High intensity: > 70% of max HR > 60% of VO <sub>2</sub> max 60–80% W max***	2-3	≥ 30 min.
Dynamic strength training Leg, hip, core and shoulder muscles	70% of 1 RM****	2	8–12 reps, 2–3 sets

\* Max HR = Maximal Heart Rate.

\*\* VO<sub>2</sub> max = Maximal Oxygen Uptake.

\*\*\*\* RM = Repetition Maximum. 1 RM corresponds to the maximum weight that can be lifted through the entire exercise movement one time.

<sup>\*\*\*</sup> W max = Maximal workload.

# Definition

Chronic obstructive pulmonary disease (COPD) is defined as follows: "Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" (1).

#### Cause and risk factors

COPD is primarily caused by smoking (80–95%), but the disease can also occur in nonsmokers. Increasing age, heredity, low socioeconomic group, occupational exposure to industrial pollutants and urban environments increase the risk of developing the disease (2). Despite the fact that the risk of developing COPD is not influenced by gender, we know that the effect of smoking is larger for women. People born with a deficiency of the enzyme alpha1-trypsin can develop COPD, above all if they smoke. When it comes to smoking, there is a clear dose-response relation, that is, the more years of smoking the greater the risk of developing COPD (2).

#### Prevalence/Incidence

COPD is a public health disease that occurs mostly in older persons. In the Nordic countries, 4–6 per cent of the adult population have COPD (2). The prevalence among 45-yearold smokers is 5 per cent, and rises thereafter to 25% for 60-year-old smokers, and 50% of smokers who are 75 years old (2). Approximately 50 per cent have mild COPD, just over a third moderate COPD, and the remainder severe COPD. Mortality has increased during the 1990s and 2000s. According to the cause of death registry, in 2003, 2558 people with COPD died in Sweden. Mortality is related to the severity of the disease.

#### Pathophysiology

COPD is a disease characterised by airflow limitation, which is only reversible in certain cases. The disease is progressive and characterised by an inflammatory process in the airways and lung tissue. Consequently, there is a loss of elastic recoil and increased airway resistance, which limits both inhalation and exhalation capacity. At a later stage of the disease, a thickening of the vessel walls occurs, which has a negative effect on the gas exchange, and can lead to both hypoxia (low oxygen levels) and hypercapnia (high carbon dioxide levels). In severe cases, elevated blood pressure in the pulmonary circulation can develop, i.e., pulmonary hypertension. This affects the right side of the heart with right-sided heart failure, cor pulmonale, which in turn can lead to the development of oedema in the body. Dynamic hyperinflation can also occur, where an increased amount of air remains in the lungs (3). The dynamic hyperinflation results in a deterioration of the

length-tension relationship of the diaphragm muscle, which leads to increased respiratory effort.

COPD is not only a lung disease but also a systemic disease, that is, other organs and systems in the body are also affected (4). People with COPD often have reduced cardiovascular capacity, impaired peripheral skeletal muscle strength, hormonal changes (reduced levels of anabolic steroids), systemic inflammation, and an increased energy expenditure at rest. This limits their ability to be physically active (5, 6). The peripheral skeletal muscle shows both structural and biochemical changes: decreased number of type I fibres (oxidative) and high number of type II fibres (glycolytic), decreased muscle mass, decreased capillary density, and reduced number of aerobic enzymes (7).

#### Symptoms and diagnosis

The diagnosis is made on the basis of symptoms such as chronic cough, coughed up mucous, dyspnoea, increased respiratory work, increased production of secretions, hyper-reactivity, and a long history of smoking and symptom development. The diagnosis is confirmed with a lung function test, where FEV% is less than 0.70. FEV% is the ratio of FEV<sub>1</sub> (forced expiratory volume in one second) to (F)VC (FVC = forced vital capacity and VC = vital capacity, where the highest value of FVC and VC is used) (FEV% = FEV<sub>1</sub>/(F) VC). Establishing a COPD diagnosis requires also a reversibility test, that is, a spirometric examination after inhalation of beta2 agonists. COPD is classified into four stages based on the FEV<sub>1</sub> value. People with an FEV% less than 0.70 and FEV<sub>1</sub> equal to or greater than 80 per cent of expected value have pre-clinical COPD, an FEV<sub>1</sub> between 50–79 per cent – mild COPD, an FEV<sub>1</sub> between 30–49 per cent – moderate COPD, and an FEV<sub>1</sub> under 30 per cent of expected value – severe COPD (1).

#### Prognosis

People with reduced lung function (FEV<sub>1</sub> < 50% of expected value) have a higher mortality (8). If they also present with pulmonary hypertension, the prognosis is even worse (9). People with hypoxia (reduced oxygen level in the blood) and hypercapnia (elevated level of carbon dioxide in the blood) also have poorer survival, as do those with impaired nutritional status and functional status (e.g., shorter walking distance) (10, 11). Middle-aged people with moderate or severe disease who quit smoking live an average of seven years longer than those who continue to smoke.

#### Treatment principles

Quitting smoking is the most effective treatment and results in reduced mortality as well as reduced symptoms (cough and production of secretions). Rehabilitation that includes exercise training, education, a review of diet, etc., is important and improves physical capacity, quality of life and dyspnoea (12). The pharmacological treatment includes bronchodilators like tiotropium, ipratropium and beta2 agonists. Inhaled steroids are recommended for

people with an  $\text{FEV}_1$  lower than 50 per cent of expected value (13). Continuous oxygen treatment for people with respiratory failure is necessary and increases longevity (14). People with COPD should also be vaccinated against influenza and pneumococci prophylactically.

# Effects of physical activity

Exercise training and physical activity have been shown to have positive effects both physiologically and psychologically. In addition to improvement in physical capacity after a period of training, patients with COPD who have taken part in training are less afraid of exerting themselves and become more physically active in their daily lives (15, 16). The quality of life (disease control and dyspnoea) improves, the sense of well-being increases (17), and morbidity decreases (18). On the other hand, no training study has shown a change in lung function (16).

## Effects of aerobic fitness training

Oxygen uptake capacity (VO<sub>2</sub> max), which is reduced in people with COPD, increases significantly after a period of training (19, 20). Endurance capacity also increases significantly (21). Minute ventilation (VE), heart rate, dyspnoea, blood lactate levels and hyper-inflation are decreased for the same exercise (19, 20, 22, 23). The oxidative enzymes (24) and oxygen extraction (25) of skeletal muscle are improved as a result of a period of training. The maximal workload increases 13–24 per cent, while endurance capacity increases by an average of 87 per cent, that is, the greatest effect is achieved in endurance capacity (26).

## Effects of strength training

Resistance training for the legs improves muscle strength and muscle endurance (27, 28). Aerobic capacity can also improve (29, 30).

## Effects of aerobic training combined with strength training

A combination of strength training and aerobic training improves both muscle strength and aerobic capacity (31, 32).

## Long-term effects

Studies that looked at long-term effects of exercise training have shown that training must be kept up, even if at a somewhat lower level, in order to maintain the positive effects achieved (16).

## Indications

All people with COPD who have a lower quality of life and/or lower physical capacity should be offered rehabilitation that includes exercise training (1). The training can occur when the patients are in a stable phase of the disease, but also in close connection to a period of exacerbation (33). Everyone with COPD can take part in exercise training, regardless of age and severity of the disease.

## Prescription

The physical performance capacity of people with COPD is reduced and engaging in some form of exercise training is of great value, both physically and psychologically to everyone. All exercise training should be balanced, that is, include aerobic training (fitness training), strength training (endurance strength) and flexibility training (see Table 1) (34). The training should start with a warm-up component and end with cool-down and stretching.

To begin with, the training should occur under controlled forms and under the direction of a physiotherapist. In connection with training, it is important to measure oxygen saturation. Saturation should not fall below 88–90 per cent. If the saturation decreases, in the first place the workload (intensity) and/or the duration of the training should be reduced. Pursed-lip breathing can be used during training to maintain the saturation at an acceptable level, that is,  $\geq$  90 per cent. For hypoxemic people and people who desaturate during training (SaO<sub>2</sub> < 88%), oxygen supplementation should be given during training (14). It has also been shown that normoxemic people with COPD can exercise at a higher intensity and thereby see more improvement if they receive supplemental oxygen during training (21). However, patients who require supplemental oxygen during training outside medical care. People with a low body mass index (BMI < 22) should be recommended to take nutritional supplements to help increase peripheral muscle strength and aerobic capacity. Pre-medicating with bronchodilators can be recommended for patients who usually have the assistance of these medications.

Patients with mild and severe COPD can perform aerobic exercise at a high intensity (22, 35). For untrained individuals, however, it can be good to begin at a low intensity. Patients with severely limited ventilation can be recommended to begin with strength training or only flexibility training.

Type of training	Intensity	Frequency (times/week)	Duration
Aerobic fitness training	Low intensity: 55–70% of max HR* 40–60% of VO <sub>2</sub> max**	2–5	≥ 30 min.
	High intensity: > 70% of max HR > 60% of VO <sub>2</sub> max 60–80% W max***	2-3	≥ 30 min.
Dynamic strength training Leg, hip, core and shoulder muscles	70% of 1 RM****	2	8–12 reps, 2–3 sets

#### Table 1. Description of different types of training.

\* Max HR = Maximal Heart Rate.

\*\* VO<sub>2</sub> max = Maximal Oxygen Uptake.

\*\*\* W max = Maximal workload.

\*\*\*\* RM = Repetition Maximum. 1 RM corresponds to the maximum weight that can be lifted through the entire exercise movement one time.

**Aerobic training** can be carried out at low intensity or high intensity and either as continuous or interval training. The effects of the two types of training are equivalent (36). All activities involving large muscle groups, and thereby loading the oxygen-transporting organs, are beneficial. Suitable activities include cycling, walking, and fitness training on land or in the water (26). For interval training, 2–3 minutes of high intensity training should be alternated with 1–2-minute intervals of low intensity training or active rest. The training should continue for at least 8–10 weeks (26). The greatest effect of training (measured as oxygen uptake) is achieved through high intensity training (22, 37).

**Strength training** should include endurance strength training and above all target the muscles used for movement (38). Training for core and shoulder muscles should also be included. Each exercise should be performed 8–12 times in 2–3 repetitions at an intensity of 70 per cent of 1 RM (RM = repetition maximum, 1 RM corresponds to the maximum weight that can be lifted through the entire exercise movement one time) (26). To begin with, however, it is completely sufficient to perform only one set. A rest period of 1–3 minutes should be added between sets. The training should continue for at least 8–10 weeks. For low intensity training (40–50% of 1 RM), the training can occur daily; for higher intensity (70–80% of 1 RM), however, training should occur 2 times per week (37, 39, 40).

**Flexibility training** should cover mobility exercises for the neck, shoulders, thorax, thigh and calf muscles, and be included in every training session.

# Functional mechanisms

In aerobic training, there is an increase in the skeletal muscle of the enzymes that stimulate oxidative metabolism and oxygen extraction improves (7). The number of mitochondria increases and blood lactate levels fall for the same degree of workload, that is, oxygen can be metabolised better and the aerobic capacity therefore improves (20). Minute ventilation decreases and oxygen uptake capacity (VO<sub>2</sub>) increases (19, 20, 22). In strength training, the cross-section surface area of type I and type IIa fibres increases. Quality of life and symptoms improve through exercise training. This is probably an effect of both a physical and psychological nature.

# Functional tests

A functional test should always be conducted before physical training begins, in part to facilitate planning of an appropriate training programme, and in part to facilitate evaluation of the training. All testing should include measurement of saturation.

#### Cycle test and treadmill test

Standardised maximal or submaximal tests are carried out to investigate the patient's tolerance and limitations with respect to physical exertion. Heart rate, ECG, blood pressure, oxygen saturation, shortness of breath, exertion and chest pain should be recorded both during and for a short time after the test. Note: If heart disease is suspected, an ECG and blood pressure should be measured up to 5 minutes after the loading stops.

#### Walking test

Standardised walking tests are often used in clinical contexts to assess physical capacity in relation to activities of daily life. The Incremental Shuttle Walking Test (ISWT) (41) is a maximal test in which walking speed is increased every minute. The Endurance Shuttle Walking Test (ESWT) (42) is an endurance test that uses the same speed throughout the test. In both of these tests, the patient walks round two cones placed 9 metres apart. In a 6- or 12-minute walk test, the patient is encouraged to walk as far as possible in 6 or 12 minutes, respectively, on a measured stretch of hallway (43, 44). In all of the walking tests, the walking distance, heart rate, oxygen saturation, and perceived exertion and shortness of breath are measured on the Borg scale (45).

## Muscle function

Both dynamic muscle strength and endurance can be measured with isokinetic devices. Dynamic muscle strength can in addition be measured by repetition maximum (RM). A suitable way to measure dynamic endurance strength is to have the person perform

a maximum number of repetitions at a given load. After a period of training, the test is repeated with the same load. An increase in the number of repetitions is an indication of an increase in muscle endurance.

#### Perception of quality of life and symptoms

General health-related quality of life can be measured with the Short-Form Health Survey (SF-36) (46), while disease-specific quality of life is often measured with the Chronic Respiratory Questionnaire (CRQ) or St. George's Respiratory Questionnaire (48). The severity of symptoms can be measured with a visual analogue scale (VAS) or the Borg scale.

# Risks

No serious events need occur if the patient has undergone a functional test with ECG recording before commencing training, so that the physical limitations the patient demonstrates are known to the person in charge of or instructing the training. No strenuous training should occur if the disease is deteriorating. Many patients with COPD also have decreased cardiac function and high blood pressure. Blood pressure should therefore be monitored during the training.

# Acknowledgement

I would like to thank Olav Kåre Refvem, Licensed Physician, Pulmonary Disease Specialist, and Carl C. Christensen, MD, Glittreklinikken, Hakadal, Norway, for constructive views and updates.

# References

- 1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD Executive Summary. American Journal of Respiratory and Critical Care Medicine. 2007 Sep 15;176:532-55.
- Lundbäck B. KOL-prevalens, incidens och riskfaktorer [COPD prevalence, incidence and risk factors]. In: Larsson K, Ed. KOL. Kroniskt obstruktiv lungsjukdom [Chronic Obstructive Pulmonary Disease]. Stockholm: Boehringer Ingelheim AB; 2006.
- 3. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2001;164:770-7.
- 4. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003;21:347-60.
- 5. Bernard S, LeBlanc P, Whittom F, Carrier G, Jobin J, Belleau R, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 1998;158:629-34.
- 6. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. American Journal of Respiratory and Critical Care Medicine 1996;153:976-80.
- 7. Mador MJ, Bozkanat E. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. Respiratory Research 2001;2:216-24.
- 8. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). European Respiratory Society Task Force. Eur Respir J 1995;8:1398-420.
- 9. Barbera JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. Eur Respir J 2003;21:892-905.
- 10. Bowen JB, Votto JJ, Thrall RS, Haggerty MC, Stockdale-Woolley R, Bandyopadhyay T, et al. Functional status and survival following pulmonary rehabilitation. Chest 2000;118:697-703.
- 11. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000;55:789-94.
- Rabe KF, Beghe B, Luppi F, Fabbri LM. Update in chronic obstructive pulmonary disease 2006. American Journal of Respiratory and Critical Care Medicine 200715; 175:1222-32.
- 13. Wise RA, Tashkin DP. Optimizing treatment of chronic obstructive pulmonary disease. An assessment of current therapies. American Journal of Medicine 2007;120:S4-13.
- Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane database of systematic reviews (Online) 2005;4:CD001744.
- 15. Bendstrup KE, Ingemann Jensen J, 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;10:2801-6.

- 16. Hill NS. Pulmonary Rehabilitation. Proceedings of the American Thoracic Society 2006;3:66-74.
- 17. Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane database of systematic reviews (Online) 2002:CD003793.
- Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation. A randomised controlled trial. Lancet 2000;355:362-8.
- 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. American Journal of Respiratory and Critical Care Medicine 1997;155:1541-51.
- 20. Maltais F, LeBlanc P, Jobin J, Bérubé C, Bruneau J, Carrier L, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Crit Care Med 1997;155;555-61.
- 21. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. American Journal of Respiratory and Critical Care Medicine 2003;168: 1034-42.
- 22. 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. The American Review of Respiratory Disease 1991;143:9-18.
- 23. 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.
- 24. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, LeBlanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. American Journal of Respiratory and Critical Care Medicine 1996;153:288-93.
- 25. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez De Suso JM, Moreno A, et al. Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 1999;159:1726-34.
- 26. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2005;172:19-38.
- 27. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. Eur Respir J 2002;19:1072-8.
- 28. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, et al. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2004;170:870-8.

- 29. Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. Eur Respir J 1996;9:2590-6.
- Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax 1992;47:70-5.
- 31. Bernard S, Whittom F, LeBlanc P, Jobin J, Belleau R, Berube C, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 1999;159:896-901.
- 32. Ortega F, Toral J, Cejudo P, Villagomez R, Sanchez H, Castillo J, et al. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2002;166:669-74.
- Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality. A systematic review. Respiratory Research 2005;6:54.
- 34. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health. Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1081-93.
- 35. Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. Chest 1991;100:618-23.
- 36. Arnardottir RH, Boman G, Larsson K, Hedenstrom H, Emtner M. Interval training compared with continuous training in patients with COPD. Respiratory Medicine 2007;101:1 196-204.
- 37. ATS. Pulmonary rehabilitation-1999. American Thoracic Society. American Journal of Respiratory and Critical Care Medicine 1999;159:1666-82.
- 38. Hodgkin J, Celli BR, Connors GL, Eds. Pulmonary Rehabilitation. Guidelines to success. 3. edn. Baltimore: Lippincott Williams and Wilkins; 2000.
- 39. British Thoracic Society. Pulmonary Rehabilitation. Thorax 2001;56:827-34.
- 40. Storer T. Exercise in chronic pulmonary disease. Resistance exercise prescription. Med Sci Sports Exercise 2001;33:S680-S6.
- Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 1992; 47:1019-24.
- 42. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk. A new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. Thorax 1999;54:213-22.
- Guyatt G, Sullivan M, Thompson P, Fallen E. The 6-minute walk. A new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132: 919-32.
- 44. McGavin C, Groupta S, McHarty G. 12-minute walking test for assessing disability in chronic bronchitis. Br Med J 1976;1:822-3.

- 45. Borg GA. Psychophysical bases of perceived exertion. Medicine and Science in Sports and Exercise 1982;14:377-81.
- 46. Ware J, Scherbourne C. The MOS 36-Item Short-Form Health Survey (SF-36). Conceptual framework and item selection. Med Care 1992;30:473-83.
- 47. 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.
- Jones P, Quirk F, Baveystock C, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The American Review of Respiratory Disease 1992; 145:1321-7.