

## Comprehensive Treatment of Dyspnoea in Chronic Obstructive Pulmonary Disease Patients

a report by

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Dyspnoea is the most common symptom of patients suffering from chronic obstructive pulmonary disease (COPD). It progresses relentlessly with the natural history of disease. Increased breathlessness leads to inactivity and related peripheral muscle deconditioning, resulting in a vicious cycle that leads to further inactivity, social isolation, fear of dyspnoea and depression. Patients with severe COPD become less mobile and reduce their activities of daily living. This article summarises the different ways to treat dyspnoea in patients with COPD, with special attention to non-pharmacological treatment.

Knowledge of the factors contributing to exercise-induced dyspnoea is important to the development of therapeutic interventions and counselling for these patients. Chemoreceptors and receptors in the airways, lung parenchyma and respiratory muscles provide sensory feedback via vagal, phrenic and intercostal nerves to the spinal cord, medulla and higher centres of the central nervous system (CNS).<sup>1</sup>

Dyspnoea is “a term used to characterise a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses.”<sup>2</sup> Breathlessness is characterised by measurable intensity and qualitative dimensions, which may vary depending on the individual, the underlying disease and other circumstances.<sup>3</sup>

### Pathophysiological Factors of Dyspnoea in COPD

Pathophysiological factors known to contribute to exertional dyspnoea in these patients include increased intrinsic mechanical loading of inspiratory muscles, i.e. the intrinsic positive end-expiratory pressure (PEEPi), increased mechanical restriction of the thorax, inspiratory muscle weakness, increased ventilatory demand relative to capacity, gas exchange abnormalities, dynamic airway compression, cardiovascular factors and any combination of the above.<sup>3</sup>

A better understanding of the underlying mechanisms is necessary for clinicians to improve their ability to treat patients with breathlessness. Many of the therapeutic interventions currently available relieve dyspnoea by addressing a combination of different mechanisms, namely:

- reduction in ventilatory demand;
- reduction in ventilatory impedance; and
- improvement in ventilatory muscle function.<sup>4,5</sup>

### Exercise Training and Breathing Manoeuvres

Reduced ventilatory demand may be obtained by reducing the metabolic load. Patients with COPD can achieve physiological benefits from well-designed programmes of exercise training. Substantial improvements in dyspnoea, exercise tolerance and health-related quality of life can be obtained as a result of exercise training programmes in mild to severe COPD.<sup>6</sup> The improvements in exercise tolerance have been found to be associated with physiological changes such as:

- improved muscle function (including more rapid oxygen uptake kinetics following exercise onset);<sup>7</sup>
- altered breathing pattern, consisting of higher tidal volume and lower breathing frequency leading to a reduced dead space/tidal volume ratio and, thus, a lower ventilatory requirement for exercise;<sup>8</sup>
- reduction in lactic acidosis, minute ventilation (VE) and heart rate for a given work rate;<sup>6</sup>
- enhanced activity of mitochondrial enzymes; and
- capillary density in the trained muscles.<sup>9</sup>

Intensity of exercise training is of key importance.<sup>6,9</sup>

‘Breathing retraining’ is a term for a range of techniques aimed at reducing dynamic hyperinflation, increasing strength and endurance of the respiratory muscles and optimising the pattern of thoraco-

abdominal motion.<sup>10</sup> This term covers different techniques, such as:

- **Inspiratory muscle training.** Inspiratory muscle weakness and/or dysfunction has been suggested to be among the contributors to dyspnoea in COPD patients. Different modalities of inspiratory muscle training have been shown to decrease dyspnoea through improvement in inspiratory muscle function. However, the clinical long-term effectiveness of this modality in COPD patients must be confirmed.<sup>10</sup>
- **Pursed-lips breathing.** This technique involves exhalation through a resistance created by constriction of the lips. Although this manoeuvre is often spontaneously adopted by COPD patients, it is also routinely taught as a breathing retraining exercise in pulmonary rehabilitation programmes, because it is thought to alleviate dyspnoea. However, some patients with COPD obtain relief of dyspnoea with this technique whereas others do not. Pursed lips breathing can have a variable effect on dyspnoea when performed volitionally during exercise by patients with COPD. The effect is related to the combined change in the tidal volume and end expiratory lung volume and their impact on the available capacity of the respiratory muscles to meet the demands placed on them in terms of pressure generation.<sup>10,11</sup>
- **Diaphragmatic breathing.** Using this technique, the patient is told to move the abdominal wall predominantly during inspiration and to reduce upper rib cage motion. For a long time suggested to be effective in reducing dyspnoea in COPD patients, this modality has recently been found to be accompanied by increased asynchronous and paradoxical breathing movements and increased work of breathing with related worsening in dyspnoea.<sup>12</sup>

### Oxygen Supplementation and Air–Heliox Mixtures

Decreasing ventilatory demands and/or gas density have recently been shown to improve exercise tolerance, symptoms and quality of life.<sup>13</sup> One way to reduce metabolic load is oxygen supplementation. Hypoxia has no dyspnoenic effect *per se*; it causes dyspnoea by stimulating the VE.<sup>14</sup> Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance of the hypoxaemic COPD patient through different mechanisms:

- reduction in hypoxic stimulation of the carotid bodies;
- pulmonary vasodilation; and
- 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 acidemia.<sup>15</sup> Recent studies indicate that reduction in hyperinflation, i.e. reduction in ventilatory impedance, also plays an important role in the oxygen-related relief of dyspnoea.<sup>16</sup> Interestingly, supplemental oxygen generally increases exercise tolerance in patients with only mild to moderate hypoxaemia.<sup>17</sup>

Despite these positive physiological results, there is evidence suggesting that mild hypoxaemia accelerates peripheral muscle adaptation such that the use of supplemental oxygen during training of mildly hypoxaemic patients may not be advantageous.<sup>18</sup> This seems to have been confirmed by early studies that failed to demonstrate benefits of supplemental oxygen during rehabilitation.<sup>19–23</sup> Nevertheless, a recent double-blind study of non-hypoxaemic patients with severe COPD showed that patients who trained with oxygen supplementation increased training intensity and endurance more rapidly than patients trained without.<sup>24</sup>

Manipulating gas density – for example, through heliox breathing – has also been shown to be beneficial in relieving symptoms and improving exercise capacity, because it facilitates gas emptying during expiration. As a result, the amount of expiratory flow limitation and operational lung volumes decreases, reducing ventilatory impedance and, ultimately, leading to greater exercise tolerance.<sup>25</sup>

### Reducing the Central Ventilatory Drive

Another possibility is to reduce ventilatory demand by decreasing the central drive by opiates.<sup>26</sup> Opiates have been shown to decrease VE at rest and during sub-maximal exercise. They can alter the central processing of neural signals within the CNS to reduce sensations associated with breathing. Also, the drug's cardiovascular effects are thought to be responsible for relieving dyspnoea. Therapeutic doses of opioids induce peripheral vasodilation, reduce peripheral vascular resistance and inhibit baroreceptor response. Furthermore, opioids reduce the anxiety associated with dyspnoea. There is also speculation that they may act directly on opioid receptors in the airways.<sup>27</sup> Despite safety concerns, these drugs do have a place in the management of patients in the terminal phase of their disease.<sup>28</sup>

No consistent improvement in dyspnoea over placebo has been shown with anxiolytics.<sup>10</sup> Nonetheless, the US Agency for Toxic Substances and Disease Registry (ATSDR) states that physicians should “recommend a trial of anxiolytic therapy on an individual basis”.<sup>2</sup>

### Altering Pulmonary Afferent Information

Decreasing central drive, i.e. reducing ventilatory demand, obtained by altering pulmonary afferent information to central controller, may potentially reduce dyspnoea. However, there are many concerns about the real usefulness of such interventions in a clinical setting.<sup>4</sup> The following must be considered:

- there is speculation that opioids may act directly on opioid receptors in the airways;<sup>27</sup>
- aerosolised topical anaesthesia has inconsistent effects on dyspnoea;<sup>29</sup>
- vagal blockade has highly variable effects on dyspnoea;<sup>30</sup> and
- intact VE response to exercise in post-transplanted vagally denervated subjects has been reported.<sup>31</sup>

Also, inhaled lidocaine lessens breathlessness associated with bronchoconstriction in asthma.<sup>32</sup> Inhalation of furosemide alleviates the sensation of dyspnoea induced by constant-load exercise testing in patients with COPD.<sup>33</sup>

### Assisted Ventilation

In 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 in such patients. Several studies have examined the acute effects of different modalities of ventilatory assistance during exercise on dyspnoea and exercise tolerance in advanced COPD. Continuous positive airway pressure (CPAP) and different modalities of ventilatory assistance delivered through nasal or facial mask during exercise reduces dyspnoea and work of breathing and enhances exercise tolerance in COPD patients.<sup>34,35</sup> An inspiratory support provides symptomatic benefit by unloading and assisting such overburdened ventilatory muscles, whereas CPAP counterbalances the PEEPi.<sup>36</sup>

A randomised study showed that domiciliary non-invasive positive-pressure ventilation added to long-term oxygen resulted in improvement in dyspnoea and quality of life, without affecting survival over a two-year period.<sup>37</sup> However, larger studies are needed before this therapy can be recommended routinely. Adding home nocturnal non-invasive ventilation to daytime exercise training has been found to significantly increase exercise capacity and improve quality of life

compared with exercise training alone.<sup>38</sup> Nocturnal non-invasive assisted ventilation is not necessarily directed at exercise and peripheral muscle adaptation. The main purpose is to correct night-time blood gases with a carry-over through the day. The result should be an improvement in function, including the ability to complete a daily exercise programme. This may be analogous to optimal pharmacological therapy.<sup>34</sup>

Despite these promising physiological and clinical studies,<sup>34–38</sup> the role of assisted ventilation in pulmonary rehabilitation, if any, is still to be defined. Two similar studies of well-structured programmes of exercise training with proportional assisted ventilation have given conflicting results.<sup>39,40</sup>

### Bronchodilators

As mechanical factors appear to predominate in the pathophysiology of dyspnoea in COPD patients, it is reasonable to try to alleviate these with drugs that improve bronchodilation, principally by producing airway smooth muscle relaxation. Bronchodilators are the mainstay of treatment in COPD.<sup>41</sup>

### Beta Agonists

Inhaled long-acting beta 2 agonists improve forced expiratory volume at one second (FEV<sub>1</sub>), control of symptoms and, in some trials, exercise, capacity and health status.<sup>42</sup> Beta 2 agonists have been shown to reduce dynamic hyperinflation and dyspnoea during exercise and a relationship has been found between changes in resting inspiratory capacity (an index of dynamic hyperinflation) following inhaled salbutamol and dyspnoea during light exercise in COPD patients with expiratory flow limitation.

### Anticholinergics

In stable COPD, oxitropium bromide was found to reduce breathlessness and improve the walking distance independently from changes in FEV<sub>1</sub>.<sup>43</sup>

Tiotropium is a non-selective anticholinergic agent that exhibits kinetic receptor selectivity for the muscarinic M1 and M3 receptors. In clinical trials, patients receiving tiotropium once-daily showed significant improvements in trough, peak and mean FEV<sub>1</sub>, dyspnoea and health-related quality of life, as well as fewer COPD exacerbations and hospitalisations, compared with patients receiving placebo and ipratropium. The effect of tiotropium on dyspnoea has been measured by the transition dyspnoea index (TDI).<sup>44</sup> The improvement in TDI of tiotropium subjects was statistically significant compared with placebo. It also tended to increase

with duration of use and sometimes exceeded the threshold of clinical significance. Also, the effect of tiotropium on dyspnoea has been associated with a reduction in hyperinflation, as assessed by an increase in inspiratory capacity.<sup>45</sup>

### Theophylline

With oral theophylline, there is a dose-dependent improvement in exercise tolerance, reduced thoracic gas volume and a modest but significant decrease in dyspnoea related to improvement in respiratory muscle performance, beside the bronchodilator effects.<sup>4</sup>

### Conclusion

The conclusion from the above studies is that multiple tools are available in the treatment of dyspnoea in COPD patients. Apart from the consolidated 'old' modalities, such as drug intervention, exercise training as evaluated by evidence-based medicine is a valuable adjunct to pharmacological treatment of COPD.<sup>15,16,54,61</sup> Therefore, the modalities discussed should be used as adjuncts to a well-designed comprehensive respiratory rehabilitation programme that includes other interventions, such as education, nutrition and psychological counselling, and is tailored to the specific patient. ■

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