The patients with severe Chronic Obstructive Pulmonary Disease and chronic respiratory insufficiency

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ABSTRACT: The patients with severe Chronic Obstructive Pulmonary Disease and chronic respiratory insufficiency. N. Ambrosino, M. Di Giorgio, A. Di Paco.

Caring for patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages III and IV with chronic respiratory failure is difficult independent of whether the target is survival or quality of life (QOL). The role of inhaled drug therapy in this specific set of very severe COPD patients has not previously been assessed. The only drug able to prolong survival in these patients is long-term oxygen therapy, whereas there is little evidence to indicate long term domiciliary mechanical ventilation in the routine management of stable hypercapnic patients. Supplemental oxygen during exercise reduces exercise breathlessness and improves exercise capacity of the hypoxaemic patient. Pulmonary rehabilitation including nutritional supplementation is a significant component of therapy, even in these severe patients. Relief of dyspnoea with drugs such as morphine should not be denied to severely disabled patients who share poor QOL with cancer patients. Non-invasive ventilation has been used as a palliative treatment to reduce dyspnoea.

Lung Volume Reduction Surgery may improve mortality, exercise capacity, and QOL in selected patients, but is associated with significant morbidity and an early mortality rate in the most severe patients. Lung transplantation is a final step in end-stage patients, but short- and long-term outcomes remain significantly inferior in relation to other “solid” organs recipients.

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Keywords: Dyspnoea, quality of life, exercise, oxygen, non invasive mechanical ventilation, lung transplantation, lung volume reduction surgery, opioids.

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Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and invalidity worldwide. This differs from mortality caused by other diseases such as cardiovascular disease and cancer as in this case age-adjusted mortality continues to increase [1]. COPD guidelines or recommendations generally do not address patients with end-stage disease, although such patients are frequently seen in clinical practice by family physicians and respiratory specialists. Caring for the most severe patients i.e. those with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages III and IV with chronic respiratory insufficiency is difficult and represents an important economic burden [1]. In this brief review we address the management of such patients, beginning with the size of the problem, we describe the actual weapons available to limit the severe outcome and costs of care.

Epidemiology, natural history, comorbidities

In an Italian study of prevalence rate, GOLD stages III-IV were 4.5 and 0.4% respectively in males and 2.2 and 0.3% in females [3]. It is more difficult to evaluate the prevalence of chronic respiratory insufficiency in COPD patients. Probably the best proxy to evaluate prevalence of chronic respiratory insufficiency is the use of long-term oxygen therapy (LTOT) for chronic hypoxaemia and long-term home mechanical ventilation (HMV) for chronic hypercapnia. The estimated number of Italian patients on LTOT is 50,000 (estimated prevalence of about 50 per 100,000) [4].

The Eurovent study, a survey conducted in 16 countries [5] estimated the prevalence of HMV as 6.6 per 100,000 people with a large variation among the countries. The COPD users in this survey were more likely to be male and aged > 65 yrs. The survey showed that 34% of HMV users (7,000 people) had parenchimal lung diseases including COPD.

The overall mortality among subjects with GOLD Stage III or IV COPD has been reported to be 42.9/1000 [6], women on LTOT being at a greater risk of death than men [7]. Increased mortality has been observed in older patients with lower body mass index (BMI), a need for oxygen utilisation and greater hyperinflation, reduced exercise capacity [8]. Cause-specific mortality has been reported: cardiovascular 27%, respiratory 35%, cancer 21%, other 10% and unknown 8% [9].

Among severe COPD patients, those admitted to Intensive Care Unit (ICU) with an acute exacerbation are re-admitted to the hospital within six
months and have a median survival of two years, and 50% of patients [10]. Their six year mortality rate is 85% and is mainly influenced by pre-ICU admission quality of life (QOL) [11]. Prediction of survival status after ICU may be enhanced by considering arterial oxygen tension, serum albumin, BMI, disease duration and time elapsed since the first hospitalisation [12]. In these patients the major determinants of hypercapnia at discharge are inspiratory work, respiratory muscle strength, and breathing pattern [13].

**Comorbidities**

COPD affects many organ systems in addition to the lungs [14]. Indeed in a study undertaken [9] only 40% of deaths were definitely or probably related to COPD. The risk of atherosclerosis, cardiovascular disease and mortality is further increased in smoking COPD patients [15], and treatment with statins is associated with improved survival [16]. In addition to an inflammatory process in the lung itself, systemic inflammation plays an important role in COPD. Patients with COPD have higher levels of C-reactive protein, which is a strong predictor of COPD hospitalisation and death, independent of smoking and lung function [17].

**Therapeutic options**

The main intervention in the management of such severe COPD patients is summarised in the table.

**Inhaled Drug Therapy**

Only smoking cessation [18] and LTOT [19] improve survival in COPD, an effect maybe due also to the prevention of exercise induced oxidative stress [20]. Studies have shown an association between inhaled corticosteroids and a reduction in mortality and re-hospitalisation [21]. A large, randomised, controlled clinical trial on more than 6000 COPD patients [22] indicates a statistically non significant advantage in survival by using inhaled combination of beta2 long acting agonists with steroids. Nevertheless the real effectiveness of inhaled drug therapy in the subset of very severe patients has not been specifically assessed yet. Oral corticosteroids as maintenance treatment in patients with end-stage respiratory disease are an independent risk factor for death, and should be avoided in most cases [23].

**Long term domiciliary non-invasive mechanical ventilation**

Adverse to the evidence supporting the use of non-invasive positive pressure ventilation (nPPV), for other causes of chronic respiratory failure like restrictive thoracic diseases, there is conflicting evidence concerning the benefits of long term nPPV in stable hypercapnic COPD patients. A review of literature indicates that currently, there is little evidence for the use of mechanical ventilatory support in the routine management of these patients. However, further large studies may be able to identify subsets of patients able to take advantage from this therapy, especially those with frequent exacerbations and hospitalisations [24].

**Rehabilitation**

Regular physical activity may reduce lung function decline and the risk of developing COPD among active smokers [25] and reduce the risk of both hospital admission and mortality [26], possibly due to the counteracting increase of exercise-associated oxidative stress [27]. Several studies provide scientific evidence that rehabilitation improves in the short and long term, several of the variables associated with poor outcomes, such as exercise capacity, dyspnoea, QOL [28-30]. Pulmonary rehabilitation is provided also to most severe patients, indeed studies report the beneficial effects of physiotherapy in COPD patients with chronic respiratory insufficiency [31] also in the ICU setting [32, 33].

In these severe COPD patients extreme breathlessness and/or peripheral muscle fatigue may prevent patients from higher levels of exercise intensity. Increased inspiratory muscle work may contribute to dyspnoea and exercise limitation. A recent review provides little support for oxygen supplementation during exercise training for COPD patients, but the evidence is very limited [34]. Studies with a larger number of participants and strong design are required to permit strong conclusions, especially for functional outcomes such as symptom alleviation, QOL and ambulation. Several studies have shown that ventilatory assistance delivered through a nasal or facial mask during exercise, may reduce dyspnoea and work of

| Table - Main interventions in the management of severe COPD patients |
|---------------------------------------------------------------|
| Inhaled Drug Therapy                                           |
| Long Term Oxygen Therapy                                       |
| Long term domiciliary mechanical ventilation                   |
| Rehabilitation                                                 |
| Oxygen supplementation                                         |
| Ventilatory assistance                                         |
| Neuromuscular electrical low-voltage stimulation               |
| Lung Volume Reduction Surgery                                  |
| Lung Transplantation                                           |
| Nutritional Therapy                                            |
| Management of Dyspnoea                                         |
| Opiates                                                       |
| Oxygen                                                        |
| Heliox-Oxygen mixtures                                         |
| Treatment of acute on chronic respiratory failure with         |
| Non invasive ventilation                                       |
| Non invasive ventilation as a palliative measure               |
| Patient - Doctor communication and End of Life Decisions       |
breathing and enhance exercise tolerance in COPD patients [35]. These findings differ from the results of physiological studies, where the additional benefit of assisted ventilation on exercise tolerance, dyspnoea and health status was not unanimously demonstrated when compared with training alone. In chronic hypercapnic COPD, nPPV could be administered whilst walking with unchanged ventilator settings compared with settings used at rest, thus resulting in improved oxygenation, decreased dyspnoea and increased walking distance. suggesting that this could play a role in palliative care [36]. Larger prospective controlled studies should be undertaken to determine if assisted ventilation may eventually have routine applicability, in particular subgroups of patients [37].

Small controlled studies of Neuromuscular electrical low-voltage stimulation in severe COPD patients have reported benefits by inducing an increase in the muscular oxidative capacities [35].

**Lung Volume Reduction Surgery**

Lung volume reduction surgery (LVRS) is used to treat patients with severe emphysema by removing the most damaged areas of the lung, thus reducing hyperinflation. This technique has been shown to improve mortality, exercise capacity, and QOL in selected patients with upper lobe disease and poor exercise capacity compared with patients randomised to medical therapy, nevertheless this modality is associated with significant morbidity and an early mortality rate in the most severe patients [38]. For these reasons, and because of the high risk of the procedure for patients with the most severe disease, alternatives have been studied, including bronchoscopic lung volume reduction and endobronchial valve placement [39].

**Lung transplantation**

Lung transplantation is an option for a more limited number of patients. Despite recent significant progress, both short- and long-term outcomes remain significantly inferior for lung relative to other “solid” organs transplantation [40]. Pulmonary function generally improves after lung transplantation, but exercise capacity remains below predicted values, primarily due to a peripheral muscle myopathy [41]. Pulmonary rehabilitation programmes can improve the exercise tolerance and QOL in both short and long term after lung transplantation [42]. Long-term results of lung transplantation are limited as a result of significant complications that impair survival: bronchiolitis obliterans is the most important long-term complication of lung transplantation resulting in decreased pulmonary function [40].

**Nutritional Therapy**

Nutritional depletion is a common problem in COPD patients and is associated with a poor prognosis in stable COPD patients with and without respiratory failure [43]. Patients with COPD are at risk of a low fatty mass (FFM) and a low FFM is prevalent even among subjects with normal BMI [44]. In COPD patients there is also a relationship between the severity of disease and nutrition. Semi-starvation and muscle atrophy are equally distributed among disease stages, but the highest prevalence of cachexia is reported in GOLD stage IV [47]. As increase in body weight, muscle mass and strength has been associated with better exercise tolerance and survival, improving peripheral muscle function is a possible therapeutic target in these patients. Pharmacological approach to this problem (e.g. anabolic steroid, growth hormone, and testosterone supplementation) is still questioned [43].

**Management of Dyspnoea**

In patients with advanced emphysema, dyspnoea is often incapacitating and commonly indicates the onset of the final stage of this illness. The most effective treatments for dyspnoea in COPD are bronchodilators at all stages of disease, and LVRS in most severe stages which have been proposed to improve the mechanical impairment. Pulmonary rehabilitation is prescribed to reduce ventilatory demand. In end-stage disease a range of other less well validated approaches have been attempted [46].

**Opiates** reduce sensations associated with breathing. Therapeutic doses of opioids induce peripheral vasodilation, reduce peripheral vascular resistances and inhibit baroreceptors response. These drugs reduce the anxiety associated with dyspnoea, and should have a place in the management of the terminal phase of disease [47]. Despite safety concerns, a recent meta-analysis has shown that morphine may significantly reduce dyspnoea, in patients with cancer, without significantly accelerating death in patients in whom mechanical ventilation was withdrawn [48]. Epidural methadone perfusion at thoracic level can effectively palliate dyspnoea and improve exercise capacity and QOL in patients with advanced emphysema, without resulting in deterioration of respiratory control or lung function [49].

**Oxygen.** Decreasing ventilatory demands and/or gas density have been recently shown to improve exercise tolerance, symptoms, and QOL [50]. Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance of the hypoxaemic COPD patient by different mechanisms: reduction of hypoxic stimulation of the carotid bodies, pulmonary vasodilation, increase in arterial oxygen. The latter two mechanisms may potentially reduce carotid body stimulation at heavy levels of exercise by increasing oxygen delivery to the exercising muscles and reducing carotid body stimulation by lactic acidaemia. Recent studies also indicate that reduction in hyperinflation, that is decrease in ventilatory impedance, plays an important role in the oxygen-related relief of dyspnoea [51]. A systematic review [52] of the short-term efficacy of ambulatory oxygen from single-assessment studies in
COPD indicates that oxygen improved the primary outcomes relating to endurance and maximal exercise capacity.

**Heliox-Oxygen mixtures.** Manipulating gas density using heliox breathing has also been shown to be beneficial in relieving symptoms and improving exercise capacity, as it facilitates gas emptying during expiration. As a result, the amount of expiratory flow limitation and operational lung volumes decreases, thus reducing ventilatory impedance and ultimately leading to greater exercise tolerance [53].

**Treatment of acute on chronic respiratory failure**

According to the International consensus conference on nPPV for acute respiratory failure [54] the addition of nPPV to standard medical treatment of patients with acute on chronic respiratory failure due to acute exacerbations of COPD may prevent the need for intubation and reduce the rate of complications and mortality. The reduction of complications related to the endotracheal intubation and to the weaning from the invasive mechanical ventilation is the main factor affecting mortality. nPPV can be administered outside of the ICU. This statement has been confirmed by several prospective, randomised, controlled studies included in a recent meta-analysis [55]. Therefore nPPV should be considered as the “first line” treatment of this condition, leaving invasive mechanical ventilation as the “second line” in case of failure.

In addition nPPV has also been used increasingly as an alternative to invasive ventilation in patients with a “do not intubate” order with acute respiratory failure, including COPD. The Society of Critical Care Medicine has recently charged a Task Force with developing an approach for considering use of nPPV for patients who choose to forego endotracheal intubation. The use of nPPV for patients with acute respiratory failure could be classified into three categories:

1) nPPV as life support with no preset limitations on life-sustaining treatments;
2) nPPV as life support when patients and families have decided to forego endotracheal intubation; and
3) nPPV as a palliative measure when patients and families have chosen to forego all life support, receiving comfort measures only. The Task Force suggested an approach to use nPPV for patients and families who choose to forego endotracheal intubation. nPPV should be applied after careful discussion of the care goals, with explicit parameters for success and failure, by experienced personnel, and in an appropriate healthcare settings [56].

**Cognitive function and end of life decisions**

The ability to function in activities of daily life (ADL), as well as the QOL of a patient with COPD, may be further complicated by psychological complaints or even a concurrent mental disorder. Although the physical illness itself probably contributes to the occurrence and severity of the psychological complaints, this does not mean that these complaints will be resolved once the respiratory complaints are treated. Hypoxaemic COPD patients, in LTOT, may show reduced QOL, decreased ability to cope with ADL, cognitive function, and depression [57, 58]. COPD patients surviving acute on chronic respiratory failure and requiring mechanical ventilation suffer worsened perceived health status and cognitive function than stable COPD patients on LTOT who have never previously required intensive/intermediate care units admission. After discharge the health and cognitive status may improve to levels similar to those of stable COPD patients on LTOT [59].

Only few patients with severe COPD discuss End-of-Life issues with their physicians. Although, end stage COPD patients have less ability to perform ADL than patients with lung cancer [60], these patients receive less home nursing and palliative care than the former, despite having similar preferences for palliation [61]. There is a lack of information from professionals regarding diagnosis, prognosis and social support. Lack of planning of End-of-Life care, results in difficult decisions being deferred, so that few patients complete advance directives [62]. Such advance directives are not allowed in all countries and are influenced also by religious habits [63]. Decision aids, can increase awareness of benefit without illusions, and risks of therapies and can improve adherence to the interventions chosen [64]. Advance directives increase patient autonomy by their specifying treatment choices and indicating surrogate decision makers [65]. In European respiratory intermediate care and high dependency units, an End-of-Life decision is taken for 21.5% of patients admitted. Withholding of treatment, do-not-intubate/do-not-resuscitate orders and nPPV as the ventilatory care ceiling are the most common procedures. Competent patients are often involved, together with nurses [66].

**Future perspectives**

Improving the quality of care for end stage patients should be a major goal of present medical intervention. Until recently, little attention was paid to the healthcare needs of the most severe COPD patients, despite their poor life expectancy and the ever declining health status. The 6-yr mortality of COPD patients requiring ICU admission is high, survivors have a worse QOL compared with pre-ICU admission, but three quarters of them are still self-sufficient [11]. All this data and the above mentioned therapeutic perspectives should support us to positively face the problems of these severe patients too.

For the future we need a substantial new approach to the management of these patients. We need more research involving patients. For instance there is no convincing trial on the effectiveness of inhaled therapy available to these patients with such severe comorbidities. We need shared guidelines to support the personal feelings of both patients and care givers (doctors, relatives etc.)

**Critical Care Medicine** has recently charged a Task Force with developing an approach for considering use of nPPV for patients who choose to forego endotracheal intubation. The use of nPPV for patients who choose to forego all life support, receiving comfort measures only.
and we must encourage discussion on end of life decisions. Improving communications, decision aids and advanced directives may be helpful [67].

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THE PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC RESPIRATORY INSUFFICIENCY

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