



EUROPEAN RESPIRATORY UPDATE

Recent advances in COPD: pathophysiology, respiratory physiology and clinical aspects, including comorbidities

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Owing to its major and better recognised burden from both individual and societal perspectives, chronic obstructive pulmonary disease (COPD) is an area of intensive epidemiological, fundamental and clinical research, leading to the publication of more than 10,000 papers each year in the PubMed database. Among these, many report important advances in the understanding of and care for COPD. Epidemiological aspects are the topic of another manuscript in this issue of the *European Respiratory Review* [1], while the treatment of COPD and its exacerbations will be addressed in other reviews in upcoming issues. Thus, the present paper will focus on more fundamental aspects of pathophysiology, resting and exercise lung mechanics, respiratory muscles and gas exchange, together with more clinical topics, including respiratory symptoms and comorbidities. The purpose of the authors is clearly not to be exhaustive but to focus on points that are likely to have some impact on clinical practice in the relatively short term.

PATHOPHYSIOLOGY

Cigarette smoking is the leading cause of COPD in Western countries. Cigarette-associated noxious agents injure the airway epithelium and drive the key processes that lead to specific airway inflammation and structural changes [2]. Once these agents are removed, repair processes should, ideally, bring the airways back to their normal structure and function. In general, an inadequate repair process is thought to play a key role in the development of chronic airflow obstruction in some, but not all, smokers. Indeed, in many subjects most of the inflammatory changes continue despite smoking cessation [3]. This failure of bronchial inflammation to resolve might contribute to systemic changes and ongoing bronchial and lung matrix degradation. In addition to persistent airway inflammation, other major phenomena involved in the disease

initiation and progression include increased oxidative stress and protease–antiprotease imbalance. Several studies have established that airway obstruction in COPD is due to changes affecting small airways and lung parenchyma while the contribution of proximal airway epithelium remodelling is less clear [4–6]. The decline in forced expiratory volume in 1 s (FEV₁) in COPD is mainly related to thickening of the walls of small conducting airways and obstruction of these airways by mucous exudates [7].

Oxidative stress and protease–antiprotease imbalance

Oxidative metabolism is over-activated in COPD [8]. The major external source of oxidants is cigarette smoke. Bronchial inflammation involving phagocytes, such as neutrophils and macrophages, adds an internal production of oxidants. Antioxidants such as the glutathione system and the haemoxygenase (HO)-1 pathway may counteract oxidative stress. This complex antioxidant system may be insufficiently efficient, since a reduced HO-1 expression has been described in macrophages from lung tissue and bronchoalveolar lavage (BAL) of smokers with COPD [9, 10]. Moreover, the subtle molecular regulation of HO-1 and its key protein regulators, such as Nrf2, Bach1 and Keap1, is modified in COPD. Western blot, immunohistochemical and laser scanning confocal analyses have revealed that the level of Nrf2 protein level is significantly decreased in whole lung tissue and alveolar macrophages (cytosol and nucleus) in patients with emphysema compared with smokers without emphysema. Conversely, Bach1 and Keap1 levels were increased in patients with emphysema. These modifications were associated with a parallel decrease in the expression of HO-1, glutathione peroxidase 2 and NQO1 at the cellular level in macrophages, which was inversely correlated with airway obstruction and hyperinflation indices, indicating a profound defect in this potential antioxidant system [11].

Proteases are produced by various cells within the airways. Their activity is regulated by the production and release of antiproteases, such as α_1 -antitrypsin, secretory leukoprotease inhibitor and tissue inhibitor of metalloproteinases (TIMPs). Inherited α_1 -antitrypsin deficiency is a well-known cause of COPD with a predominant emphysematous phenotype [12]. Cigarette smoke inhibits the activity of antiproteases and phagocytes are a major source of proteases; the macrophages from COPD patients have been shown to be less able to release TIMPs in response to stimulation. COPD outcomes, such as

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lung function and morphometry assessed by high-resolution computed tomography, were found to be related to changes in sputum content of proteases/antiproteases [13]. Proteases interact with the lung extracellular matrix, which leads to elastin and collagen degradation and then to the lung destruction that characterises emphysema. Matrix metalloproteinase (MMP)2 expression has been shown to be related to lung peripheral inflammation and COPD progression [14].

Inflammatory cells

Neutrophils are granulocytes that have been associated with COPD and the corticoreistance reported in this disease. Their number is increased in BAL, sputum, bronchial glands and smooth muscle of patients with COPD. The lung periphery is not spared and distal lung inflammation is mainly of neutrophilic phenotype in COPD. The increase in neutrophil numbers can result in an increased release of oxidants and proteinases, perpetuating the imbalances in favour of lung destruction. In addition, neutrophil elastase increases macrophage and epithelial cell activation and represents a major stimulus of mucus production and secretion by epithelium goblet cells and glands, which is a hallmark of COPD. This increase in neutrophil number and activation is due to the production of several cytokines, including interleukin (IL)-8 and CXC chemokine ligand (CXCL)1. Receptors for IL-8 are present on blood and sputum neutrophils and, to a lesser extent, in epithelial cells. This cytokine is a potential target for innovative therapeutic avenues in COPD [15]. Increased eosinophil numbers have also been reported in COPD patients during exacerbations, but their relevance to COPD changes is less clear than in asthma and their presence is associated with corticosteroid response [16].

Macrophages are found from the trachea to the alveoli. They are attracted and activated by smoking. Thus, increased numbers of macrophages are present in the airways, distal airways, BAL and sputum of patients with COPD. They are mostly derived from migrating monocytes: few divide *in situ*. They migrate into the lung in response to various chemoattractants, such as CC chemokine ligand (CCL)2 and CXC chemokine receptor (CXCR)2. They display features of activated cells related to the severity of the disease [17]. They perpetuate lung inflammation by releasing several mediators, including oxidants such as H₂O₂, superoxide anion, proteases (MMP9) and growth factors and chemokines. Macrophages are orchestrators for the recruitment and activation of mononuclear leukocytes (monocytes and T-lymphocytes). Additionally, they release transforming growth factor- β , which contributes to the airway wall changes [15]. Dendritic cells are also activated by cigarette smoke exposure. However, cigarette smoke induces both the release of IL-8 and the suppression of Toll-like receptor 9-induced interferon (IFN)- α secretion by plasmacytoid dendritic cells [18]. This activation may contribute to neutrophilic inflammation and poor immune response to viral infection, leading to recurrent exacerbations of COPD. The population of dendritic cells is increased in the airways of smokers but there is no definitive data involving dendritic cells in the course of COPD in smokers.

B-lymphocytes are important agents in the adaptive immune system. They have been found to participate in COPD inflammation [19], being organised in follicle-like structures and related to the severity of the disease [20]. A specific antigen reaction is a

hypothesis put forward in order to better understand COPD progression; T-regulation may play a role in this possible B-cell-mediated response. T-lymphocytes are present in the airways of COPD patients [21]; both CD4+ and CD8+ cells have been described, with a predominance of CD8+ lymphocytes correlated with the decrease in lung function. T-helper cell type 1 (Th1) cells expressing CXCR3 receptors are activated by IFN- γ . There are some data relating the role of CD8+ cells to the persistence of adenoviral infection. Leptin is a complex mediator produced by adipose cells and is involved in various metabolic processes, including the energy balance. Leptin has been described as a potential regulator of lymphocyte lifespan within the airways of COPD patients [22]. It has the potential to act as a pro-inflammatory cytokine, promoting the attraction, activation and survival of mononuclear cells in the airways. The production of RANTES (regulated upon activation, normal T-cell expressed and secreted) is increased, as shown in the sputum of patients with COPD. This cytokine activates and recruits T-lymphocytes, inducing the release of various products that alter type-1 pneumocytes, contributing to emphysema. Regulatory T-cells (Tregs) are special T-lymphocytes that are important for the control of immunity and in preventing autoimmune reactions by inhibiting T-cell responses [23]. The best described population of Treg is CD4+, and expresses CD25 and a transcription factor FOXP3. In COPD patients, Tregs were reported to be decreased or increased in number in BAL, and associated with B-cells follicles [24]. Th17 are recently described lymphocytes linked to neutrophilic inflammation and able to abrogate FOXP3 and Tregs. Conversely, they release IL-22 and promote IL-10 and epithelium remodelling.

Structural changes

The permanent airflow limitation that defines COPD might be linked to structural changes. Emphysema is characterised by a loss of lung parenchyma with a possibly increased apoptosis of endothelial and epithelial alveolar cells. In proximal and smaller airways, the bronchial epithelium is modified. Squamous cell metaplasia and goblet cell hyperplasia are hallmarks of smoking-induced COPD. The loss of CC10+ cells (Clara cells) in the distal airways is another finding in this disease. Subepithelial changes are not specific to asthma and basement membrane thickening is significantly greater in endobronchial biopsies from COPD patients when compared with normal subjects [25]. The glands are enlarged and increased in number. The smooth muscle mass is increased but there are controversial reports on its contribution to airflow obstruction, in comparison to the findings reported in asthma. These pathological changes translate to hypersecretion and airway obstruction. All these features of remodelling have been attributed either to the direct deleterious effect of the cigarette smoke content or to an indirect effect of persisting inflammation in the airways [26].

RESPIRATORY PHYSIOLOGY

During recent years, several major advances have occurred in the comprehension of respiratory physiology in COPD. Many may have significant clinical implications regarding the disease definition and diagnosis, estimation of prognosis using functional indices, assessment of therapeutic indications and response to treatments. They mostly relate to spirometry, exercise testing, pulmonary mechanics and respiratory muscles.

Spirometry

Optimal criteria to define COPD-related airflow obstruction

The definition of obstruction remains a highly controversial issue. Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines continue to define airflow limitation by a fixed FEV₁/forced vital capacity (FVC) threshold of 0.7, independently of age and sex. This is in marked contradiction with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines, which clearly recommend that the lower limit of normal (LLN) criterion is used. Several large series in which investigators assessed lung function in adults challenge the GOLD guidelines. The first study [27], performed in 14,506 adults, found that the fixed ratio (as compared to the 1993 European Community for Steel and Coal (ECSC) study [28]) has a high negative but a low positive predictive value, particularly in patients aged >50 yrs (fig. 1): the false positive rate was 33% in the 61–70 yr age range. Similarly, in the NHANES-III (Third National Health and Nutrition Examination Survey) population, the proportion of older adults misclassified by the fixed ratio was nearly one-fifth, whereas nearly one-half of young adults were false-negative with GOLD guidelines, in comparison

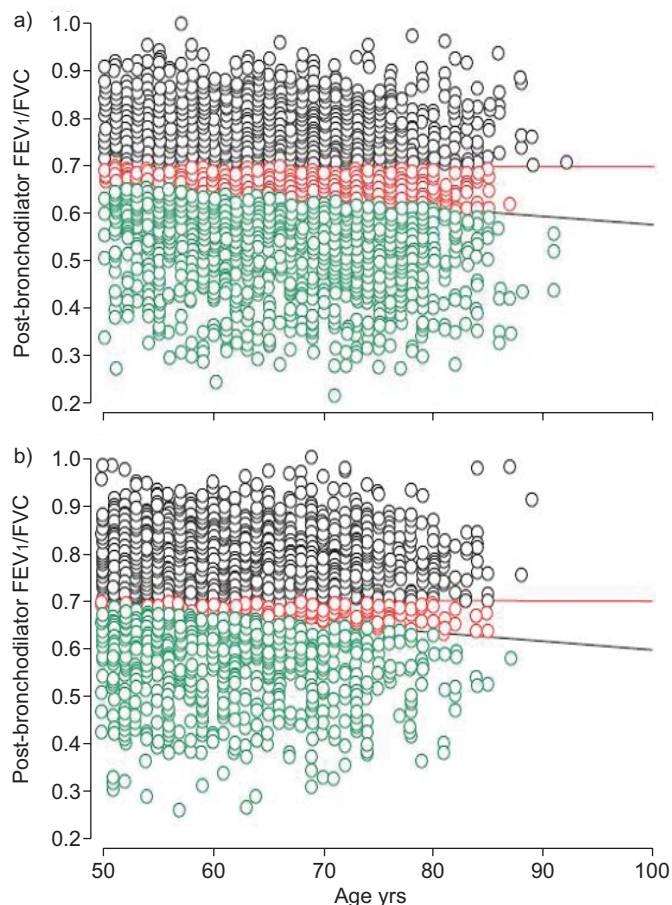


FIGURE 1. Post-bronchodilator forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) ratio in subjects aged >50 yrs. Red line corresponds to the fixed 0.7 cut-off, the black line to the age- and sex-specific lower limit of normal (LLN). Red circles represent false positive subjects with the fixed ratio, green ones are true positive according to LLN. Reproduced and modified from [27] with permission from the publisher.

with the fifth percentile criteria [29]. A third study compared the GOLD and British Thoracic Society (BTS) guidelines (FEV₁/FVC <0.7 for both, BTS requiring also a FEV₁ <80% predicted) to published equations (including ECSC/ERS) and their corresponding LLN [30]. The prevalence of airway obstruction according to these criteria was evaluated in the NHANES survey, a health survey in England (UK) and a longitudinal study in Dutch population. With most prediction equations, the LLN was <0.7 at a mean age of 42 yrs in males and 48 yrs for females. The prevalence of obstruction with the 0.7 criterion reached 45% in healthy subjects aged 60 yrs or more. Using LLN derived from prediction equations lowered the prevalence to between 12.3% and 15.5% in healthy lifelong nonsmokers. Underestimation of airflow obstruction in younger patients with the GOLD criteria was confirmed in a longitudinal study [31]. Among adults aged 20–44 yrs included in the European Community Respiratory Health Survey (1991–1993) and re-evaluated in 1999–2002, the LLN criteria detected 5.1% of patients with airflow obstruction, among whom only 45.6% were below the 0.7 cut-off. Subjects with airflow obstruction that were missed by the fixed ratio were younger and 64% were females. During follow-up, the proportion of subjects exhibiting a FEV₁ <80% pred, chronic cough or phlegm, or being treated for respiratory problems was significantly higher in misidentified subjects than in those without airflow obstruction by both criteria.

All these studies converge to challenge the diagnostic value of GOLD criteria, which aimed to simplify the diagnosis of airflow obstruction and COPD, and be applicable for a simple screening in a worldwide perspective. The false-negative rate in young subjects at risk and the false-positive rate in older patients appear unacceptably high in these recent studies. The LLN seems to be much more reliable for defining obstruction, particularly for screening purposes. The impact of these studies on future GOLD guidelines remains to be determined.

Reversibility in COPD

COPD is usually defined as a poorly reversible obstructive disorder. However, previous data showed a wide range of reversibility in clinically well-defined COPD. This hypothesis was verified in the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial data, which included at baseline a reversibility test with a combination of high-dose ipratropium (three puffs) and salbutamol (four puffs) [32]. FEV₁ and FVC responses were highly variable according to chosen criteria (ATS/ERS: >200 mL and >12% from baseline; >15%; >10% pred). A majority (53.9%) of patients reached the ATS/ERS threshold for reversibility. Older patients, those with a better St George's Respiratory Questionnaire (SGRQ) score or those with low number of pack-years were less responsive with this criterion. The proportion of patients with volume response only (FVC) increased with the severity of airflow obstruction. Although this responsiveness was obtained in optimal conditions (high dose, adequate withholding of previous drugs, spirometry at peak bronchodilation) and varied greatly according to applied criteria, it appears larger than expected and precludes the use of these reversibility criteria to differentiate COPD from asthma. In clinical practice, reversibility is often assessed in COPD patients by spirometry alone. However, thoracic gas compression during forced expiration is a major event and flow at the

mouth may considerably differ from the thoracic volume change measured by plethysmography. Dedicated software analysing expiratory flow *versus* box volume signal has been developed previously to estimate FEV₁ corrected for gas compression (NFEV₁). Bronchodilators decrease lung resistance and expiratory flow limitation, which may also reduce gas compression during expiration, *i.e.* the difference between expired lung volume and volume measured by a plethysmograph. An index of gas compression was defined as (NFEV₁-FEV₁)/NFEV₁. This per cent compression was much higher at baseline in COPD (32%) than in controls (10%). Thoracic gas compression (per cent compression) decreased after albuterol only in COPD patients. Multiple regression analysis showed that 23% of FEV₁ improvement was predicted by reduction of gas compression. The relevance of this new index for predicting the clinical benefit of bronchodilators remains to be determined, as forced expiration strongly differs from resting and exercise conditions.

Exercise testing

Field tests as prognostic tools and markers of therapeutic effects

The 6-min walk test (6MWT) remains the most popular test for the evaluation of exercise tolerance in COPD patients. It is simple and well standardised, but its interpretation criteria remain controversial. The prognostic value of the walk test was evaluated every 6 months in a large cohort of COPD patients of variable severity [33]. Receiver operating characteristic curves were used to define the best prognostic cut-off, which was 350 m, corresponding to 67% and 54% of predicted according to the equations of ENRIGHT and SHERRILL [34] and TROOSTERS *et al.* [35], respectively. A potential bias in the study is the under representation of female patients, for whom a specific cut-off might be useful. The advantage of this fixed cut-off is to simplify the interpretation of the 6MWT, in comparison with predicted values, which are rarely used in clinical practice.

Besides 6-min walk distance, pulse oximetry is currently used to monitor the test and may add useful information. The prognostic value of peak desaturation during the test was evaluated in COPD patients from Spain and the USA [36]. The mortality rate of those with exercise desaturation (arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) <90% or a drop of >4 %) was nearly doubled. Exercise desaturation was not confined to patients who were severely hypoxaemic at rest, since the best cut-off value of arterial oxygen tension (P_{a,O_2}) to predict desaturation was <74 mmHg. A distance <361 m also predicted mortality in patients with FEV₁ <50% pred, confirming the cut-off value defined by COTE *et al.* [33]. However, in multivariate analysis S_{p,O_2} decrease was no longer a significant predictor, whereas resting P_{a,O_2} remained in the model. The 6MWT is currently used to evaluate the impact of treatment. The classical 54 m defined by REDELMEIER *et al.* [37] as the minimal significant difference is, to date, the only available criteria. Most clinicians find it too high in daily practice, especially for patients with severe COPD, and this goal is reached by few drugs in therapeutic trials. The threshold values for improvement were reanalysed by PUHAN *et al.* [38] in COPD patients included in previous rehabilitation trials. They used three complementary methods: reproducibility determination (standard error to the mean), empirical

effect size and standardised mean response and changes in patients achieving a validated minimal important difference with classical instruments (SGRQ, Chronic Respiratory Questionnaire (CRQ) and the feeling thermometer). The standard error to the mean across studies was 35 m (~10% from baseline) and the empirical effect size was 42 m. The proportion of patients achieving an improvement >35 m was 50.7%, which was comparable to the CRQ response rate (60.4%). Among the 19 analysed trials, a response >35 m was achieved in 12 (63%), whereas only 15% were positive with the 54 m cut-off.

Although less currently performed than the 6MWT, the shuttle walk test offers the advantages of being perfectly standardised and highly related to peak oxygen consumption. The minimum clinically relevant improvement with this test needed to be defined for clinical use and trials; this analysis was done in patients assessed before and after pulmonary rehabilitation [39]. Perceived change in exercise performance was evaluated by a Likert scale. Mean shuttle walking distance increased after rehabilitation, with no relationship between baseline value and subsequent improvement. Mean improvement was 47.5 m for patient feeling slightly better, and 78.7 m for those reporting better exercise tolerance.

Endurance shuttle testing may also be performed, usually at 80% of maximum test. With the sensitivity of the 6MWT to bronchodilation being controversial, the responsiveness of endurance shuttle was tested after a single dose of salmeterol in 20 stable COPD patients (baseline FEV₁ 52% pred) [40]. Dyspnoea and inspiratory capacity (IC) were also measured every other minute during the test. Despite a moderate improvement in FEV₁, a marked increase in exercise performance (160 ± 277 m) was observed with active treatment. Dyspnoea also decreased at isotime. IC manoeuvres performed with a portable exercise monitor were not acceptable in 12 out of 20 patients and the reduction of dynamic hyperinflation in the remaining patients was of borderline significance. Endurance shuttle test appears to be a promising tool for the evaluation of new drugs, although the minimal clinically important difference with this test remains to be determined.

Exercise tests to assess the mechanisms of exercise limitation

Dynamic hyperinflation is a key component of COPD and occurs when ventilatory demand increases, particularly during exercise [41]. Its relationship with exercise limitation is well established in moderate to severe COPD patients. However, patients with milder disease often complain of dyspnoea, a symptom poorly correlated with the level of airflow obstruction.

Focusing on this population, OFIR *et al.* [42] evaluated exercise tolerance on a cycleergometer in patients with stage 1 COPD (post-bronchodilator FEV₁ 91% pred), compared with controls matched for age and sex. Dynamic hyperinflation was evaluated by the standard IC technique. In patients, peak oxygen uptake ($V'O_2$) was reduced by 20% and a significant increase in end expiratory lung volume (0.54 ± 0.34 L) appeared at the end of exercise, together with a rapid, shallow breathing. Ventilatory requirement for a given workload was higher and dyspnoea/work slope was steeper in COPD patients. Dyspnoea for an 80-W workload was highly related to inspiratory reserve volume and IC in the whole study population. As stated by

the authors, their COPD group may not be perfectly representative of mild COPD patients discovered by screening, as they exhibited increased plethysmographic functional residual capacity, markedly decreased forced expiratory flow between 25% and 75% of FVC and a low diffusing capacity of the lung for carbon monoxide (DL_{CO}). In addition, gas exchanges were not evaluated. In practice, dynamic hyperinflation should, therefore, be considered as a potential cause of dyspnoea even in mild COPD patients. Besides ventilatory limitation, dynamic hyperinflation may also have haemodynamic consequences through changes in intrathoracic pressures. This hypothesis was previously demonstrated in healthy subjects during experimental flow limited exercise [43]. It was tested in GOLD stage 3 and 4 patients characterised by a severe resting hyperinflation, defined as an IC/total lung capacity (TLC) ratio <25% [44], which was previously shown by the same team to be a negative prognostic factor [45]. Haemodynamic compromise was indirectly assessed by the oxygen pulse. It was significantly decreased in COPD patients at rest and during exercise. Oxygen pulse at peak exercise was also significantly correlated to resting IC/TLC ratio in the whole population (fig. 2). The relationship was, however, smaller in the COPD group alone ($r=0.46$). At isotime during the test, oxygen pulse was always lower in patients with IC/TLC ratio >25%. However, in multivariate analysis, handgrip force was the most significant predictor of peak O_2 pulse. Abnormal kinetics of cardiac output during exercise were also demonstrated in COPD patients, together with a lowered kinetics of peripheral microvascular O_2 delivery [46]. Improvement of cardiac output during exercise with Heliox [47] further supports the detrimental role of hyperinflation, which increases intrathoracic pressures.

These studies confirm the complexity of mechanisms limiting exercise in COPD, with a variable combination of central (dynamic hyperinflation and cardiac output) and peripheral (muscle atrophy and dysfunction) factors. Determination of the predominant mechanism in individual patients might prove

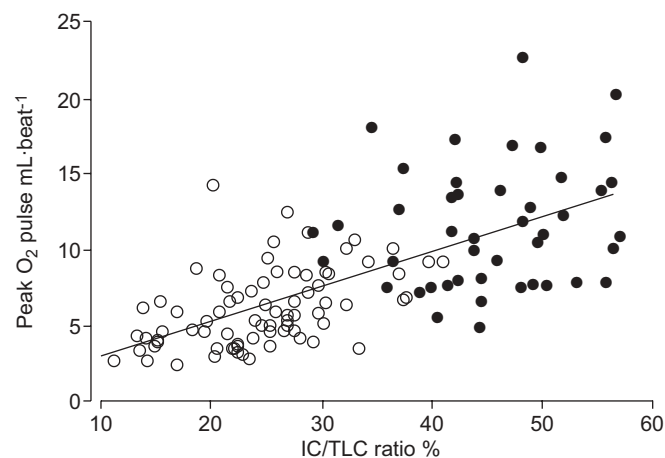


FIGURE 2. Correlation between inspiratory capacity (IC)/total lung capacity (TLC) ratio and oxygen pulse at peak exercise in chronic obstructive pulmonary disease (COPD) patients (○) and controls (●). $r=0.65$; $p<0.0001$. Correlation is lower in COPD patients ($r=0.46$). Reproduced from [44] with permission from the publisher.

useful for targeted treatment. Haemodynamic parameters might prove useful in the selection of patients for lung reduction surgery.

Pulmonary mechanics

Expiratory flow limitation and forced oscillation

Expiratory flow limitation (EFL) is a major consequence of COPD as it promotes dynamic hyperinflation, particularly during exercise. EFL may be detected by the negative expiratory pressure (NEP) method, but its availability is limited, and it may be replaced by the simple but qualitative abdominal manual compression. The forced oscillation technique (FOT) can also be used to detect EFL [48]. Breath reactance (the out of phase or imaginary part of the pressure–flow signal) is analysed during the application of forced oscillation at 5 Hz. In case of EFL, expiratory reactance falls as the oscillatory signal cannot pass through the choke points. The concordance between FOT and NEP has been evaluated in COPD patients [49]. Using FOT, EFL was detected in 53% of patients, whereas a high proportion of tests (24.8%) were considered unsuitable for NEP analysis. The two methods disagreed in only 7.9% of cases. Post-bronchodilator improvement of EFL was detected by FOT in 13 out of 15 patients. FOT thus appears to be an attractive technique for the noninvasive detection of EFL, with the additional advantage of an automatic, “objective” algorithm. The relevance of impulse oscillometry (an alternative to forced oscillation) to evaluate reversibility was also assessed in COPD patients [50]. At baseline, variations of resistance and reactance between inspiration and expiration were larger in COPD patients than in controls. After tiotropium administration, FEV1 increased by only 4% in COPD patients, whereas all components of impulse oscillometry improved. The improvement of peripheral airway resistance was assessed by the difference between low frequency (5 Hz) and high frequency (20 Hz) resistance (also called frequency dependence of resistance). Only inspiratory resistance improved significantly post-bronchodilator. The better sensitivity of inspiratory parameters and, particularly, reactance for the evaluation of the bronchodilator effect was also observed in flow limited patients (fig. 3) [51]. Frequency dependence of resistance was also improved after bronchodilator, suggesting a reduced heterogeneity of the respiratory system. In addition, changes in reactance followed those in inspiratory capacity.

Forced oscillation resistance and reactance provide useful parameters for the assessment of COPD severity [52]. The technique may also detect significant changes during recovery from an exacerbation. Time course of FOT and spirometry improvement was assessed on three occasions over a 6-week period after an exacerbation in COPD patients [53]. The largest part of improvement was observed at 1 week. Although spirometric changes were significant, the largest improvement was seen in inspiratory and expiratory reactance, whereas resistance did not decrease significantly. Changes in reactance correlated with improvement in symptoms and health-related quality of life (SGRQ) scores.

FOT has the advantage of being noninvasive and effort independent, and is thus applicable to patients with severe dyspnoea. Its usefulness in the long-term follow up of COPD patients remains to be determined [54].

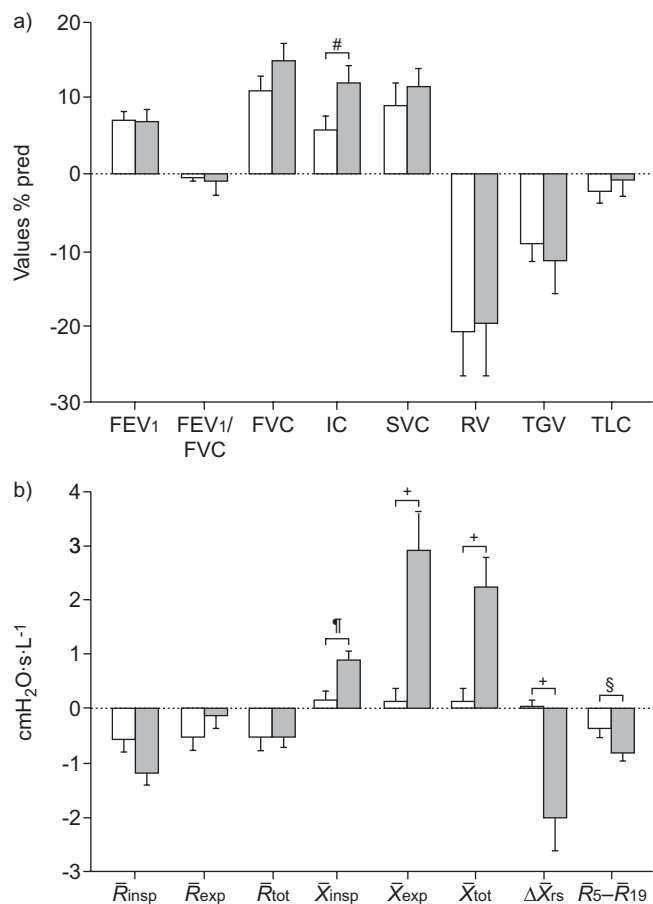


FIGURE 3. Changes of a) spirometric, plethysmographic, and b) impedance data at 5 Hz induced by bronchodilator in flow limited (□) and nonflow limited (■) patients at baseline. % pred: % predicted; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; IC: inspiratory capacity; SVC: slow vital capacity; RV: residual volume; TGV: thoracic gas volume; TLC: total lung capacity; \bar{R}_{insp} : mean inspiration resistance; \bar{R}_{exp} : mean expiration resistance; \bar{R}_{tot} : mean whole breath resistance; \bar{X}_{insp} : mean reactance during inspiration; \bar{X}_{exp} : mean reactance during expiration; \bar{X}_{tot} : mean total reactance; $\Delta\bar{X}_{rs}$: mean difference in reactance; $\bar{R}_5-\bar{R}_{19}$: mean difference in resistances at 5 and 19 Hz. #: $p=0.04$; *: $p=0.05$; +: $p=0.001$; §: $p=0.031$. Reproduced from [51] with permission from the publisher.

Nitrogen washout

The single-breath nitrogen washout test (SBN₂) is a classic test of small airways involvement [55], although its prognostic value in early COPD remains controversial [56, 57]. The relationships between SBN₂ and airway inflammation were evaluated in COPD patients not taking corticosteroids [58]. The slope of phase III increased with neutrophil inflammation as assessed by bronchial biopsies, BAL and induced sputum. The most significant relationship was found between the slope of phase III and BAL neutrophil elastase/neutrophil ratio, even after adjustment for FEV₁ level. The SBN₂ test was unrelated to the presence of other inflammatory cell types. These results confirm the role of neutrophilic inflammation in small airways and/or alveolar dysfunction. Monitoring of SBN₂ could be useful for the evaluation of new anti-inflammatory strategies in COPD, although multiple-breath washout might be more sensitive in this context [59, 60].

Respiratory muscles

Inspiratory muscle endurance

Although not routinely measured, inspiratory muscle endurance (IME) is probably more relevant than inspiratory muscle strength (as measured by maximal inspiratory pressure ($P_{I,max}$)) in COPD, particularly for the evaluation of the impact of inspiratory muscle training (IMT). The test may be performed with a constant threshold load or an incremental one. A previous study showed a significant impact of a high-intensity IMT on incremental endurance test, dyspnoea and walking distance [61]. A second study compared the responsiveness of the two techniques after IMT using interval training [62]. IMT significantly improved the performance during both tests, but the incremental test appeared more sensitive. However, patients modified their breathing pattern during training, shortening inspiratory time and duty cycle. Thus, a precise evaluation of treatment effect justifies an adequate control of the breathing pattern during the test. IME testing might also help to select the best COPD candidates for IMT [63] or other innovative approaches [64, 65].

Neural respiratory drive

Mechanical abnormalities (hyperinflation or increased work of breathing) together with cellular and molecular alterations lead to diaphragmatic dysfunction in COPD, although some compensatory mechanisms exist [64]. Neural respiratory drive may be assessed by diaphragmatic electromyogram (EMG) but few data are available in COPD. LUO and co-workers [66, 67] have developed a specific oesophageal catheter with multiple electrodes, allowing an optimal sampling of diaphragm EMG and neural drive. The same electrode was used in COPD patients to enable a comparison to age-matched healthy controls [68]. EMG during spontaneous breathing was normalised as the percentage of individual maximal EMG (defined as the maximal EMG value obtained during inspiration to TLC, $P_{I,max}$, maximal sniff manoeuvres or maximum voluntary ventilation) and thus expressed as EMG_{di} % max. In comparison with controls, COPD patients exhibited a markedly increased neural drive (EMG_{di} % max) at rest (mean 28% versus 9%). In COPD patients, EMG_{di} % max was inversely correlated to FEV₁ (fig. 4) and vital capacity. EMG_{di} % max reached 51% in the most severe patient, indicating a major increase in load/capacity ratio. Unfortunately, the relationships between these EMG data and dyspnoea, health-related quality of life or relevant pulmonary function test parameters (hyperinflation, airway resistance and exercise tolerance) were not determined. Therefore, the clinical relevance of this method remains to be assessed.

CLINICAL CONSEQUENCES OF COPD FROM A PRIMARILY “RESPIRATORY” PERSPECTIVE

It is now widely acknowledged that COPD clinical manifestations are not restricted to the respiratory system: it is of utmost importance to recognise that the impact of COPD on individuals is the consequence of both respiratory and extra-respiratory features of the disease, in order to offer the global and integrated care that is required to improve the patient's health status. Extra-respiratory diseases associated (and possibly causally linked with COPD) will be the topic of the following section of this review. Here we will focus on the impact of exacerbations, cough and sputum production and dyspnoea.

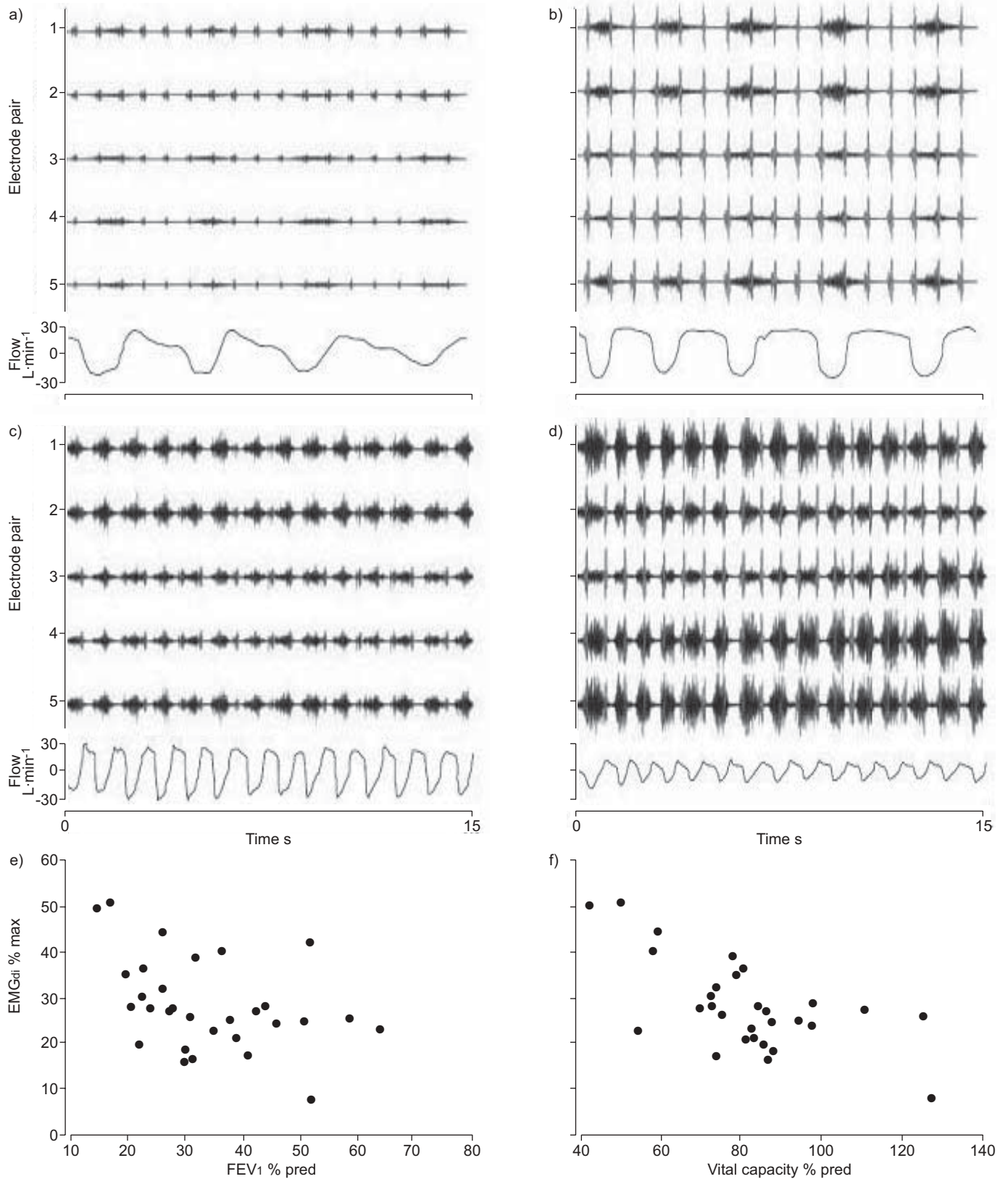


FIGURE 4. Representative diaphragm electromyogram (EMG) tracings at rest (a and b) and during maximum voluntary ventilation (c and d) in a healthy subject (a and c) and in a severe chronic obstructive pulmonary disease patient (b and d). Relationship between diaphragm EMG (as a percentage of the maximum; EMG_{di} % max) and e) forced expiratory volume in 1 s (FEV₁; $r^2=0.4$; $p<0.001$) or f) vital capacity ($r^2=0.61$; $p<0.001$). Reproduced and modified from [68] with permission from the publisher.

Exacerbations

The definition of exacerbations has been the topic of several reviews, guidelines and consensus statements, which reflects that it does not represent a trivial issue [69–71]. This point is illustrated by the finding that only half of diary-detected exacerbations are reported to physicians [71]. One consequence is that it may be difficult to compare data on exacerbations from studies with various definitions of these events. However, data on the long-term impact of COPD exacerbations provide quite convergent results.

Previous studies suggested that a subset of patients exhibit exacerbations more frequently, which is not explained only by the severity of airflow obstruction [71]: more recently, a study of severe, early-onset COPD probands and their relatives found that predictors of frequent exacerbations were chronic cough and phlegm production, episodic wheezing, pneumonia, active smoking, exertional dyspnoea and lower lung function [72]. A familial aggregation of exacerbations was observed, suggesting a genetic component of the “frequent exacerbator” phenotypes.

Obviously, the occurrence of an exacerbation is associated with an increased risk of hospitalisation and death. However, it also impairs patients’ health status quite dramatically, as demonstrated by BOURBEAU *et al.* [73] (fig. 5). In this study, patients were instructed to report all increases in respiratory symptoms that lasted ≥ 24 h. Despite these efforts towards early identification and care for exacerbations, these episodes were associated with marked (up to a mean of 14 points) worsening in SGRQ impact and activity domains. During the second week following the onset of exacerbation, a clinically significant deterioration of impact scores was still observed in 37% of patients. The change in health status that accompanies exacerbations is largely related to their impact on daily activity, which is itself the consequence of airflow obstruction, dyspnoea and impaired exercise tolerance (as illustrated by the 1.4-point increase in the BODE (body mass index, FEV₁ for airflow obstruction, dyspnoea, and 6-min walk distance for exercise tolerance) index that is observed during exacerbations).

Importantly, patients with frequent exacerbations are also characterised by other pejorative long-term outcomes, including a more rapid decline in lung function, poorer health status at steady state and increased mortality [71]. Corresponding data have come from cohort studies including unselected patients in a “real-life” context. They leave an important question unanswered: are the poorer long-term outcomes causally linked to exacerbation frequency and severity, or are all these features independent consequences of an increased disease severity? Recently, ANZUETO *et al.* [74] gathered data from two 1-yr randomised placebo-controlled trials testing the effect of a bronchodilator in almost 1,000 patients with moderate-to-severe COPD. In the placebo group, they confirmed that higher exacerbation frequency is associated with more loss of FEV₁, impairment in quality of life and increase in dyspnoea with time. Interestingly, they also found that a lower exacerbation frequency after pharmacological intervention was associated with more marked changes in terms of lung function, dyspnoea and health status. Such results do not allow the conclusion that there is a causal link between exacerbations and other outcomes, but they do suggest a possible temporal relationship.

Finally, in a cohort study COTE *et al.* [75] showed that frequent exacerbations have a negative long-term impact on the BODE index, a well known prognostic factor in COPD.

Exacerbations should not be considered as purely respiratory episodes: they are associated with systemic inflammation, the persistence of which predicts their recurrence [76] and is associated with poorer prognosis of COPD [77]. In addition, exacerbations are associated with an increase in depressive symptoms when they occur, which is easily understandable, and their repetition is associated with an increased prevalence of depression at steady state [78], which participates in health status and daily activity impairment.

Cough and sputum production

Chronic bronchitis was included in the 2006 GOLD classification as stage 0 COPD. It has since been removed from this classification and is now only considered to be a clinical signature of an increased risk of developing COPD. These changes were the consequence of attempts to find the best compromise between communication requirements to improve COPD awareness in the population and scientific data. Indeed, chronic bronchitis is not present in all COPD patients and initial studies assessing its prognostic value in smokers gave conflicting results [79]. An analysis of the Copenhagen City Heart Study found that chronic bronchitis was not an independent risk factor of subsequent occurrence of airflow obstruction once tobacco smoking was taken into account [80]. However, the so-called GOLD stage 0 was associated with an excess rate of FEV₁ decline. Furthermore, other studies showed an increased incidence of COPD in males with chronic bronchitis [81] and an increased disease severity in patients with severe α_1 -antitrypsin deficiency-related emphysema who exhibit chronic cough and phlegm production [82]. In addition, symptoms of chronic bronchitis are of some prognostic value when survival is considered [83, 84].

Exacerbations could represent one of the links between chronic sputum production and prognosis, since sputum production is associated with more frequent exacerbations, which in turn are associated with a poorer prognosis, as outlined above. For instance, a cohort study of 433 COPD subjects found that

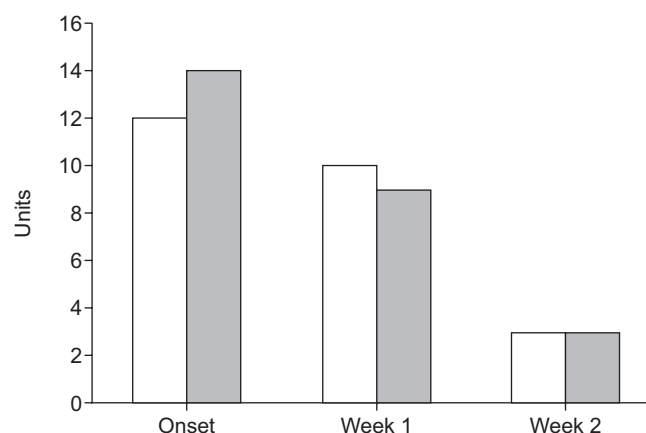


FIGURE 5. Mean changes (worsening) in St George's Respiratory Questionnaire activity (□) and impact (■) domain scores at onset of exacerbations and 1 and 2 weeks later, as compared with baseline values. Data taken from [73].

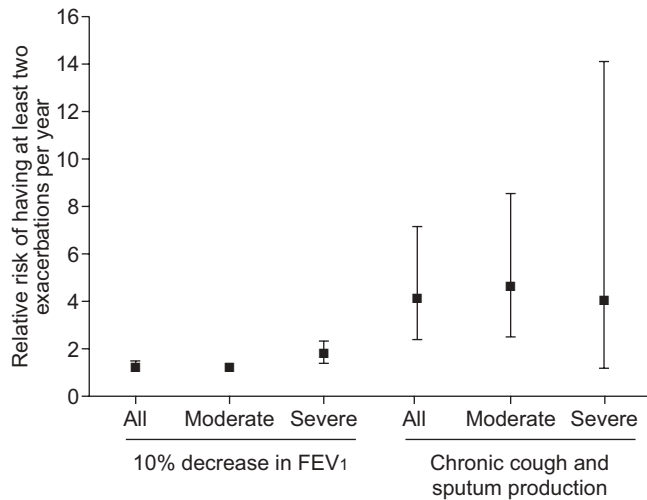


FIGURE 6. Effect of independent predictors of frequent exacerbations (*i.e.* forced expiratory volume in 1 s (FEV₁) and cough and sputum production) in a cohort of 433 patients with chronic obstructive pulmonary disease: relative risk (95% CI) of having at least two exacerbations during the previous year are presented for all, moderate and severe exacerbations. Data taken from [85].

frequent exacerbations (at least two within the previous year) were reported by 55% of COPD subjects with chronic bronchitis and by 22% of patients without this feature (fig. 6) [85]. In that study, logistic regression found that FEV₁ and chronic bronchitis were the only independent predictors of frequent exacerbations. These findings were in line with that of the prospective East London COPD cohort follow-up [86] and of a cross-sectional study of general practitioner-diagnosed COPD [87].

One difficulty when studying the impact of chronic bronchitis is that it does not appear to be a stable feature in COPD, being markedly influenced by smoking continuation or cessation [80]. Studying its relationship with exacerbations is also difficult, since cough and sputum production are themselves features of exacerbations [85]. Finally, there are few tools to assess their clinical impact on patients [88].

Thus, an important question remains open, *i.e.* is it worth targeting the pathophysiological mechanisms (such as epidermal growth factor receptor [89]) that play a role in sputum production when trying to modify the natural history of COPD?

Dyspnoea and health status

The most global measure of COPD impact on patients is obviously health status or health-related quality of life. As mentioned above, exacerbations and their frequency are major determinants of health status. Dyspnoea and its consequences for activity represent another major determinant of health status. Other symptoms such as fatigue must not be underestimated [90]. Interestingly, the symptomatic impact of COPD on individuals may be modified by sex.

In a wide study using the Short Form-12 generic health-related quality of life questionnaire in >9,000 COPD patients in daily practice, health-related quality of life was found to be poorer in females, older subjects and patients with more severe COPD [91]. The poorer health-related quality of life in females contrasted

with a greater frequency of moderate-to-severe airflow obstruction and dyspnoea (Medical Research Council (MRC) grades 4–5) in males, suggesting a sex effect influencing the impact of COPD on health status. Another Spanish study in daily practice found that the variable affecting the disease burden the most (as assessed using the clinical COPD questionnaire) was dyspnoea, followed by the degree of airflow obstruction [92]. Similar findings were provided by several other studies, underlying the major role of dyspnoea as a determinant of health status [93].

The influence of sex on how COPD affects health-related quality of life is not restricted to a global, quantitative effect on scores: it is also characterised by variations in the determinants of health status: DE TORRES *et al.* [94], who also found worse health-related quality of life scores in females than males using the SGRQ, performed separate analyses of these determinants in males and females. Dyspnoea was again the most potent predictor of health-related quality of life in both sexes. Exercise capacity (6-min walk distance) and comorbidity (Charlson index) were other independent predictors of health status in males, while oxygenation (P_{a,O_2}) was the only one in females. In both sexes, physiological variables reflecting the severity of airflow obstruction (FEV₁) or hyperinflation (IC/TLC ratio) were related to health-related quality of life in univariate but not multivariate analysis. This finding may appear surprising at first, but it is most likely related to the obvious interaction between these variables and dyspnoea: interestingly again, another paper by the same team found that independent determinants of dyspnoea were also different in males and females ($n=50$ per group) [95].

Dyspnoea is related to both respiratory (hyperinflation and impaired gas exchange, *etc.*) and extra-respiratory (muscle dysfunction, heart disease, anaemia and depression, *etc.*) features of COPD. Its role in health-related quality of life impairment relates to the unpleasantness of the symptom itself and to its effect on daily activity, which can be measured using questionnaires or motion sensors (pedometers or accelerometers). Several studies found that, even in moderately severe COPD (GOLD stage 2, BODE score 1), daily activity is notably reduced [96]. A similar, although nonsignificant, trend also exists in mild disease. The reduction in daily activity worsens with increasing severity and is paralleled by increasing dyspnoea MRC grade (fig. 7). It correlates with every individual component of the BODE score, higher correlations being observed with the GOLD stage and BODE score. Some extra-pulmonary parameters are also correlated with measures of daily activity, independently of GOLD stage and BODE score; they include left cardiac dysfunction (as assessed by levels of N-terminal pro-B-type natriuretic peptide and echocardiography) and systemic inflammation (as assessed by C-reactive protein (CRP) levels) [97]. Among respiratory physiological variables, maximal voluntary ventilation appears to be more associated with daily activity than markers of severity of airflow obstruction (FEV₁) and hyperinflation (IC) [98].

All these correlations lead to an important question: what are the causal relationships here and what is their direction? For example, are reduced physical activity and systemic inflammation relatively independent markers of severity? Are patients with systemic inflammation sicker in terms of, *e.g.* muscle or heart dysfunction, which impairs their activity? Or

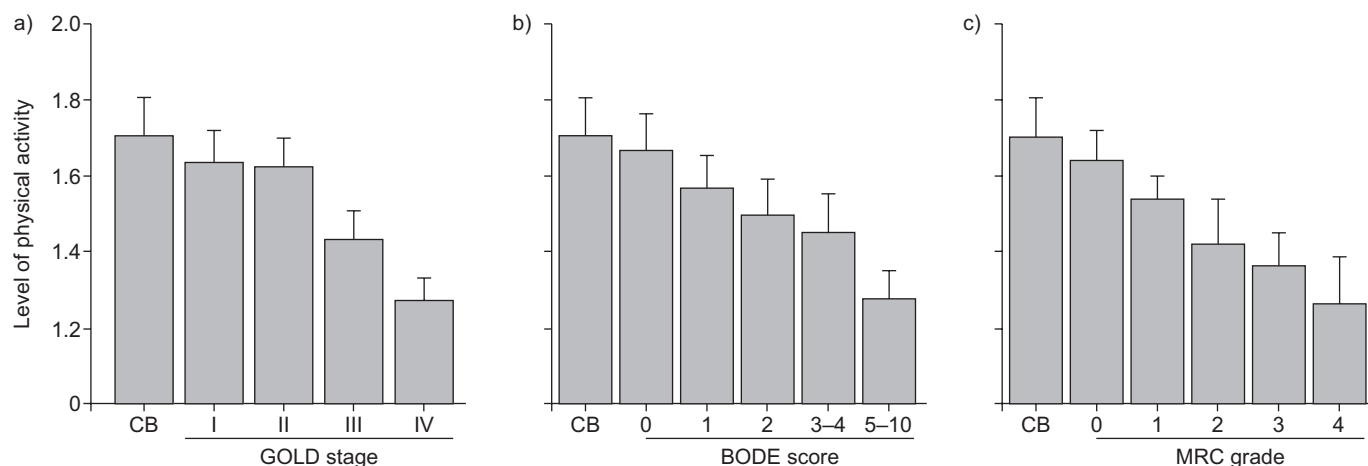


FIGURE 7. Level of physical activity by Global Initiative for Obstructive Lung Disease (GOLD) stage, BODE (body mass index, FEV₁ for airflow obstruction, dyspnoea, and 6-min walk distance for exercise tolerance) score and dyspnoea Medical Research Council (MRC) grade in 163 patients with chronic obstructive pulmonary disease. Physical activity level ≥ 1.70 : active; 1.40–1.69: predominantly sedentary; <1.40 : very inactive. CB: chronic bronchitis. Reproduced and modified from [96] with permission from the publisher.

does regular physical activity exert a protective effect against systemic inflammation? The same questions remain unanswered for exercise capacity (as measured using 6MWT or maximum $V'O_2$) or lung and respiratory muscle function (as measured with $DLCO$ or maximal expiratory pressure) [99], which all correlate with daily activity. A protective effect of daily physical activity on general and respiratory health in COPD has been suggested by longitudinal data from the Copenhagen City Heart Study. In enrolled patients, regular activity at entry in the study was associated with lower rates of exacerbation, death and lung function decline during follow-up [100, 101].

Implications for routine practice

In patients with COPD, careful assessment of symptoms and their impact is required in order to define targets for intervention. On average, from a respiratory perspective, health status is mostly impaired by exacerbations on the one hand and dyspnoea on the other, with its negative effect on daily activity. Other more general factors, such as fatigue or comorbidities, play an important role. The respective role of respiratory and extra-respiratory determinants of health status likely varies markedly between individuals and sex may be involved in these variations. Therefore, the approach of the COPD patient has to be individualised using appropriate measurement tools. In routine practice, careful medical history of exacerbations, questionnaires on cough and sputum, dyspnoea, activity and health status are available. However, although they all have been validated for collective use in clinical studies, their relevance for individual care is not firmly established, especially with regards to health status measurements.

COMORBIDITIES

COPD has been primarily considered as a respiratory disease characterised by permanent and progressive airflow obstruction, but the importance of extrapulmonary manifestations has not been acknowledged until recently [102, 103]. In recent years, investigators have focused their attention on the findings that many COPD patients suffer from other chronic illnesses. These

chronic illnesses occurring in patients with COPD have been called comorbidities (*i.e.* coexisting chronic disorders or diseases, regardless of whether the comorbid conditions were or were not directly related to COPD) [104] or systemic manifestations (implying that COPD was responsible, at least in part, for these coexisting illnesses). This section describes major chronic illnesses found in patients with COPD, reviews the evidence linking COPD with these illnesses and examines their impact on morbidity and mortality in patients with COPD.

Chronic illnesses and their prevalence in COPD subjects

Systematic assessment of coexisting illnesses has highlighted their high prevalence in subjects with COPD. For example, in a recent large study of inpatients and outpatients with COPD undergoing pulmonary rehabilitation, 51% of the patients reported at least one other disease in addition to COPD [105]. In this study, metabolic diseases (systemic hypertension, diabetes and/or dyslipidaemia) and heart diseases (chronic heart failure and/or coronary heart disease) were the most frequently reported comorbid combinations (61% and 24%, respectively) [105]. Several studies revealed that COPD subjects often suffer from other illnesses, including nutritional depletion characterised by low body mass index and/or low fat free mass index [106, 107], osteoporosis [108], tobacco-related cancers (*e.g.* lung cancer) [109, 110] and neuropsychiatric disorders [111–113]. Although the prevalence of various coexisting illnesses in patients with COPD varied greatly among studies, depending on the different methods used to ascertain comorbidities and the different population samples [114], patients with COPD consistently had a high prevalence of coexisting illnesses. Major chronic illnesses present in patients with COPD and their potential consequences in COPD subjects are listed in table 1.

High prevalence of coexisting chronic illnesses is not limited to COPD subjects, but has also been reported in patients with other chronic diseases. CHARLSON *et al.* [115] studied 5,861 consecutive patients seen in a general medicine practice at an urban academic medical centre in New York, NY, USA. An

TABLE 1 Major chronic illnesses present in patients with chronic obstructive pulmonary disease (COPD); all may contribute to health status impairment

Extrapulmonary disease	Possible consequences in COPD patients
Cardiovascular disease	Increased mortality Increased dyspnoea (chronic heart failure) Reduced physical activity
Cancer (including lung cancer)	Increased mortality
Malnutrition	Increased mortality Low fat free (muscle) mass Skeletal muscle weakness Increased dyspnoea Reduced exercise capacity
Anaemia	Increased dyspnoea Possibly increased mortality
Osteoporosis	Fractures
Depression	Increased mortality
Diabetes	Increased respiratory infections
Obstructive sleep apnoea	Sleepiness Pulmonary hypertension Hypoventilation

interesting finding was that major chronic diseases (*e.g.* congestive heart failure, dementia, ischaemic heart disease, stroke, diabetes, cancer, asthma, COPD, depression and hypertension) were associated with at least one of the other diseases in 60–90% of cases [115]. Furthermore, 26% of patients had three or more chronic diseases [115]. A major question is whether coexisting chronic illnesses found in COPD subjects are merely related to common risk factors (*e.g.* aging, tobacco smoking and genetic predisposition) or are also consequences, at least in part, of the pulmonary and/or systemic inflammation that characterise COPD.

Pathogenesis of coexisting chronic illnesses in COPD subjects

The possible impact of COPD on coexisting illnesses has been particularly studied for cardiovascular diseases. Retrospective cohort studies have found that patients with COPD have increased prevalence of cardiovascular diseases (*e.g.* coronary heart disease and chronic heart failure) and/or cardiovascular events [116, 117]. In these studies, risk factors for cardiovascular diseases (*e.g.* smoking) were not systematically taken into account and no conclusion could be drawn regarding the potential role of COPD in developing cardiovascular disease. SIN *et al.* [118] analysed subjects included in the NHANES follow-up study and concluded that individuals in the lowest FEV₁ quintile had increased cardiovascular mortality and increased mortality from ischaemic heart disease, independently of age, sex and smoking. These authors suggested that the lung processes may be causally linked to cardiovascular disease because airway inflammation can incite and propagate systemic inflammation (*e.g.* CRP and fibrinogen), which in turn may contribute to the progression of atherosclerosis [118, 119]. In a recent population-based study, logistic regression models adjusting for age, sex, race, smoking, body mass index and

education found increased prevalence of hypertension and cardiovascular diseases in COPD subjects with severe airflow obstruction (GOLD stage III and IV), further reinforcing the hypothesis that COPD was causally associated with cardiovascular diseases [120]. Recently, JOHNSTON *et al.* [121] studied the relationship between the severity of airflow obstruction, based on GOLD criteria, and the prevalence and incidence or recurrence of cardiovascular diseases in a large cohort of US adults (n=14,681 subjects), aged 45–64 yrs, from 1987 to 2001. These authors confirmed a crude association between lung function impairment and prevalent and incident or recurrent cardiovascular diseases; importantly, this association was greatly reduced after adjusting for covariates, including age, sex, race, smoking, comorbid hypertension and diabetes, cholesterol levels and fibrinogen levels, indicating that the association between COPD and cardiovascular diseases may be largely mediated through established risk factors [121]. Thus, although COPD subjects clearly experience increased cardiovascular morbidity and mortality, it is yet unclear whether COPD significantly contributes to the development of cardiovascular diseases or whether these findings merely reflect the high prevalence of cardiovascular risk factors in this population.

An original relationship may exist between COPD and lung cancer. These two diseases often coexist and lung cancer is a major cause of death in subjects with COPD (see below). Although these findings have been ascribed to cigarette smoke exposure, lung cancer has long been known to be more prevalent in COPD subjects compared with smokers [110]. Recently, two separate groups studied the relationships between airflow obstruction, emphysema and lung cancer in current and ex-smokers undergoing repeated low-dose computed tomography scans for early detection of lung cancer [122, 123]. These studies revealed that emphysema, which occurred in 30–40% of long-term smokers, was related to lung cancer independently of sex, age, smoking habits and airflow obstruction [122, 123]. Although the biological mechanisms relating emphysema to lung cancer remain unknown, it was suggested that bronchoalveolar stem cells (BASC) proliferate to replace damaged alveolar cells and that abnormal BASC proliferation due to carcinogens present in cigarette smoke may result in lung cancer [124]. It is likely that common mechanisms are involved in COPD/emphysema pathophysiology and in lung carcinogenesis.

SIN *et al.* [108] reported an increased prevalence of osteoporosis and osteopenia in males and females with COPD. Potential risk factors of osteoporosis present in COPD subjects include nutritional depletion, smoking, hypogonadism, reduced physical activity and corticosteroid therapy. Importantly, the prevalence of osteoporosis increased with airflow limitation independently of age, smoking status, medications, physical activity and body mass index [108]. A recent study also suggested that emphysema was associated with osteoporosis independently of body mass index, smoking and age in a small cohort (n=65) of male COPD subjects [125]. These studies suggest that biological mechanisms may directly link airflow limitation and emphysema to osteoporosis. Such a direct relationship has also been suggested for several other coexisting illnesses (*e.g.* anaemia). However, no data show unequivocally that COPD is directly responsible for osteoporosis and other coexisting illnesses.

Implications for care

Current therapies (e.g. bronchodilators and inhaled corticosteroids), which are mostly targeted toward airflow limitation and airway inflammation, have only shown modest impact on overall mortality in COPD subjects [126, 127]. The recent recognition that coexisting illnesses are highly prevalent and have a negative impact on patient functioning and mortality has opened new therapeutic opportunities. For example, cohort studies have suggested that therapies targeting cardiovascular diseases (e.g. statins and beta-blockers) [128, 129] reduce mortality in COPD subjects, but these findings will require confirmation in randomised controlled trials [130]. Recently, FABBRI and RABE [131] proposed that COPD should be considered as a component of a broader syndrome that was called “chronic systemic inflammatory syndrome”. The authors proposed that patients should be diagnosed with this syndrome if they had three or more components of the following: age >40 yrs, smoking history >10 pack-yrs, symptoms and abnormal lung function compatible with COPD, chronic heart failure, metabolic syndrome and increased CRP [131]. They also proposed that novel strategies involving a comprehensive approach to management of COPD risk factors (e.g. smoking and inactivity) and careful assessment and treatment of coexisting illnesses may dramatically improve mortality and patient-related outcomes. Therapeutic trials are urgently needed to confirm these interesting hypotheses.

MULTIDIMENSIONAL ASSESSMENT OF COPD IN CLINICAL PRACTICE

As detailed above, COPD is a complex disease with both respiratory and extra-respiratory consequences, which all impact on patients' health status. This underlines the need for the multidimensional assessment of COPD patients, as with the BODE score [132]. However, the use of such tools needs to be preceded by multiple validation studies: it was very recently shown that their predictive value may vary between settings and populations. Indeed, the BODE index overestimated 3-yr all-cause mortality by 39% in a Spanish cohort of 342 patients, while it underestimated it by 36% in a Swiss cohort of 232 patients [133]. Recalibration improved the performance of the score as a predictor of prognosis. But it is also important that scores used in clinical practice fit not only to specialist settings but also to primary care. In that respect, CELLI *et al.* [132], the developers of the original BODE index, studied a simplified BOD score [134]. In their study, PUHAN *et al.* [133] developed and validated a new index called ADO (age, dyspnoea and airflow obstruction (FEV₁)). In their cohorts, ADO and recalibrated BODE had similar accuracy for risk prediction [133]. This study emphasises the need for careful validation of prognostic scores in various settings, before their use is widely disseminated.

CLOSING REMARKS

The recent years have provided clinicians and researchers with major advances in the understanding of underlying mechanisms in COPD, although several questions remain unanswered. In this constantly evolving context, regularly updated guidelines are here to help clinicians to optimise care for their individual patients [103].

STATEMENT OF INTEREST

None declared.

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