Management of severe COPD

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide, and the burden of the disorder will continue to increase over the next 20 years despite medical intervention. Apart from smoking cessation, no approach or agent affects the rate of decline in lung function and progression of the disease. Especially in the later phase, COPD is a multicomponent disorder, and various integrated intervention strategies are needed as part of the optimum management programme. This seminar describes largely non-pharmacological interventions aimed at improving health status and function of disabled patients. Exacerbations become progressively more troublesome as baseline lung function declines, commonly necessitating hospital admission and associated with the development of acute respiratory failure.

This is the fourth Seminar in a series about COPD

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation. Classification or staging systems proposed so far have been largely based only on the degree of airflow limitation despite the recognised imperfect relation between the extent of limitation and the presence of symptoms.[1,2] A classification of disease severity into four stages was recommended in 2001.[1] Severe COPD according to this classification is characterised by a ratio of the forced expiratory volume in 1 s (FEV_1) to the forced vital capacity (FVC) of less than 70% and FEV_1 between 30% and 50% of predicted, with or without chronic symptoms of cough and sputum production. At this stage, shortness of breath and repeated exacerbations have a major adverse effect on patients' quality of life.[1] Very severe COPD is characterised by severe airflow limitation (FEV_1 <30% predicted) or the presence of chronic respiratory failure. At this stage, quality of life is generally much impaired and exacerbations can be life threatening.

During the past decade there has been recognition that COPD is a heterogeneous disease with differing underlying disease processes. Furthermore, besides primary effects in the lung, COPD as a chronic disease has secondary effects on other systems, such as the muscles and circulation, and tertiary effects, which involve an interaction between patients and their environment.[3] The influence of some of these factors on the outcome for COPD patients is well documented.[4–7] Therefore, staging systems that offer a composite picture of disease severity are highly desirable. Previous studies have found that various independent factors are important in the pathophysiology of severe COPD. Ries and colleagues[8] reported as significant factors exercise tolerance, airflow limitation, lung volume, and flow rates. Wegner and co-workers[9] identified exercise capacity, ratings of dyspnoea and quality of life, airway obstruction, and pulmonary hyperinflation.[9] Mahler and Harver reported that dyspnoea ratings, maximum respiratory pressures, and lung function independently characterise the condition of patients with COPD.[10]

The important roles of such simple measurements as dyspnoea and bodyweight as measures of disability and as predictors of overall and COPD-related mortality are now well appreciated.[4,5,7,11] A multidimensional staging system consisting of body-mass index, airflow limitation, dyspnoea, and exercise capacity classifies COPD patients more accurately and predicts outcome for these patients.[12]

Staging systems based on single biological outcome measures such as FEV_1 could also contribute to feelings of hopelessness in these severely disabled patients because no response to pharmacological treatment is apparent and non-pharmacological treatments, although helping to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities, are not easily accessible for most of these patients. Especially for patients whose disease is judged to be incurable, overall care has to address physical, psychological, social, and spiritual problems.[13]

Patients' perspectives and treatment preferences

An effective management programme for patients with severe or very severe COPD has to centre on adequate management of symptoms and maintenance of a reasonable quality of life. Studies in severely ill patients have shown that they have very poor quality of life in terms of emotional, social, and physical functioning. Unrecognised psychological disorder and unmet information needs are common.[14] Depression and anxiety are important problems. Of patients referred for lung transplantation, more than one in four showed clear psychological distress characterised by high degrees of depression, anxiety, and somatic complaints that would require attention by mental-health professionals. This observation is particularly important because the presence of mental-health disorders greatly affects medical outcome.[15]

Search strategy and selection criteria

The material covered in this review is based on an extensive search of the published work, participation in expert meetings, and many years of research on the subject. A systematic MEDLINE search was done with key words including "chronic obstructive pulmonary disease", "severity", "palliative care", "respiratory failure", "cor pulmonale", and "muscle wasting" up to June 2004 .

Patients with endstage COPD consider physicians' ability to provide information to be very important. Patients with severe COPD desired information in five content areas: diagnosis and disease process; treatment; prognosis; what dying might be like; and advanced care planning.[16] Honouring of the treatment preferences of these severely disabled patients is crucial to the provision of high-quality care. Understanding of patients' preferences depends on the assessment of how they view the burden of treatment in relation to its possible outcomes and the likelihood of such outcomes. The functional and cognitive outcomes of a given therapy play an even greater part than the risk of death in the preferences of patients with severe COPD, and these patients understand probabilistic thinking and incorporate it into their preferences.[17] Therefore, patients' preferences with regard to specific interventions have to be discussed by the physicians and the patients.

Pharmacological therapy for severe COPD

The judicious use of appropriate medications is the recommended approach to provide symptomatic relief in patients with severe to very severe COPD. Long-acting inhaled β_2-agonists, such as salmeterol and formeterol, significantly improve symptoms, exercise capacity, and health status in patients with COPD.[18–21] Tiotropium, an anticholinergic agent administered once daily, produces similar or greater improvement to β_2-agonists in dyspnoea and in the proportion of patients achieving meaningful changes in health status.[22–25] There is compelling evidence, at least in patients with more severe COPD, that a major benefit of bronchodilator therapy is improvement of lung emptying during expiration; this reduction in dynamic hyperinflation greatly contributes to the decrease in exertional breathlessness and to an improvement in exercise performance.[26,27] Both long-acting β_2-agonists and long-acting anticholinergic agents also reduce rates of exacerbations in COPD.[21,23–25] Use of theophyllines in the management of COPD remains controversial. Particularly in more severe COPD, theophyllines produce bronchodilatation with variable effects on exercise tolerance and symptoms.[28–33] Several studies have shown that combinations of β_2-agonists, anticholinergic agents, and theophylline can achieve additional improvements in lung function and health status.[34–41]

Especially in patients with more severe COPD with FEV_1 of less than 50% predicted and repeated exacerbations, regular treatment with inhaled steroids lowers the frequency of exacerbations and improves health status. The combination of glucocorticoids with long-acting β_2-agonists is more effective than the individual components.[42–46]

Exacerbations

Acute exacerbations are important events in severe to very severe COPD and represent a major societal and emotional burden for these patients.[47–49] The definition of an acute exacerbation is still imprecise and is generally made in operative terms based on the type and number of symptoms, such as an increase in cough or sputum production, worsening of dyspnoea, or changes in sputum purulence. In most patients with severe COPD, acute exacerbations represent real life-threatening periods, frequently complicated by respiratory failure.[50] Exacerbations have been defined as worsening of symptoms requiring changes in normal treatment or in terms of increasing use of health care.[51–53] More recently, an acute exacerbation was defined as a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variation, which is acute in onset and necessitates at least a change in regular medication.[54] Clearly, the severity of exacerbations and the extent of health-care use depend largely on the severity of the underlying COPD and coexisting disorders, and acute exacerbations become progressively more troublesome as baseline lung function declines.

Aetiology of acute exacerbations of COPD

The main aetiological factors in acute exacerbations in general are thought to be viral and bacterial infections and air pollutants. In patients with more severe COPD, studies have focused on the role of bacteria in the pathogenesis of acute exacerbations. Some studies investigated the type of bacterial pathogens isolated in sputum of patients admitted to hospital for acute exacerbations and analysed a possible relation between lung function and the type of bacteria isolated. Patients with more compromised lung function had a higher frequency of infections with *Pseudomonas aeruginosa* and other gram-negative bacteria than those less severely affected, which suggests that patients with more advanced lung disease might need different pharmacological therapy from those with milder disease.[55,56] Another study confirmed the higher frequency of bacterial infections in patients with severe impairment in lung function but did not find any relation between the type of bacteria isolated and the degree of lung-function impairment. The outcomes in terms of hospital stay or subsequent need for admission to the intensive-care unit were not related to the presence or the type of bacterial infections.[57] Newer molecular techniques have shown that bacterial colonisation, a common finding in patients with clinically stable COPD,[58–60] is not stable and that there is frequent turnover of discrete strains of *Haemophilus influenzae* that elicit specific host responses to outer-membrane proteins.[61,62] A change in the strain but not the organism is therefore likely to be the cause of the symptoms of an exacerbation. A meta-analysis on antibiotic treatment in acute exacerbations of COPD concluded that patients with more severe exacerbations are more likely to benefit from antibiotic treatment than those with less severe exacerbations.[63] Viral infections of the lower respiratory tract in patients with COPD can also

cause direct damage to the airway epithelium, resulting in loss of ciliated epithelium, increased mucus production, sloughing of necrotic cells into the airway lumen, and increased plasma exudation.[64] Studies with PCR to detect virus mRNA have shown viruses in around 30% of patients with acute exacerbations of COPD, rhinoviruses predominating.[65] However, the contribution of viruses to acute exacerbations in severe and very severe COPD remains to be defined. Air pollution has been recognised as a cause of exacerbations over the past 40 years, and there is now overwhelming evidence that the amount of air pollution, especially particulates, is associated with acute exacerbations.[66–70]

Risk factors for acute exacerbations

Few studies have assessed possible risk factors for the development of acute exacerbations; most have investigated factors predicting hospital admission for acute exacerbations. The influence of airflow limitation on risk of hospital admission is still controversial.[71–73] In one study, muscle weakness was associated with high use of health services for COPD.[74] Among external factors, influenza vaccination lowers the risk of admission for exacerbations, whereas high air pollution is related to a higher risk.[68,75] Kessler and colleagues[72] reported on predictive factors for hospital admission in a series of 64 patients with COPD followed up for at least 2·5 years. They found that the risk of being admitted was significantly increased in patients with low body-mass index and in those with a limited 6 min walking distance. But above all, the risk of hospital admission for acute exacerbations was significantly increased by gas-exchange impairment and pulmonary haemodynamic worsening; high arterial carbon dioxide tension ($PaCO_2$) and mean pulmonary arterial pressure were independently related to the risk of admission for acute exacerbations.[72] Neither the severity of airflow obstruction nor the degree of hypoxaemia was predictive of hospital admission. Among a wide variety of modifiable and non-modifiable potential risk factors, previous admissions, low FEV_1, and prescription of long-term oxygen therapy were independently associated with a higher risk of admission.[76]

Assessment of acute exacerbations

Patients with acute exacerbations of COPD typically present with increased cough, changes in sputum volume and purulence, and greater breathlessness, wheezing, and chest tightness. Increased breathlessness is a prominent symptom in acute exacerbations. It can be explained by airway narrowing, increased ventilation/perfusion mismatch, and increased metabolic state. Several potential mechanisms of acute exacerbations could exert their influence by reducing the calibre of the airways. In a longitudinal study of patients with moderate to severe COPD, significant decreases in peak expiratory flow rates (PEFR), FEV_1, and FVC were observed during exacerbations; the recovery time was related to the extent of the decreases, and the reduction in PEFR was greater in patients with increased dyspnoea.[77] These findings are supported by intervention studies that have used FEV_1 as an outcome measure and shown significant increases in PEFR and FEV_1 on recovery.[78–81] An increased metabolic state associated with systemic inflammatory response can also cause an increase in breathlessness.[82,83] A significant relation was reported between the change in breathlessness and the reduction in resting oxygen consumption after recovery from acute exacerbations of COPD.[82] In that study, other symptoms such as fatigue, disturbed sleep, and loss of appetite improved significantly during admission for acute exacerbations. Hypoxaemia is a common problem in acute exacerbations. Worsening of ventilation/perfusion matching is the most important determinant of hypoxaemia in this setting, although low mixed venous oxygen tension is a contributing factor.[84] The latter feature can be explained by higher oxygen use resulting from the increased work of breathing as well as by inadequate cardiac compensating capacity to increase cardiac output. Finally, especially in severe COPD, dynamic hyperinflation, impeding the ventilatory pump, is a contributing symptom to the breathlessness experienced during these acute events. Measurements of arterial blood gases are therefore very important in the assessment of patients with acute exacerbations. Generally, an arterial PaO_2 of less than 7·3 kPa or a $PaCO_2$ of more than 7·0 kPa, with accompanying acute or acute-on-chronic respiratory acidosis, indicates acute respiratory failure and is an indication for hospital admission. Particular attention should be paid to changes in mental status, which might also indicate the presence of respiratory failure.

Management of acute exacerbations

Pharmacological management of exacerbations focuses on increases in bronchodilator therapy, antibiotics in some patients, and the addition of oral corticosteroids. Several randomised controlled trials have shown that, compared with placebo, oral and nebulised corticosteroids accelerate the rate of improvement in lung function during an exacerbation, and that oral corticosteroids can shorten the hospital stay.[78,79,85–87] Treatment with 30 mg prednisolone for 7–10 days is sufficient. Controlled oxygen therapy is commonly part of the treatment scheme to overcome hypoxaemia. Especially in severe COPD, oxygen therapy can have the unintended adverse effect of inducing hypercapnia. The underlying mechanisms are a reduction in ventilation associated with removal of the hypoxic stimulus and increasing ventilation/perfusion inequality caused by release of hypoxic vasoconstriction. Patients who retain carbon dioxide are characterised by a significant increase in true alveolar dead-space ventilation.[88] If respiratory

acidosis develops, non-invasive positive-pressure ventilation is a useful alternative to conventional positive-pressure ventilation. The management of acute ventilatory failure in COPD is discussed in more detail later. Identification of patients with favourable outcome after medical therapy could be helpful for risk stratification: malnutrition, a high physiology score (APACHE II), and the degree of airflow limitation are unfavourable indicators of outcome of acute exacerbations of COPD treated medically.[89]

Outcome of acute exacerbations

Outcome and prognosis of COPD are still poorly documented. Connors and colleagues[90] studied more than 1000 patients admitted to hospital with severe hyperbaric exacerbations of COPD. Half of these patients had to be admitted to intensive-care units, and 35% needed mechanical ventilation. Hospital mortality in that study was 11%. A more striking observation was that after discharge a third of the patients died within 6 months and half died within 2 years. Higher acute physiology score, age, and poor functional status before admission increased the risk of death. Improved survival was predicted by greater body-mass index and albumin concentration, higher ratio of PaO_2 to fraction of inspired oxygen, and the presence of cor pulmonale and congestive heart failure. The investigators concluded that patients and health-care staff should be aware of the likelihood of poor outcomes after hospital admission for acute exacerbations of COPD associated with hypercapnia. Similar results of high in-hospital mortality and poor 1-year survival of patients admitted to intensive-care units were confirmed by others.[91] Non-invasive ventilation decreases the need for intubation and the in-hospital mortality associated with acute exacerbations and is now considered an evidence-based intervention strategy.

Further prospective studies of outcome of acute exacerbations of COPD, based on adequate staging of the disease process, are needed to support adequate decision-making in their management.

Fluid homoeostasis in severe COPD

COPD commonly leads to massive oedema and the development of cor pulmonale. The mechanisms by which patients with COPD retain salt and water are not completely understood. Little information is available on changes in body fluid volumes in patients with COPD, and the few available data are conflicting.[92–96] Although there is certainly volume excess at advanced stages when gross oedema is present, the extent to which expansion of the extracellular volume occurs at earlier stages is not clear. Both hypoxaemia and hypercapnia can affect renal sodium excretion in severe COPD. Clinically stable hypercapnic patients commonly show impaired excretion of sodium and water, and correlations have been found between the degree of hypercapnia and the impairment in sodium excretion. Renin and aldosterone concentrations are inversely correlated with total sodium loss, in both patients with severe but stable COPD and those with acute respiratory failure.[97–100] Hypoxaemia causes a significant fall in urinary sodium output with no changes in water excretion, probably related to a decline in glomerular filtration rate.[101] Correction of hypoxaemia results in increased natriuresis.[102] Patients with COPD probably have impaired ability to excrete sodium and their kidneys are likely to be in a sodium-retaining state, particularly evident when hypoxaemia and hypercapnia develop.

Renal blood flow is also severely depressed in patients with acute exacerbations and extensive oedema. Cardiac output is generally normal even in patients with severe COPD; therefore, the renal fraction—that part of the cardiac output flowing through the kidneys—must be reduced.[96] Severe hypoxaemia is associated with reduced renal flow.[103–106] In the presence of hypercapnia, renal perfusion also progressively falls and this vasoconstrictor mechanism withstands vasodilatory stimuli.[104,107,108] Several neurohumoral systems have been investigated in patients with COPD. The findings show that both antinatriuretic and natriuretic systems are activated in COPD.[96,99–101,109–116]

De Leeuw and Dees[117] have formulated a vascular theory to explain disturbed fluid homoeostasis in COPD. They postulate that underfilling is the driving force behind the continuous expansion of the extracellular volume; carbon dioxide acts as a potent vasodilator and an increased carbon dioxide tension will substantially lower peripheral vascular resistance and increase arterial capacity. Furthermore, owing to the reduction in precapillary tone, the point of filtration equilibrium in the capillaries will move distally, resulting in increased extravasation and loss of plasma volume. Consequently, the effective circulating volume will be reduced and the reduction will stimulate the sympathetic nervous system, renin, and arginine vasopressin. The kidney will respond with vasoconstriction and sodium retention to restore intravascular volume and tissue perfusion. Since the whole volume cannot be kept within the vascular system, oedema develops. As long as hypercapnia is maintained or worsens, there will be continuing vasodilation, retention of sodium and water, and expansion of oedema. The use of diuretics will even aggravate this vicious circle by further stimulating sodium loss and compensatory renin activation.

Management of ventilatory failure in COPD

Respiratory failure is a common occurrence in the management of severe COPD. It occurs when the respiratory system cannot maintain adequate ventilation in the presence of major abnormalities in respiratory mechanics. The ability of medical treatment to reverse severe respiratory failure in these patients is limited. Respiratory failure can be part of the clinical picture

during acute exacerbations or in chronic stable COPD patients.

Acute respiratory failure

The aim in managing respiratory failure in acute exacerbations of COPD is to prevent tissue hypoxia and control acidosis and hypercapnia while medical therapy works to improve lung function and reverse the precipitating cause of the exacerbation. pH is the best marker of severity and reflects acute deterioration in alveolar hypoventilation compared with the chronic stable state.[84,118]

A stepwise approach consisting of three complementary interventions can now be proposed in the management of these patients.[119,120] The first step is based on drug treatment and on appropriate management of oxygen. Theoretically, respiratory stimulants could be part of such a medical treatment programme. However, various studies have reported that doxapram, the most widely used and most effective respiratory stimulant, can provide only minor short-term improvement in blood gas tensions.[121] Controlled oxygen therapy in management of acute exacerbations requires regular monitoring of pulse oximetry and arterial blood gases for PaO_2 to be maintained at more than 6·6 kPa without a fall in pH below 7·26, or at more than 7·5 kPa if the pH is satisfactory.[120]

The second step in the management of acute respiratory failure is the early use of non-invasive ventilation to prevent further worsening and clinical deterioration. In non-invasive positive-pressure ventilation the patient receives air or a mixture of air and oxygen from a flow generator through a full facial or nasal mask, and ventilation is increased by unloading of fatigued ventilatory muscles. Non-invasive ventilation as an adjunct to usual medical care significantly reduces mortality, need for endotracheal intubation, risk of treatment failure, and length of hospital stay.[122–129] A meta-analysis on outcome with non-invasive ventilation showed that this intervention shortened the stay in hospital by more than 3 days; the length of stay did not differ between intensive-care units and medical wards, which suggests that non-invasive ventilation could affect future use of resources.[130] A cost-effectiveness study of ward-based non-invasive ventilation for acute exacerbations of COPD confirmed that it is a highly cost-effective treatment that both reduced total costs and improved mortality in hospital; allocation to the non-invasive ventilation group in this UK study was associated with a reduction in costs mainly through reduced use of intensive-care units.[131] Long-term survival after non-invasive ventilation at 1 year of follow-up has varied in different studies from 58% to 87%.[132]

There is very strong evidence for delivering non-invasive ventilation as soon as the patient develops moderate respiratory acidosis with a pH of 7·35 or lower and raised $PaCO_2$.[120] The final treatment step is endotracheal intubation and mechanical ventilation, which should be reserved for patients in whom non-invasive ventilation is contraindicated, for those meeting intubation criteria despite non-invasive ventilation, and those who need immediate endotracheal intubation on admission.[119] However, assessment of the appropriateness of mechanical ventilation and the associated admission to the intensive-care unit should take into account the severity of the underlying disease, the reversibility of the precipitating cause, the quality of life of the patient, and the presence of severe comorbidities.

Chronic respiratory failure

Management of respiratory failure in chronic stable COPD largely relies on long-term oxygen therapy. Two large studies in the 1970s showed improved survival when oxygen was used for at least 15 h per day in patients with hypoxaemia due to COPD.[133,134] The current recommendation is when the PaO_2 falls below 7·3 kPa while the patient is clinically stable to advise long-term oxygen therapy for at least 15 h per day. However, the standard of care for long-term oxygen therapy should be continuous administration with ambulatory capability.[135] The mechanisms by which long-term oxygen therapy improves survival remain unknown. No survival benefit is seen with lesser degrees of hypoxaemia.[135,136] Oxygen settings should be adjusted for rest, exertion, and sleep, to meet the individual patient's needs. Oxygen taken while exercising improves endurance.[137,138] Otherwise, no physiological or symptomatic benefit can be derived from oxygen breathed for short periods before or after submaximal exercise in patients with moderate to severe COPD.[139] Short-term use of ambulatory oxygen is associated with significant improvements in health-related quality of life in COPD patients who do not meet criteria for long-term oxygen therapy but who show substantial exertional desaturation.[140] Air travel is difficult for hypoxaemic patients with COPD. The PaO_2 during air travel should be maintained above 6·7 kPa (50 mm Hg). For high-risk patients, the goal should be to maintain PaO_2 during the flight at the same value at which the patient is clinically stable at sea level. Patients will also need oxygen supplementation if the altitude at the destination is substantially greater than at home.

Preliminary results from two multicentre European trials comparing non-invasive ventilation with long-term oxygen therapy in COPD suggest that non-invasive ventilation does not improve survival but might reduce the need for hospital admission in these patients.[141,142] Until further data are available, non-invasive ventilation can be considered in patients who have symptoms of nocturnal hypoventilation despite maximum bronchodilator therapy, who cannot tolerate long-term oxygen therapy even with careful administration, or who have repeated admissions to hospital with acute hypercapnic ventilatory failure.[120]

Muscle wasting

Prevalence

For many decades weight loss was thought to be an inevitable and irreversible component of the terminal progression of the disease process. Wasting of body cell mass, the actively metabolising and contracting tissue, is an important systemic manifestation because loss of more than 40% of this tissue is incompatible with life. Loss of body cell mass can be clinically recognised by weight loss in general and loss in fat-free mass in particular. In clinically stable patients with moderate to severe COPD, depletion of fat-free mass has been reported in 20% of COPD outpatients and in 35% of those eligible for pulmonary rehabilitation.[143,144] In patients with acute respiratory failure, nutritional depletion is reported in up to 70%.[145]

Pathogenesis

Weight loss, particularly loss of fat mass, occurs if energy expenditure exceeds dietary intake. Muscle wasting is a consequence of an imbalance between synthesis and breakdown of protein. Impairments in total energy balance can occur simultaneously, but these processes can also be dissociated because of altered regulation of substrate metabolism.[146] Several studies have provided evidence for involvement of systemic inflammation in the pathogenesis of tissue depletion in patients with COPD.[147–150] Systemic inflammation could modify energy homoeostasis partly by interaction between cytokines and leptin metabolism. Leptin is synthesised by adipose tissue and is the afferent hormonal signal to the brain regulating fat mass.[151,152] Disturbances in the tightly regulated equilibrium between protein synthesis and breakdown can also be induced by systemic inflammation at least by activation of the ATP-dependent ubiquitin-proteasome pathway.[153,154] Direct effects of tumour necrosis factor on differentiated skeletal muscles have been reported; treatment with this factor reduces the total protein and myosin heavy-chain content in a manner dependent on time and concentration.[155] Muscle wasting might also be the result of a decreased number of fibres, resulting from changes in the regulation of skeletal-muscle regeneration or activation of apoptotic pathways.[156,157] New insights into the regulation of the processes of atrophy and hypertrophy could provide opportunities for modulation of these processes in the future.[158]

Diagnosis

If the body is considered to be a single compartment, measurement of weight and height provides a simple assessment of nutritional status. Serial measurements of bodyweight can disclose progressive involuntary weight loss, which is generally considered to be clinically relevant when it exceeds 5% over a month or 10% over 6 months. Two methods are commonly used to compare the patient's weight with reference data. Actual bodyweight can be related to the ideal bodyweight as derived from height, frame size, and sex.[159] Nutritional depletion is generally and arbitrarily defined as bodyweight of less than 90% of the ideal. Bodyweight can be corrected for body size by calculation of body-mass index; a value between 18·5 kg/m^2 and 25·0 kg/m^2 is generally taken as normal, depending on the changes in body composition.[160] The assessment of nutritional status according to bodyweight provides no qualitative information on body tissues. Partitioning of the body can be simply achieved by anthropometry, bioelectrical impedance, or dual-energy X-ray absorptiometry.[161,162] A fat-free-mass index (fat-free mass in kg divided by height squared) of less than 16 kg/m^2 in men and 15 kg/m^2 in women is taken as an indicator of active body-tissue depletion.[159]

Consequences

Nutritional depletion is a predictor of mortality in patients with COPD.[4,5,163–165] In a large population of hypoxaemic patients with COPD treated with long-term oxygen therapy, Chailleux and colleagues[165] showed that survival improves with increasing body-mass index and was best for obese patients. In addition to the consequences of low bodyweight on mortality, nutritional depletion is an important determinant of muscle strength, exercise capacity, exercise response, and impaired health status in patients with COPD.[166–171] Nutrition depletion is also related to morbidity in acutely ill patients with COPD; there is an increased need for mechanical ventilation in acute exacerbation,[89] an increased risk of early non-elective readmission in patients previously admitted for an exacerbation,[172] and an increased duration of ventilatory support after lung transplantation or lung-volume-reduction surgery.[173,174] Nutritional depletion is also associated with increased rates of hospital admission in hypoxaemic patients with COPD treated with long-term oxygen therapy at home, independently of the severity of airflow limitation.[165]

Management

The outcome of nutritional intervention in patients with COPD can be hampered by various factors: non-compliance, inadequate baseline assessment of energy requirements, or substitution of regular meals by supplements. Furthermore, dietary advice for high-protein, high-carbohydrate, calorie-dense foods contrasts with what health-care providers generally advise as a healthy diet, and weight loss in patients with COPD can promote positive feedback from the social environment.[175] Although a meta-analysis of reported randomised trials of calorie supplementation given for more than 2 weeks found no significant improvements in anthropometry, lung function, or exercise capacity, the researchers advocate that nutritional support should be combined with an anabolic stimulus such as exercise to optimise outcome.[176] Use of an anabolic stimulus aims to avoid a

preferential increase in fat mass after restoration of energy balance. The combined treatment of nutritional support and exercise increases bodyweight and results in a significant improvement in fat-free mass and respiratory-muscle strength.[177] Increases in bodyweight and fat-free mass, associated with improvements in ventilatory-muscle function, handgrip strength, peak work capacity, and health status have been reported in depleted patients with nutritional supplementation therapy incorporated in a pulmonary rehabilitation programme.[178] The clinical relevance of treatment response was further shown in a post-hoc analysis showing that weight gain and increase in respiratory-muscle strength were associated with significantly better survival.[5] Especially in severe COPD, poor weight gain after nutritional supplementation is related to an increased systemic inflammatory response.[148] Further characterisation and unravelling of the pathophysiological abnormalities involved in tissue wasting could enlarge the perspective for nutritional intervention, not merely by protein-energy supplementation to reverse weight loss, but also by targeted metabolic modulation of specific problems in subgroups of COPD patients through nutritive and non-nutritive actions.

Pulmonary rehabilitation

Definition and eligibility criteria

The concept of rehabilitation, involving holistic efforts to restore patients with debilitating and disabling disease to a state of optimum functioning, is a fairly recent approach in pulmonary medicine. Pulmonary rehabilitation has been defined as a multidimensional continuum of services directed to people with pulmonary disease and their families, generally by an interdisciplinary team of specialists, with the goal of achieving and maintaining the individual's maximum degree of independence and functioning in the community.[179] According to a European Respiratory Society task force, pulmonary rehabilitation is a process that systematically uses scientifically based diagnostic management and assessment options to achieve the best daily functioning and health-related quality of life of individual patients with impairment and disability due to chronic respiratory diseases as measured by clinically or physiologically relevant outcome measures.[180] Most of these definitions refer to the philosophical concept of rehabilitation as the restoration of the individual to the fullest medical, mental, emotional, social, and vocational potential of which he or she is capable. Although all COPD patients benefit from exercise, pulmonary rehabilitation should be considered particularly for those who have persistent dyspnoea or other respiratory symptoms, reduced exercise tolerance, restriction in activities because of their disease, or impaired health status. Pulmonary rehabilitation is therefore indicated in those COPD patients with manifested functional deficit after optimum pharmacological treatment. The GOLD guidelines recommend addition of pulmonary rehabilitation in the management of all COPD stages except stage 1.[1] Therefore it is part of the optimum management of patients with severe and very severe COPD.

Goals and outcome

The goals of rehabilitation in COPD are multifactorial, including decrease and control of respiratory symptoms, increase in physical capacity, improvement in health status, reduction of the psychological influence of physical impairment and disability, prevention of complications and exacerbations, and ultimately prolongation of life.[1] There is much evidence that rehabilitation improves dyspnoea on exertion and that associated with daily activities in COPD. Favourable outcomes have been reported after pulmonary rehabilitation in maximum exercise tolerance, peak oxygen uptake, endurance time during submaximal testing, functional walking distance, and strength of peripheral and respiratory muscles. Pulmonary rehabilitation also results in a clinically significant improvement in disease-specific and general measures of quality of life.[181–184] The effect size of pulmonary rehabilitation largely exceeds what can be achieved by the best pharmacological therapy. This intervention is therefore judged to be evidence based with respect to both exercise tolerance and symptoms of dyspnoea and fatigue.[1] These effects are long-lasting (>1 year), and not necessarily related to improvements in exercise ability.[182,183,185] The incremental costs of achieving improvements beyond the lowest clinically important difference in dyspnoea, emotional functioning, control of the disease, and exercise tolerance vary widely between studies.[181,183] The inpatient phase of pulmonary rehabilitation is especially expensive. A cost-usefulness analysis done in conjunction with a randomised controlled trial of pulmonary rehabilitation versus standard care showed that pulmonary rehabilitation was cost-effective.[186] Data on prevention of complications and exacerbations and on reduction of mortality are scarce and conflicting. One study found that COPD patients taking part in a rehabilitation programme spent significantly fewer days in hospital than non-participants, although the number of admissions did not differ.[184]

Although each patient enrolled in a rehabilitation programme has to be treated individually in terms of specific physiopathological and psychopathological impairment, exercise training is the cornerstone of rehabilitation. Striking physiological and biological responses to training can be observed. At a given degree of exercise, significant reductions in blood lactate, carbon dioxide production, minute ventilation, oxygen consumption, and heart rate were observed, as well as significant improvements in aerobic enzymatic capacity in the muscles of the legs; these enzymatic changes were related to the reduction in exercise-induced lactic acidosis in these patients.[187,188]

A particular challenge in severe COPD is the intensity of training. Most COPD patients are unable to achieve high-intensity training, defined as a training intensity of 80% of baseline maximum power output. However, the intensity of training achieved is not influenced by the initial baseline maximum oxygen consumption, age, or the degree of airflow limitation. Despite the impossibility of maintaining high-intensity training, significant improvement in exercise capacity can be obtained and there is physiological adaptation to endurance training.[189] For patients with severe COPD, isolated conditioning of peripheral skeletal muscles, by means of a cumulative set of individual limb exercises, results in significant improvements in measures of upper and lower peripheral-muscle performance.[190]

Better understanding of the pathophysiological mechanisms contributing to functional impairment will contribute to optimisation of future intervention strategies.

Surgical treatment procedures in severe COPD

Lung-volume-reduction surgery

Some years ago, the technique of lung-volume-reduction surgery was devised to reverse some of the devastating effects of emphysema.[191] This technique was first proposed in conjunction with lung denervation[192] and was discarded after the initial experience owing to the high mortality risk. Observations about the physiological behaviour of patients with emphysema during and after lung transplantation led to the reconsideration of volume reduction by Cooper.[193] Reported results of lung-volume-reduction surgery have consistently shown benefit with acceptable mortality and varying morbidity.[194–200]

These fairly uniform results have, surprisingly, been obtained despite the use of a wide array of surgical strategies including bilateral and unilateral approaches, open and thoracoscopic operations, and buttressed or unbuttressed staplers.[201] Lung-volume reduction can even be achieved with unilateral bronchoscopically placed valve implants in patients with severe emphysema.[202] Consistent features among reports of successful lung-volume-reduction programmes have been meticulous selection of patients, methodical preparation of the patient with reduction of risk factors, and attentive postoperative care.[201] The presence of pronounced hyperinflation, heterogeneous distribution of destruction preferentially in the upper lobes, an FEV_1 of more than 20% predicted, and a normal $PaCO_2$ are considered as discriminating conditions favouring lung-volume-reduction surgery. However, uncertainty about morbidity and mortality, the occurrence, magnitude, and duration of benefits, and preoperative predictors of benefit led to multicentre, randomised clinical trials. The National Emphysema Treatment Trial used mortality and maximum exercise capacity 2 years after randomisation as the primary outcomes.[203] Overall mortality did not differ in this study between the patients undergoing lung-volume-reduction surgery and those assigned medical therapy only. Exercise capacity after 24 months had improved by more than 10 W in 16% of patients in the surgery group compared with 3% of patients in the medical-therapy group. Patients assigned surgery were significantly more likely than those assigned medical therapy to have improvements in the distance walked in 6 min, the percentage predicted values for FEV_1, general and health-related quality of life, and degree of dyspnoea. After interim analyses, patients with FEV_1 20% or less of the predicted value and either homogeneous emphysema or a diffusing capacity of carbon monoxide that was 20% or less of the predicted value had a high risk of death after lung-volume-reduction surgery with little chance of functional benefit.[204] The National Emphysema Treatment Trial[203] found that patients with predominantly upper-lobe emphysema and low exercise capacity had lower mortality after lung-volume-reduction surgery than the corresponding medical-therapy group. Cost-effectiveness analysis shows that lung-volume-reduction surgery is costly compared with medical therapy. The procedure might be cost-effective if benefits can be maintained over time; the cost-effectiveness ratio for lung-volume-reduction surgery compared with medical therapy was US $190 000 per quality-adjusted life-year gained at 3 years and US$53 000 per quality-adjusted life-year gained at 10 years.[205]

Lung transplantation

Pulmonary emphysema was initially thought to be a contraindication to lung transplantation, but idiopathic emphysema and α1-antitrypsin deficiency have together become the most common indication for pulmonary transplantation. These two diagnoses account for 58% of single-lung transplants in adults and 30% of bilateral-lung transplants.[206] Patients with diffuse disease, low FEV_1 (<20% predicted), hypercapnia ($PaCO_2$ >7·3 kPa), and associated pulmonary hypertension are directed towards lung transplantation.[201] The advantages of this approach have to be carefully balanced against the well-known disadvantages. Complete replacement of the diseased and non-functioning lungs can contribute to a striking improvement in pulmonary function and exercise tolerance but the paucity of available donor lungs has created a long waiting list, the operation is associated with initial morbidity and mortality, and there is a risk of chronic allograft dysfunction or bronchiolitis obliterans syndrome. Patients considering this operation must therefore be willing to accept the immediate risks of morbidity and mortality in exchange for an expected relief from dyspnoea and an uncertain effect on life expectancy.[201] Furthermore, with strict adherence to selection criteria, very few patients with emphysema are candidates for any surgical therapy.

Conclusions

In common with other chronic diseases, the image of COPD conveys a sense of despair and therapeutic futility in both patients and health professionals. The growing body of evidence for the benefits of non-pharmacological treatment in the reduction of disability and handicap from this disease emphasises the need for an individualised, multidimensional management programme, which takes into account that COPD is a systemic illness with pathophysiology extending beyond the airways. The individual and societal burden of the disease necessitates adequate provision of services to attenuate morbidity and improve quality of life for these very disabled patients. Increasing knowledge among patients about the progressive and irreversible nature of severe COPD is very important to stimulate discussions about advance care planning and decision-making in the terminal stage of disease. Physicians must be trained in understanding the heterogeneity of COPD, multidimensional management, and end-of-life management for these patients. Emotional support and compassion, communication with patients, continuity, accessibility, respect for the dignity of the patient and family, and honouring of the treatment preferences are very important skills in the management of severe COPD.

Conflict of interest statement

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