Improving Dyspnea in Chronic Obstructive Pulmonary Disease
Optimal Treatment Strategies

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Chronic obstructive pulmonary disease (COPD) is a common disease with a global impact in terms of morbidity and mortality. Patients usually consult their doctor because of symptoms, and among those, dyspnea at rest or under exercise is one of the most common. The sensation of dyspnea is experienced differently among individuals with COPD and may be based on diverse factors, such as muscle fatigue, patient perception, or trapped volumes. Treatment algorithms for COPD emphasize a stepwise approach to therapy depending on the severity of the disease, which, for reasons of convenience, is primarily based on spirometric impairment. Drugs that alter bronchial smooth muscle tone and increase inspiratory capacity have clinical efficacy for the dyspneic patient, most likely based on their effect on lung function, whereas the effects of antiinflammatory therapy with inhaled corticosteroids is more difficult to explain. The following short review aims to give an overview of the available clinical information of clinical trials performed over the last couple of years.

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Dyspnea is one of the most common symptoms in chronic obstructive lung disease and it is invariably present in all severity stages either at rest or under conditions of exercise. Dyspnea, unlike other outcomes for therapeutic interventions, is, however, a subjective phenomenon. One of the earlier detailed discussions of dyspnea by Richards (1), as early as 1953, acknowledges the differences in definitions given by chest physicians, psychiatrists, and cardiologists, and it could still be hypothesized that today the same presentation of a given patient with dyspnea would unfortunately be diagnosed and approached very differently by different medical specialists. In pulmonary medicine, he describes the immediate cause as a “disproportion between actual ventilating and breathing capacity,” whereas in cardiac disease at early stages, “muscular fatigue associated with inadequate cardiac output” may be the major factor.

It has also long been recognized that disease stage and perception are of crucial importance. Dyspnea in the exercising athlete, in a patient with asthma or emphysema, or as a consequence of a tracheal tumour is fundamentally different, and again, Richards (1) noted that “nowhere in medicine, perhaps, does the patient, whole and entire, so much need to be considered as in the field of respiration.”

This had led to structured attempts to define and/or assess the symptom of dyspnea (covered elsewhere in this issue), but there is ample evidence that there is still a lack of agreement among different disciplines in medicine as to what dyspnea actually means to a patient and how it will be perceived with varying severity of disease.

There is no debate that dyspnea is relevant in chronic obstructive pulmonary disease (COPD). In a recent article by Rennard and colleagues (2), it is clearly shown that about 50% of all patients with COPD present with shortness of breath on most days. Although there are differences in reporting the symptom of dyspnea in different countries, the principle hold true globally, with differences ranging from 70% in the United States to 22% in Spain. Whether these differences are in part related to severity of the disease, perception, and/or recording of this symptom is not evident from the published data.

DYSPNEA IN COPD

The classification of severity of COPD as defined by most common guidelines would assign a certain severity stage to the impairment of lung function, usually measured as FEV1. On the other hand, symptoms undoubtedly contribute to severity of the disease, and they are the basis of (pharmacologic) treatment. One of the basic principles laid out in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines is the predominantly symptomatic approach to treatment, with lesser emphasis on severity classification. This approach implies that patients, even those presenting with a marked reduction of their lung function, provided they are free from symptoms spontaneously or after a structured history taking, should not be treated with drugs that alleviate symptoms, such as bronchodilators, or treated with inhaled steroids. This situation changes when patients have a clear history of recurrent exacerbation therapy.

For symptomatic patients, the situation is somewhat more complex, because there is the difficulty in assigning the intensity or the severity of symptoms to a specific severity of the disease. Because symptoms undoubtedly are the main drivers for patients to visit their physician and for physicians to change medication for patients with COPD, practical guidance is needed. In a recent article by Jadad and colleagues (3), the authors have reviewed the available published evidence on how symptomatic responses to pharmacologic intervention in patients with COPD were measured. Much to the surprise of the authors and the readers, a whole array of many different instruments have been used, and the conclusions from this article were that there is a clear need for a fully developed and validated tool for measuring the effects of therapeutic interventions on symptoms in patients in clinical trials.

In clinical terms, assessment of the severity of the disease will rely on several factors that, to a varying extent, contribute to the clinical presentation of a given patient. There is, on the one hand, the respiratory system, most commonly measured by FEV1, and in more advanced disease, oxygen saturation. On the other hand, there is an increasing awareness of the role of impaired exercise capacity that reflects on other organ systems and that can be measured through standardized and relatively simple tests, such as the 6-min walking distance, and that should
be accompanied by information on dietary status and body composition, such as body mass. More recently, research has focused more on factors such as exacerbations, air trapping, and hyperinflation. As mentioned earlier, however, the immediate incentive for a patient to seek medical help and the major impairment experienced by patients is based on perceived symptoms; hence, the major role for simple dyspnea scores, and the objective measurement of this symptom to rationalize therapy.

In a factor analysis performed by Wegner and coworkers (4), the authors could demonstrate that, in individual patients with moderate to severe COPD, factors such as clinical ratings during walking distance were indeed different from the factor "hyperinflation" measured by body plethysmography, and different again from the factor "airflow obstruction." This underlines the fact that perceived treatment effects for symptomatic endpoints, such as dyspnea, might be achieved irrespective of major changes in lung function parameters, a clinical experience that is by now documented in numerous clinical trials.

THERAPEUTIC INTERVENTIONS FOR DYSPNEA

The most recent official statement of the American Thoracic Society on mechanisms, assessment, and management of dyspnea (5) summarizes systematically the therapeutic interventions available for the treatment of dyspnea. Although the evidence levels for each of those interventions vary greatly, they are listed in the present summary since it would lie beyond the scope of this contribution to discuss all available evidence in detail.

To reduce the ventilatory demand initially, it is recommended to reduce the metabolic load; and the therapeutic intervention of choice is exercise training to improve the efficiency of CO2 elimination and the use of supplemental oxygen in advanced disease. To decrease the central drive, supplemental oxygen therapy is again recommended in addition to pharmacologic therapy that should consist of inhaled pharmacologic agents, eventually in combination with opiates, anxiolytic therapy, and alteration of the pulmonary afferent information. Again, these measures aim to improve the efficiency of the CO2 elimination through altered breathing pattern. The therapies for treating and influencing dyspnea in patients are in fact a concerted action. Regimens include the use of bronchodilators, oxygen therapy, and exercise training, with the ultimate aim to reduce perception of dyspnea—for example, from severe disease to very slight dyspnea or to no symptoms at all (Figure 1). A possible technique to measure these effects could be an increase in exercise time and this has been successfully used in several studies investigating the effect of long-acting bronchodilators, such as tiotropium bromide. A recent study from Stevenson and Calverley (6) tested the possibility of combining oxygen delivery and exercise in patients with COPD. Interestingly, patients in this study had a measurable reduction in hyperinflation postexercise when breathing oxygen instead of room air, but they did not feel less breathless. This recent study illustrates the difficulty to simply relate symptoms such as dyspnea to lung mechanics and should stimulate further research into the possibility of dyspnea-relieving compounds.

Finally, for the reduction of ventilatory impedance, reduction of lung hyperinflation is the goal to maximize breathing mechanics and resistance to airflow. Conceptually, relief of dyspnea after surgical volume reduction has been attributed to the reduction of operational lung volumes and could be related to reduced dynamic hyperinflation and improved ventilatory muscle performance. The beneficial effects on dyspnea of low-level continued positive airway pressure have been assigned (1) to counterbalance the effect of increased inspiratory load on respiratory muscles and (2) to reduce a neuromechanical dissociation of the ventilatory pump. Decreasing the resistive load in these circumstances is again the domain of pharmacotherapy, acting through the reversal of bronchoconstriction.

LUNG FUNCTION AND DYSPNEA

Obviously, the primary physiologic impairment in COPD is airflow limitation as a combined result of increased resistance of (primarily) smaller airways and decreased driving pressure through altered parenchymal compliance and decreased alveolar attachments. Patient-centered outcomes, also increasingly recognized as therapeutic targets, show a weak correlation at best with the degree of airflow limitation.

Air trapping occurs in patients with airflow limitation when the frequency of breathing is too high to allow for full exhalation between breaths, and it appears that it is this retention of volume that substantially contributes to the sensation of dyspnea. Air trapping results in an increased work of breathing, and it places respiratory muscles at a mechanical disadvantage; through this, it is believed to contribute to the sensation of breathlessness. Interestingly, lung inspiratory capacity correlates reasonably well \((r = 0.3)\) with exercise endurance time, whereas FEV1 does not (7). Furthermore, the correlation among exercise endurance, inspiratory capacity, and exertional dyspnea is close. For example, the correlation between exercise endurance and inspiratory capacity is reported to be 0.52 and the correlation between inspiratory capacity and exertional dyspnea is again 0.52, both being highly significant (8). Changes in inspiratory volumes also contribute to the perceived benefits of bronchodilator therapy. A recent study by Taube and colleagues (9) assessed the perception of bronchodilator benefit in patients with COPD by measuring the changes in both forced inspiratory and expiratory volumes after the inhalation of 400 μg, assessing symptoms with the visual analog score. The correlation between absolute and relative changes in forced inspiratory volume to visual analog score and dyspnea was much tighter \((r = 0.715 \text{ and } 0.730)\) than the correlation with expiratory volumes \((r = 0.213 \text{ and } 0.389; \text{ Figure 2})\). In summary, it appears that inspiratory volumes are the best reflection of dyspnea in patients with COPD, and these are the main targets for therapeutic interventions to alleviate dyspnea.

The GOLD (10) recommends the use of bronchodilators for the symptomatic management of COPD and assigns an evidence level A for this recommendation. These drugs are given on an as-needed basis or on a regular basis to prevent symptoms. The principal bronchodilators available are β-agonists with a short and long duration of action, anticholinergics with a short and

![Figure 1](image-url). Schematic model illustrating the cumulative benefit of interventions targeting pathophysiologic mechanisms of dyspnea. Reprinted by permission from Reference 5.
long duration of action, theophylline, or a combination of any of these drugs.

Recently, a series of clinical trials with long-acting anticholinergics (tiotropium bromide) have been performed and are listed in Table 1. The studies are performed over a variable amount of time ranging from 6 wk to 1 yr, but it appears that, in a large number of individuals, shortness-of-breath scores could be positively influenced over the entire period of 1 yr compared with placebo. In general, the published evidence suggests that these findings hold true for both the Borg dyspnea score and the transitional dyspnea index (TDI). Interestingly, this effect on the TDI can be demonstrated in patients with COPD, irrespective of their immediate bronchodilator response (11).

In this context, it is noteworthy that it was suggested years ago that the use of even weak bronchodilator drugs might have a significant impact on dyspnea. In a study by Kirsten and co-workers (12), it was demonstrated that the placebo-controlled withdrawal of a standardized treatment with oral theophylline in patients with severe COPD led to a significant increase in symptoms, again assessed as a deterioration of the TDI (among other measures), compared with an insignificant change in lung function. A recent study published by ZuWallack and colleagues (13) compared the effect of oral theophylline, salmeterol, and a combination of both on dyspnea over 3 mo in patients with COPD. This large study was performed in 900 individuals, and the authors clearly showed that all bronchodilators improved dyspnea score, reaching the clinically significant “magic line” of 1 in the TDI. Notably, by comparison, there is limited evidence assessing the effects of theophylline on dyspnea at rest or under conditions of exercise in COPD.

For the group of long-acting bronchodilators, especially for anticholinergic drugs, it has been shown repeatedly that these drugs probably exert most of their symptomatic benefit not by improvement of FEV<sub>1</sub> and FVC but by having a significant effect on volumes at inspiratory capacity or functional residual capacity. A large number of placebo-controlled clinical trials of variable duration and size have demonstrated the effects of long-acting β-agonists on dyspnea in patients with COPD over the last years, and these studies (listed in Table 2) more or less uniformly demonstrate significant benefits. Importantly, there is limited information at best on the efficacy of short-acting β-agonists on dyspnea in patients with COPD using a rigid study design (14).

In clinical practice in many countries, combination therapy with inhaled corticosteroids (ICS) and long-acting β-agonists is prescribed for many patients with COPD.

Combination therapy has been studied in five large randomized trials (Table 3) with significant treatment effects, and the majority of these studies seem to suggest that the addition of an ICS (with bigger effects of higher doses in some studies) enhances the effect of the bronchodilator alone. Both drugs affect lung function through different mechanisms of action (smooth muscle tone, inflammation, plasma exudation), so that it is possible that ICS exert their effect on dyspnea via lung function improvement as well. The precise mechanism of action of steroids on dyspnea, however, is uncertain, and this raises the interesting point of whether steroids or other antiinflammatory therapy could influence the perception of dyspnea in patients with COPD. There are a number of randomized clinical trials that demonstrate the effect of ICS on the severity of breathlessness (14). These studies were performed with different steroids (triamcinolone, budesonide, fluticasone) at variable doses and, in general, significant treatment effects were reported (see Table 4).

### NONPHARMACOLOGIC INTERVENTIONS

Considering the general therapeutic aims proposed in treatment guidelines for COPD, it is evident that the improvement of inspiratory muscle function should be a target for any therapeutic intervention to improve the sensation of dyspnea. To improve inspiratory muscle function, several nonpharmacologic approaches have been suggested, with a focus on nutrition, training of inspiratory muscle groups, and positioning of a patient. Furthermore,
techniques of partial ventilatory support and, notably, minimizing the use of (oral) steroids are recommended treatment options under these conditions.

There are still unresolved numerous issues around the mechanisms leading to dyspnea in COPD in general. One of the interesting findings of a recent article by Watson and colleagues (15) is related to the fact that there are sex differences for symptoms in patients with COPD. Although these symptoms occur with the same prevalence in men and women, cross-sectionally, they are only associated with lower levels of lung function in men. Reporting of symptoms and the perception of dyspnea might therefore be influenced by other, so far unrecognized, factors in patients with COPD. Alteration of central perception could therefore also be a therapeutic goal that has in principle been recognized, but we have limited tools at hand for clinical practice.

Some interesting insights in the perception of dyspnea have been gained in patients with asthma (16). A recent study by in’t Veen and colleagues (17) demonstrated that individuals would respond very differently in their Borg score to an impairment of lung function. The differences for this perception are not quite clear. In the study of in’t Veen and colleagues (17), the authors speculated that specific inflammatory processes would modulate the perception of dyspnea under these circumstances. Notably, patients with more pronounced eosinophilic inflammation had a lesser perception of dyspnea than others, suggesting that products from eosinophils, such as eosinophil-derived neurotoxin, might alter the perception of dyspnea in these cases.

Obviously, there might be a difference of dyspnea perception between chronic disease and the acute worsening initiated experimentally through an exacerbation. Studies on the time course of symptoms of COPD exacerbations (18) would suggest that symptoms do not necessarily reflect changes in lung function, although symptoms such as dyspnea would have some predictive value for an exacerbation to occur, and that the severity of these symptoms would characterize more severe events.

Finally, perception of dyspnea may differ between patients with asthma or COPD. In an experimental approach, Rutgers and colleagues (19) challenged individuals with 5’-adenosine monophosphate, an indirect challenge acting on mast cells, and methacholine. Symptoms were measured using Borg scores and the authors found that (smoking) patients with COPD had a lower perception of dyspnea compared with (nonsmoking) individuals with asthma.

The theoretic concept that perception of dyspnea and inflammation are linked is supported by another recent article by Mahler and coworkers (20). In this randomized, placebo-controlled
CONCLUSIONS

In summary, dyspnea is the major symptom in patients with COPD, and this applies to all severities. Changes in dyspnea are not necessarily related to changes in lung function but they show some relation to the overall clinical status, and increases in dyspnea may indicate the advent of an exacerbation. There are various instruments available to measure dyspnea, but it seems that they are not uniformly used, and this has probably contributed to an incoherence of data, a lack of clear recommendations, and a cautious approach in using dyspnea as an outcome measure in clinical trials by authorities. Inhaled bronchodilators, according to most therapeutic guidelines, are considered the “gold” standard for treating dyspnea. This is based on the fact that potent bronchodilator therapy alters lung volumes and, when being assessed by inspiratory capacity and functional residual capacity, these functional effects translate directly to the decrease in symptoms and to an increase in exercise capacity. There is emerging evidence that ICS in combination with bronchodilators might also have a greater effect on the dyspnea and there is the interesting possibility that antiinflammatory therapy per se might alter the perception of dyspnea. Obviously, treatment of dyspnea is complex and should be a target for the development of truly novel drugs to treat COPD, given the enormous impact for patient-centered outcomes in this disease.

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References

### TABLE 4. EFFECTS OF INHALED CORTICOSTEROIDS ON DYSPNEA MEASURED BY DIFFERENT INSTRUMENTS

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Dose</th>
<th>Study Design</th>
<th>No. Patients</th>
<th>Baseline FEV₁ (L)</th>
<th>Dyspnea Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renkema and colleagues, 1996 (31)</td>
<td>Budesonide, 800 μg bid</td>
<td>2 yr</td>
<td>39</td>
<td>2.16 1.90</td>
<td>p &lt; 0.05 for dyspnea and wheeze score for bud vs. pl</td>
</tr>
<tr>
<td>LHS II, 2000 (32)</td>
<td>Triamcinolone, 600 μg bid</td>
<td>3 yr</td>
<td>1116</td>
<td>2.16 2.10</td>
<td>p = 0.02 on ATS questionnaire for triam vs. pl</td>
</tr>
<tr>
<td>Mahler and colleagues, 2002 (26)</td>
<td>Fluticasone, 500 μg bid</td>
<td>24 wk</td>
<td>349</td>
<td>1.23 1.32</td>
<td>Change TDI vs. pl = 1.0*</td>
</tr>
<tr>
<td>Calverley and colleagues, 2003 (28)</td>
<td>Budesonide, 320 μg bid</td>
<td>1 yr</td>
<td>513</td>
<td>0.99 0.98</td>
<td>Change vs. pl = −0.99* (0–4 scale)</td>
</tr>
<tr>
<td>Hanania and colleagues, 2003 (27)</td>
<td>Fluticasone, 250 μg bid</td>
<td>24 wk</td>
<td>368</td>
<td>1.31 1.29</td>
<td>Change TDI vs. pl = 0.7*</td>
</tr>
<tr>
<td>Calverley and colleagues, 2003 (29)</td>
<td>Fluticasone, 500 μg bid</td>
<td>1 yr</td>
<td>735</td>
<td>1.30 1.26</td>
<td>Change vs. pl = −0.08 (0–4 scale)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: ATS = American Thoracic Society; bid = twice daily; bud = budesonide; LHS II = Lung Health Study Group; pl = placebo; TDI = transitional dyspnea index; triam = triamcinolone.

* Significantly different.


