

# Dyspnoea in Health and Obstructive Pulmonary Disease

## The Role of Respiratory Muscle Function and Training

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### Abstract

A consistent finding of recent research on respiratory muscle training (RMT) in healthy humans has been an attenuation of respiratory discomfort (dyspnoea) during exercise. We argue that the neurophysiology of dyspnoea can be explained in terms of Cambell's paradigm of length-tension inappropriateness. In the context of this paradigm, changes in the contractile properties of the respiratory muscles modify the intensity of dyspnoea predominantly by changing the required level of motor outflow to these respiratory muscles. Thus, factors that impair the contractile properties of the respiratory muscles (e.g. the pattern of tension development, functional weakening and fatigue) have the potential to increase the intensity of dyspnoea, while factors that improve the contractile properties of these respiratory muscles (e.g. RMT) have the potential to reduce the intensity of dyspnoea. In patients with obstructive pulmonary disease, functional weakening of the inspiratory muscles in response to dynamic lung hyperinflation appears to be a central component of dyspnoea. A decrease in the intensity of respiratory effort sensation (during exercise and loaded breathing) has been observed in both

healthy individuals and patients with obstructive pulmonary disease after RMT. We conclude that RMT has the potential to reduce the severity of dyspnoea in healthy individuals and in patients with obstructive pulmonary disease, and that this probably occurs via a reduction in the level of motor outflow. Further work is required to clarify the role of RMT in the management of other disease conditions in which the function of the respiratory muscles is impaired, or the loads that they must overcome are elevated (e.g. cardiorespiratory and neuromuscular disorders).

Recent studies of respiratory muscle training (RMT) in healthy humans have reported post-training decreases in the perceptions of respiratory effort during exercise.<sup>[1-5]</sup> These findings suggest that improvements in the contractile properties of the respiratory muscles modify respiratory effort at a fundamental level. Abatement of unpleasant or uncomfortable respiratory effort sensations (dyspnoea) is of interest to the sports and pulmonary clinician, since this holds the promise of a management tool for those limited by these sensations. Thus, the purpose of this review is to consider the role of respiratory muscle function in the genesis of dyspnoea and to examine the evidence that specific RMT ameliorates dyspnoea. The review will draw upon evidence from healthy young adults, as well as patients with chronic obstructive pulmonary disease (COPD) and asthma.

## 1. Respiratory Effort Sensation

### 1.1 Length-Tension Inappropriateness (LTI): A Unifying Paradigm for Dyspnoea

Throughout this review we use the term 'respiratory effort sensation' to describe the distillation of sensations associated with the urge to breathe and the sensory experience that arises from the motor response to that urge. The terms 'breathlessness' and 'dyspnoea' have been used interchangeably to describe what Jonathan Meakins termed "the consciousness of the necessity for increased respiratory effort".<sup>[6]</sup> Meakins' definition of dyspnoea was the first to provide a unifying theory to explain the presence of dyspnoea in both patients and healthy volunteers, and was developed further by Moran Campbell's group in the 1960s. Campbell coined the

term 'length-tension inappropriateness' (LTI) to explain how the sensation of dyspnoea might be 'transduced' to consciousness.<sup>[7]</sup> Campbell argued that humans have a quantitative, conscious appreciation of the degree of effort associated with breathing, and that dissociation or a mismatch between the central respiratory motor activity and the mechanical response of the respiratory system may produce a sensation of respiratory discomfort (dyspnoea). More recently, the LTI paradigm has been generalised to include not only afferent sensory inputs from respiratory muscles, but information emanating from receptors throughout the respiratory system.<sup>[8]</sup> When viewed in the context of the LTI paradigm, the role of respiratory muscle function in the perception of dyspnoea becomes intuitively predictable. Thus, the intensity of dyspnoea is increased when changes in respiratory muscle length (i.e. volume) or tension (i.e. pressure) are inappropriate for the outgoing motor command. In the ensuing sections, we will explore the neurophysiological evidence that supports the validity of the LTI paradigm. Within the context of LTI, we will also consider the role of respiratory muscle function in the genesis of dyspnoea.

### 1.2 The Neurophysiology of LTI and Effort Sensation

#### 1.2.1 Motor Command

In the years that have followed Campbell's first enunciation of LTI,<sup>[7]</sup> neurophysiology has provided further evidence to support the assertion that there is a conscious awareness of the outgoing respiratory motor command to the respiratory muscles.<sup>[9-12]</sup> It has been suggested that a conscious awareness of central motor command occurs via corollary dis-

charge from the brainstem respiratory neurones to the sensory cortex during spontaneous breathing,<sup>[9]</sup> or from cortical motor centres to the sensory cortex during voluntary respiratory efforts (see figure 1, path 1).<sup>[12]</sup> The greater the magnitude of the corollary signals,<sup>[12]</sup> the greater the intensity of dyspnoea. Evidence supporting this notion stems from studies that have altered the coupling between motor outflow and muscle tension; for example, decreased muscle length,<sup>[12]</sup> fatigue,<sup>[11]</sup> and partial paralysis.<sup>[10]</sup> Each of these conditions increases the sense of respiratory effort associated with a given level of muscle tension (see section 2).

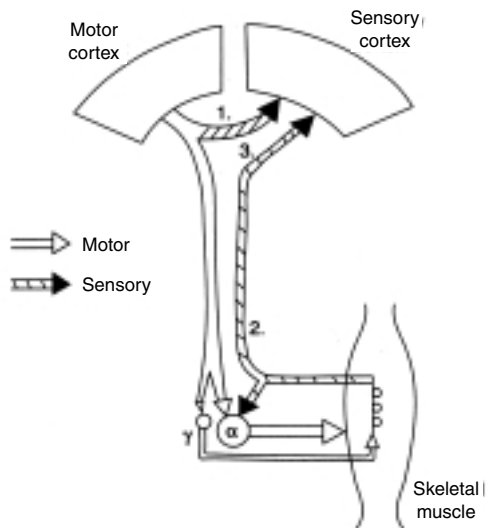
### 1.2.2 Afferent Scaling of the Mechanical Response

In the LTI paradigm, central motor outflow command is referenced to afferent feedback signals from peripheral receptors in muscle, joints and tendons. Group Ia and some group II afferents innervate muscle spindles, which signal changes in muscle fibre length (i.e. lung volume). Golgi tendon organs (group Ib afferents) signal changes in intramuscular tension and exert inhibitory influences on central

respiratory drive. Non-spindle group II fibres and many of the slower-conducting, thinly myelinated group III fibres are mechanically sensitive and respond to muscle contraction, stretch or both. Other group III afferents and group IV afferents respond to various metabolites produced during exercise or to noxious levels of mechanical strain. In the context of afferent feedback, there may also be supplemental information provided by arterial chemoreceptors (central and peripheral), pulmonary receptors (stretch, irritant and C fibres), and upper airway receptors, but their precise role is unclear and beyond the scope of this review (for detailed discussion see Banzett and Lansing<sup>[14]</sup>). Although it has been argued that sensations accompanying muscular contraction come from the activated muscle directly (see figure 1, path 2), the current consensus of opinion is that the sensory integration of feedforward and feedback mechanisms provides a fine-tuning adjustment of the exertional signal (figure 1, path 3).<sup>[8]</sup>

### 1.2.3 The Influence of Prior Experience

In LTI theory, prior experience is used to make judgements regarding the appropriateness of the motor command relative to the mechanical response.<sup>[7]</sup> Research suggests that this prior experience can have a substantial and rapid influence upon respiratory effort sensation. For example, using a simple category scale (0, 1, 2) to designate no load, small load, and moderate load, respectively, McCloskey<sup>[15]</sup> found that healthy volunteers downgrade the magnitude of effort to added respiratory loads following as few as 20 breaths against an increased background load. Similarly, Revelette and Wiley<sup>[16]</sup> asked study participants to estimate the magnitude of a series of inspiratory resistive loads before and after a 2-minute period of breathing against a non-fatiguing inspiratory load equivalent to 80% of their maximum inspiratory mouth pressure (MIP). Load estimates were significantly higher under the control condition than following the 80% of MIP loading task. Similar results to those found for the respiratory muscles were also obtained for load magnitude estimation in the elbow flexors.<sup>[16]</sup> Revelette and Wiley<sup>[16]</sup> offered two explanations for the acute at-



**Fig. 1.** Possible mechanisms for generating muscle sensations showing the neuromuscular control system with motor and sensory pathways and the  $\alpha$ - $\gamma$  linkage. Path 1 = central motor command; path 2 = feedback directly from muscle afferents; path 3 = integrated signal incorporating feed forward (path 1) and feedback (path 2) information (see text for further details) [reproduced from Cafarelli,<sup>[13]</sup> with permission].

tenuation of load magnitude estimation. First, prior loading produced long-lasting facilitation along the efferent pathway from the motor cortex to the active muscles, which reduced the level of central motor command required to produce a given tension. Secondly, prior loading elicited a sensory adaptation, similar to that observed for other sensory modalities such as taste and vision, which may have resulted in underestimation of load magnitudes.

## 2. The Role of Respiratory Muscle Tension in Effort Sensation

The contractile properties of the respiratory muscles have a potent influence upon the level of motor outflow required to bring about a given task. Accordingly, within the LTI paradigm, factors that change the contractile properties of the respiratory muscles have the potential to influence respiratory effort sensation. Factors that have been purported to influence the intensity of respiratory effort include: (i) the pattern of tension development; (ii) functional weakening of the inspiratory muscles; and (iii) respiratory muscle fatigue.

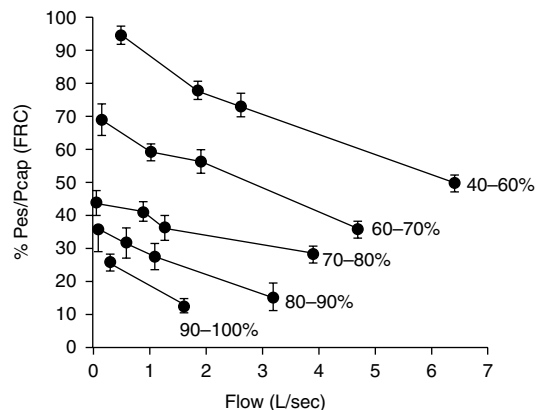
### 2.1 Pattern of Tension Development

During exercise, ventilatory drive and respiratory muscle tension (pressure) increase concomitantly in order to overcome the opposing elastic and resistive loads. The magnitude of respiratory effort sensation increases in proportion to the developed inspiratory muscle tension.<sup>[17,18]</sup> However, the pattern by which tension is generated also contributes to the perceptual response.<sup>[17,19]</sup> Most important among the factors that determine the pattern of tension development are the velocity of shortening (airflow), frequency of contraction (respiratory frequency), and the duty cycle (ratio of inspiratory time to total breath duration).<sup>[17]</sup> Changes in muscle length (tidal volume) also affect respiratory effort sensation, but to a lesser extent.<sup>[17]</sup> The perceived magnitude of respiratory effort increases in proportion to each of these factors.<sup>[17,19]</sup> Tension, velocity, frequency and duty cycle contribute independently and collectively to perceived dyspnoea, accounting for ~69% of the total variance.<sup>[17]</sup> Despite the importance of the pat-

tern by which tension is generated, available evidence does not support a significant modification of these factors following RMT. Thus, changes in effort sensation after RMT cannot be attributed to changes in the pattern of tension development.

### 2.2 Functional Weakening of Inspiratory Muscles

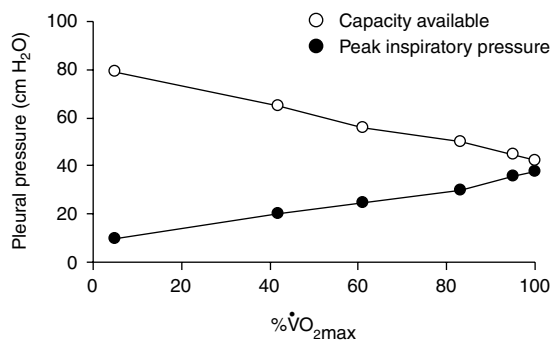
The increased ventilatory drive that occurs with exercise leads to increases in tidal volume and airflow. Based on the length-tension (volume-pressure) relationships for inspiratory muscles, a decrease in the operating length of these muscles would be expected to cause a functional weakening.<sup>[20]</sup> Similarly, a decrease in inspiratory muscle pressure with increasing airflow would be predicted based on the force-velocity (pressure-flow) relationships for these muscles.<sup>[20]</sup> The capacity of the inspiratory muscles to generate dynamic pressure has been predicted to decrease by 17% for each 10% of the total lung capacity that is accounted for by an increased tidal volume above functional residual capacity, and by 5% for each L/sec increase in inspiratory flow (see figure 2).<sup>[21]</sup> Thus, as tidal volume and inspiratory flow increase with exercise, a given level of tension represents a relatively great-



**Fig. 2.** Maximum inspiratory oesophageal pressure ( $P_{cap}$ ) expressed as % $P_{cap}$  at functional residual capacity (FRC) with occlusion, developed against varying inspiratory flow rates from zero to maximum inspiratory flow and at lung volumes from 40–100% of total lung capacity. Data are means  $\pm$  standard error (reproduced from Leblanc et al.,<sup>[21]</sup> with permission). **Pes** = oesophageal pressure.

er percentage of the maximum tension that can be developed and requires a greater motor outflow. In moderately fit, healthy individuals, the airways are overbuilt for the ventilatory challenge demanded by even maximal exercise. This preserves the capacity of the inspiratory muscles for maximal force generation by reducing end expiratory lung volume (EELV) such that muscle length is increased. Thus, the peak dynamic pressure generated by the inspiratory muscles expressed relative to the individuals' ability to generate pressure at the lung volumes and flows adopted during maximal exercise is only 40–60%.<sup>[21]</sup> In contrast, endurance-trained individuals are susceptible to expiratory flow limitation, which causes EELV to increase back toward, or even slightly above resting levels. An increase in EELV requires shortening of the inspiratory muscles and results in a reduction in their force-generating capacity. Furthermore, the high ventilatory flows achieved by endurance-trained individuals during heavy-intensity exercise exacerbate functional weakening. Accordingly, endurance-trained individuals elevate peak dynamic inspiratory muscle pressure to 90% of capacity, or greater (see figure 3).<sup>[22]</sup>

With functional weakening, the LTI paradigm predicts that the respiratory effort required to generate a given level of inspiratory muscle tension is correspondingly increased. Extending this line of reasoning, increasing the maximum pressure-generating capacity of the inspiratory muscles, their maxi-



**Fig. 3.** Peak inspiratory pleural pressure (data are means;  $n = 8$ ) during tidal breathing and capacity of inspiratory muscles for pressure generation with progressive exercise (reproduced from Johnson et al.,<sup>[22]</sup> with permission).  $\dot{V}O_{2max}$  = oxygen consumption.

um velocity of shortening, or both, would reduce the fraction of maximum pressure generated with each breath. In turn, the presumed reduction in motor outflow to the respiratory muscles would be expected to decrease the perceived sense of respiratory effort. Increases in maximum inspiratory pressure and maximum inspiratory flow have been observed consistently following relatively short periods (6–9 weeks) of inspiratory muscle training (IMT).<sup>[23,24]</sup> Moreover, a decrease in inspiratory load sensation has been observed after specific inspiratory muscle strengthening.<sup>[25,26]</sup> Most recently, Huang et al.<sup>[27]</sup> examined the relationship between changes in inspiratory muscle strength (MIP) and inspiratory muscle motor drive (mouth occlusion pressure at 0.1 seconds [ $P_{0.1}$ ]). In healthy volunteers studied at rest, the authors observed a 22% reduction in  $P_{0.1}$  during normal spontaneous breathing after 4 weeks of IMT that increased MIP by 36%. However, the increase in strength accounted for just 21% of the variation in the decrease in  $P_{0.1}$ , so the interrelationship of changes in inspiratory motor drive and inspiratory muscle strength is clearly not straight forward, at least at rest. Collectively, these findings are consistent with LTI and provide evidence that inspiratory muscle strengthening has the potential to induce significant reductions in the perceptual ratings of respiratory effort. It is reasonable to presume that the decrease in respiratory effort may be due, at least in part, to the influence of inspiratory muscle strengthening upon inspiratory motor drive.

### 2.3 Respiratory Muscle Fatigue

Just as the influence of functional weakening of the inspiratory muscles on respiratory effort sensation can be predicted by the LTI paradigm, so too can the influence of muscle fatigue. Some studies have shown that the perception of added inspiratory loads is elevated during or after fatiguing inspiratory muscle work.<sup>[11,28]</sup> Gandevia et al.<sup>[11]</sup> observed a progressive increase in the sense of effort during each of ten maximal inspiratory efforts sustained to the limit of tolerance (~30–60 seconds), and the perceived magnitude of inspiratory threshold loads was increased after this procedure. Supinski et al.<sup>[28]</sup>

found a progressive increase in effort sensation during the application of a fatiguing inspiratory threshold load that lasted for 5 minutes. One interpretation of these findings was that central motor outflow was increased to the fatigued respiratory muscles in order to maintain a given mechanical output from these muscles (central hypothesis).<sup>[11,28]</sup> Another interpretation is based on electrophysiological data that reveal a decrease in proprioceptive discharge in parallel to enhanced metaboreceptor (Type III/IV afferent) activity when diaphragm fatigue occurs (peripheral hypothesis).<sup>[29,30]</sup> Both hypotheses are consistent with the development of an imbalance between motor outflow and the perceived mechanical response, i.e. inappropriateness.

In contrast to the findings of previous studies,<sup>[11,28]</sup> Bradley et al.<sup>[31]</sup> found that the sensation of inspiratory effort during 50 seconds of resistive loading was independent of the presence of fatiguing diaphragmatic motor patterns. These apparently conflicting findings can be reconciled if the fundamental differences in experimental design are considered. The studies that reported an effect of inspiratory muscle fatigue upon respiratory effort sensation<sup>[11,28]</sup> aimed to elicit global inspiratory muscle fatigue. In contrast, Bradley et al.<sup>[31]</sup> specifically targeted their loading regimen to the diaphragm. Animal studies have shown that the diaphragm is less well supplied with proprioceptors than the intercostal muscles, and possesses relatively fewer muscle spindles than tendon organs.<sup>[32]</sup> Thus, it is possible that fatigue of the inspiratory accessory muscles contributes independently to inspiratory effort sensation.

The importance of inspiratory accessory muscle function in the aetiology of effort sensation is supported by evidence that the increase in respiratory effort during fatiguing inspiratory resistive loading correlates better with the level of activation of muscles of the rib cage and neck than with the level of activation of the diaphragm.<sup>[33]</sup> Furthermore, loaded breathing tasks preferentially fatigue the inspiratory accessory muscles.<sup>[34]</sup> This latter finding is consistent with the notion that the force-generating capacity of the diaphragm exceeds that of the accessory

muscles.<sup>[35]</sup> Intercostal accessory muscles are recruited progressively during whole-body exercise.<sup>[36]</sup> Thus, it is possible that escalating respiratory effort sensation during whole-body exercise reflects, at least in part, progressive recruitment (and perhaps also fatigue) of the relatively weaker inspiratory accessory muscles. A recruitment strategy of this type might necessitate a greater motor outflow, since recruitment of weaker muscles to achieve a given intra-thoracic pressure change would require a higher level of motor outflow. In addition to inputs from fatiguing inspiratory muscles, expiratory muscle fatigue might contribute independently to increases in respiratory effort sensation. During expiratory threshold loading, increases in respiratory effort sensation have been related to post-loading decreases in maximum static expiratory mouth pressure.<sup>[37]</sup>

So far, we have reviewed the evidence that respiratory muscle fatigue influences respiratory effort during loaded breathing. More recent studies have examined the effect of respiratory muscle fatigue upon dyspnoea during whole body exercise. Experiments that have deliberately fatigued the respiratory muscles prior to exercise, using either inspiratory pressure threshold<sup>[38,39]</sup> or resistive loading,<sup>[40]</sup> have observed an increase in dyspnoea during subsequent incremental<sup>[39]</sup> or constant load exercise.<sup>[38,40]</sup> Mador and Acevedo<sup>[38,39]</sup> noted that the increase in dyspnoea was proportional to the increase in central drive ( $P_{0.1}$  or minute ventilation) such that the slope of the relationship between these variables was not altered under the fatigued condition. These authors concluded that the increase in dyspnoea was "explained by the increase in central respiratory drive, and no additional mechanisms need be invoked".<sup>[38,39]</sup> However, the influence of fatigue *per se* on exertional dyspnoea was difficult to assess in all of these studies because changes in the breathing pattern<sup>[38-40]</sup> and the recruitment pattern of respiratory muscles<sup>[40]</sup> were observed during exercise after loaded breathing.

In healthy humans, whole body exercise elicits significant diaphragmatic<sup>[41-43]</sup> and global inspiratory muscle fatigue.<sup>[4,44,45]</sup> Thus, it is reasonable to

suggest that at least some of the intensification of respiratory effort during exercise may be due to progressive fatigue of the inspiratory muscles, and the concomitant alteration in the balance of motor outflow and mechanical response. If this were the case, amelioration of exercise-induced inspiratory muscle fatigue would be expected to attenuate the concomitant escalation of respiratory effort sensation. There is evidence that specific IMT ameliorates exercise-induced inspiratory muscle fatigue, as assessed using volitional techniques.<sup>[4,45]</sup> Moreover, amelioration of inspiratory muscle fatigue with IMT is accompanied by a reduction in the severity of exertional dyspnoea,<sup>[2,4]</sup> providing a circumstantial link between the alleviation of inspiratory muscle fatigue and the reduction in effort sensations.

### 3. Effect of Respiratory Muscle Training Upon Respiratory Effort Sensation

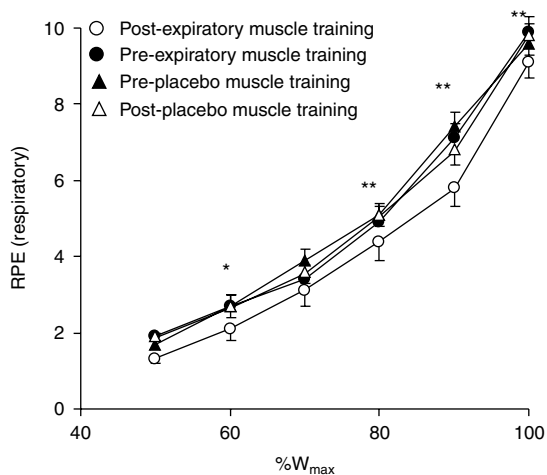
In the preceding sections we have eluded to evidence linking respiratory muscle strengthening with the reduction in respiratory effort sensation. We have also illustrated how the unifying LTI paradigm can be used to interpret the interrelationship of respiratory muscle function and effort sensation. The following section will provide some specific examples of studies in which specific RMT has improved both respiratory muscle function and respiratory effort sensation. Because the mechanical context in which the inspiratory muscles are operating has a bearing upon respiratory effort sensation, we have prefaced section 3.2 and section 3.3 with background information about the mechanical consequences of COPD and asthma, respectively.

#### 3.1 Healthy Human Volunteers

There is ample evidence that IMT with a pressure threshold load improves the maximum pressure-generating capacity of the inspiratory muscles (MIP) by 25%<sup>[46]</sup> to 45%.<sup>[4]</sup> These increases in MIP are accompanied by increases in the maximum velocity of inspiratory muscle shortening (peak inspiratory flow) of ~20%.<sup>[2,24]</sup> Within the LTI paradigm, increases in either MIP or flow-generating capacity reduce the severity of respiratory effort sensation by

decreasing motor outflow required for any given level of minute ventilation. Indeed, statistically significant reductions in respiratory effort during maximal incremental rowing<sup>[4]</sup> and cycling,<sup>[2]</sup> fixed intensity shuttle running (80% of maximal shuttle running speed),<sup>[1]</sup> and fixed intensity treadmill running to the limit of tolerance (85% of maximal oxygen uptake [ $\dot{V}O_{2max}$ ])<sup>[5]</sup> have been reported after IMT (see figure 4). Changes in inspiratory muscle strength after IMT accounted for 64%<sup>[1]</sup> and 42%<sup>[5]</sup> of the variance in respiratory effort sensation.

There is an indication that a reduction in respiratory effort sensation after IMT may require an improvement in inspiratory accessory muscle function. Suzuki et al.<sup>[47]</sup> found no significant difference in respiratory effort (Borg category ratio scale [CR-10]) during maximal incremental exercise following 4 weeks of pressure-threshold IMT. Similar magnitude increases in MIP (a measure of global inspiratory muscle strength) and maximum trans-diaphragmatic pressure led the authors to conclude that only the diaphragm had increased in strength. Thus, they speculated that respiratory effort sensation did not change because accessory muscle func-



**Fig. 4.** Ratings of perceived exertion (RPE) for respiratory effort during maximal incremental exercise for inspiratory muscle training and placebo groups pre- and post-intervention (mean  $\pm$  standard error). %W<sub>max</sub> = maximum power during cycle ergometry; \* indicates significant interaction effect ( $p \leq 0.05$ ); \*\* indicates significant interaction effect ( $p \leq 0.01$ ) [reproduced from Romer et al.,<sup>[2]</sup> <http://www.tandf.co.uk>, with permission].

tion may not have changed.<sup>[47]</sup> Increases in respiratory effort sensation during inspiratory resistive loading and exercise may be related to increases in the activity of inspiratory accessory muscles.<sup>[33,36]</sup>

The effect of expiratory muscle training upon dyspnoea remains uncertain. Suzuki et al.<sup>[3]</sup> noted a reduction in dyspnoea during maximal incremental exercise after 4 weeks of expiratory pressure-threshold training that increased maximum expiratory mouth pressure by 25%. However, minute ventilation also decreased and there was no difference in the relationship between dyspnoea intensity and minute ventilation pre- versus post-training.<sup>[3]</sup> These results suggest that expiratory muscle training does not modify respiratory effort sensations via an effect upon the interrelationship of motor outflow and the mechanical response to that outflow.

Support for the influence of acute changes in inspiratory muscle properties and/or 'prior experience' (section 1.2.3) upon respiratory effort has come from a study that used inspiratory loading immediately prior to heavy exercise.<sup>[48]</sup> Following a rowing-specific whole body warm-up protocol, plus acute loading of the inspiratory muscles ( $2 \times 30$  breaths at 40% of MIP), dyspnoea during 6 minutes of maximal rowing was reduced by 0.6 units of the Borg CR-10 when compared with the changes following a rowing-specific warm-up alone. The decrease in post-exercise inspiratory muscle strength (MIP) was more than halved for the combined protocol when compared with the rowing-specific warm-up alone (11.1% vs 4.2%, respectively). Exercise performance, defined as the mean power output during the 6-minute test, was improved by 1.2% after the combined warm-up compared with the changes after the rowing-specific warm-up alone. The change in dyspnoea accounted for 23% of the improvement in rowing performance.

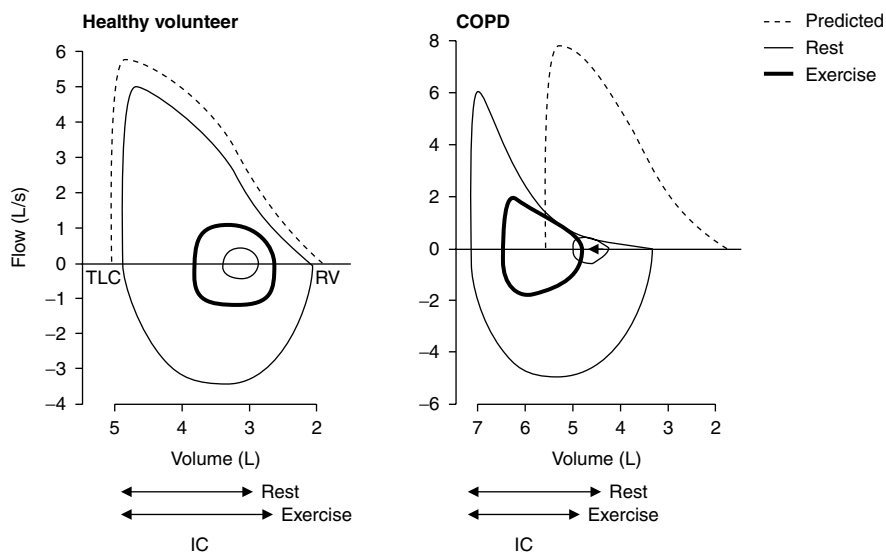
The finding of a reduction in exertional dyspnoea with acute loading is consistent with that of previous studies using Borg scales to rate respiratory effort.<sup>[17,49]</sup> The explanation for the decrease in dyspnoea might be either plasticity of load perception, through facilitatory after-discharge in the efferent pathway, or sensory adaptation (see section

1.2.3). An alternative explanation may reside in the small (albeit non-significant) increase in inspiratory muscle strength (+7% MIP) after acute loading.<sup>[48]</sup> An increase in the maximum force-generating capacity of a muscle would reduce the fractional utilisation of maximum tension generated with each breath, and therefore reduce the sense of respiratory effort.<sup>[25,26]</sup> Another possibility involves the phenomenon of postactivation potentiation, which is the transient increase in muscle contractile performance after previous contractile activity.<sup>[50]</sup> After a conditioning activity, the induced postactivation potentiation increases low- but not high-frequency tetanic force.<sup>[51]</sup> Because the hyperpnoea of exercise requires respiratory muscle motor units to discharge at relatively low rates, the force output of these motor units should be increased by acute loading. Assuming that respiratory muscle force during exercise is the same, motor unit firing rates would be expected to decrease (or be derecruited) in the presence of postactivation potentiation. A decrease in motor unit firing rate would require lower motor outflow, which would be perceived as decreased effort. Furthermore, postactivation potentiation may offset respiratory muscle fatigue by decreasing motor unit firing rate, which may delay impairment of central drive to motoneurons, neuromuscular transmission, muscle action potential propagation, and excitation-contraction coupling, all possible sites and mechanisms of fatigue.<sup>[50]</sup>

Based on the available evidence, it appears that strengthening the inspiratory muscles with chronic training, or modifying their activation and/or afferent feedback by acute loading, reduces respiratory effort sensation. These responses are consistent with the LTI paradigm.

### 3.2 Patients with Chronic Obstructive Pulmonary Disease

Within the LTI paradigm, there appears to be a strong theoretical rationale for IMT in patients with COPD. Alterations in inspiratory muscle function and respiratory mechanics disturb the normal interrelationship of motor outflow and the mechanical response to that outflow, creating inappropriateness.



**Fig. 5.** In a healthy volunteer and a typical patient with COPD, tidal flow-volume loops at rest and during exercise (peak exercise in COPD compared with exercise at a comparable metabolic load in the age-matched healthy volunteer) are shown in relation to their respective maximal flow-volume loops (reproduced from O'Donnell,<sup>[61]</sup> with permission). **COPD** = chronic obstructive pulmonary disease; **IC** = inspiratory capacity; **RV** = residual volume; **TLC** = total lung capacity.

The following section will consider these changes in detail.

Dyspnoea is the most common symptom in patients with COPD and is frequently the major reason for referral to pulmonary rehabilitation programmes.<sup>[52]</sup> Although the most obvious mechanical defect is obstruction during expiration, the most important mechanical and sensory consequences are upon inspiration. Incomplete lung emptying during airways obstruction results in dynamic lung hyperinflation. Although dynamic hyperinflation serves to maximise tidal expiratory flow, there is a requirement to breathe at higher ranges of the total lung capacity where the elastic load presented to the inspiratory muscles by the lungs and chest wall is higher (see figure 5).<sup>[53]</sup> In addition, dynamic hyperinflation reduces the functional strength of the inspiratory muscles through foreshortening of these inspiratory muscles, changes in the geometrical configuration of the diaphragm, attendant tachypnoea and increased velocity of shortening.<sup>[54,55]</sup> Dyspnoea intensity during exercise in patients with COPD correlates significantly with the extent of hyperinflation.<sup>[56,57]</sup> Further evidence that dynamic hyperin-

flation contributes importantly to exertional dyspnoea in patients with COPD stems from studies that have noted significant decreases in dyspnoea following the reduction of operational lung volumes, either pharmacologically<sup>[58]</sup> or surgically,<sup>[59]</sup> or by counterbalancing the negative effects of hyperinflation on the inspiratory muscles using continuous positive airway pressure.<sup>[60]</sup>

An additional mechanical response of dynamic hyperinflation is the maintenance of positive pressures in the airways at the end of expiration, so-called intrinsic positive end-expiratory pressure (PEEPi). Since in flow-limited patients, inspiration proceeds before tidal lung emptying is complete, the inspiratory muscles must first counterbalance the combined inward recoil of the lung and chest wall at end-expiration before inspiratory flow is initiated. This inspiratory threshold load, which continues throughout inspiration, may be present at rest and increases substantially with exercise. Furthermore, PEEPi may be involved in the causation of dyspnoea via the necessity for increased motor outflow throughout inspiration.<sup>[57,62]</sup> Patients with COPD also have a higher ventilatory demand during exercise

compared with healthy individuals because of high physiological dead space, early lactic acidosis, hypoxaemia, high metabolic demands, low arterial CO<sub>2</sub> set points, and other non-metabolic sources of ventilatory stimulation (e.g. anxiety).<sup>[63]</sup> Several studies have shown that dyspnoea intensity during exercise in patients with COPD correlates significantly with the change in ventilation expressed in absolute terms or as a fraction of the estimated maximum breathing capacity.<sup>[56,64,65]</sup> In the context of the LTI paradigm, these observations are consistent with the requirement for higher levels of motor outflow.

There is evidence that inspiratory muscle strength is lower in patients with COPD compared with healthy individuals.<sup>[66-69]</sup> Inspiratory muscle weakness would be expected to increase the intensity of dyspnoea for a given minute ventilation, since greater motor outflow is required for a given pressure generation by the muscles. However, the true prevalence of inspiratory muscle weakness in patients with COPD remains a topic for debate, and it has even been suggested that adaptations occur in these patients such that muscle strength is preserved.<sup>[55,70]</sup> Nonetheless, preservation of a normal force-generating capacity, in the face of an elevated demand for force, still suggests an increased likelihood of an overall functional deficit in patients with COPD.

Based on the factors described above, the scenario in patients with COPD is one of functional (and perhaps absolute) inspiratory muscle weakness, coupled with an increased requirement for inspiratory pressure generation. The management of exertional dyspnoea in patients with COPD is typically focused on reducing the primary contributors to this symptom,<sup>[8]</sup> namely dynamic lung hyperinflation and excessive ventilatory demand. However, specific training of the respiratory muscles may provide a useful adjunct in the overall management of dyspnoea in these patients.

The findings from a recent meta-analysis<sup>[71]</sup> lend support to the notion that IMT reduces exertional dyspnoea in patients with COPD. Lotters et al.<sup>[71]</sup> examined 15 studies, seven of which included mea-

asures of dyspnoea. Studies included in the analysis used randomised-controlled trials and set training loads  $\geq 30\%$  of MIP in the treatment group. The effect sizes for changes in dyspnoea during exercise and daily activities (assessed using Baseline and Transition Dyspnoea Indexes [BDI and TDI])<sup>[72]</sup> were statistically significant and the largest of any of the outcomes assessed. These findings add support to the earlier recommendations of the joint panel of the American College of Chest Physicians and the American Association of Cardiovascular and Pulmonary Rehabilitation (ACCP/AACVPR).<sup>[73]</sup> In their appraisal of RMT, the ACCP/AACVPR considered not only physiological responses to RMT (e.g. respiratory muscle strength and lung function), but also clinical outcomes such as dyspnoea and exercise capacity. They concluded that in studies where inspiratory muscle strength was increased with training, there was evidence to support a significant reduction in dyspnoea.<sup>[73]</sup> Of the eight randomised and controlled studies of RMT that were reviewed by the AACCP/AACVPR, three studies measured dyspnoea.<sup>[74-76]</sup> Two of these studies reported a significant increase in inspiratory muscle strength (MIP) and a reduction in the severity of dyspnoea, as measured using the BDI and TDI, in response to RMT.<sup>[74,75]</sup> As has been observed in healthy individuals (see section 3.1), both studies reported significant negative correlations between the changes in MIP and the changes in dyspnoea ratings after RMT.<sup>[74,75]</sup> In contrast, Larson et al.<sup>[76]</sup> observed no change in 'shortness of breath' as measured on a five-point scale. However, these authors failed to provide evidence that this scale was appropriate (valid, reliable and sensitive) for measuring dyspnoea and their results must be viewed in this light.<sup>[76]</sup>

More recent studies provide further evidence that an increase in inspiratory muscle strength with IMT ameliorates respiratory effort sensations in patients with COPD. In these studies, dyspnoea was quantified either during exercise,<sup>[77-79]</sup> in response to a loaded breathing task,<sup>[80,81]</sup> using the BDI/TDI,<sup>[79,82]</sup> or using the Chronic Respiratory Disease Questionnaire.<sup>[81]</sup> All of these studies reported significant

improvements in MIP and respiratory effort sensation post-IMT. Furthermore, in those studies where post-IMT changes in exercise tolerance were assessed, most found a significant improvement.<sup>[77,78,80-82]</sup> The influence of an increase in respiratory muscle endurance (with RMT) upon dyspnoea is unclear. If it is the magnitude of increased inspiratory muscle strength that most directly influences dyspnoea (by permitting a reduction in motor outflow), an increase in respiratory muscle endurance would only be expected to modify respiratory effort sensation if it acted to diminish respiratory muscle fatigue. Scherer et al.<sup>[83]</sup> reported improvements in both the severity of dyspnoea during daily activities (assessed using BDI/TDI) and exercise tolerance (6-minute walking distance) after a training regimen that was aimed primarily at improving respiratory muscle endurance. However, the differences in dyspnoea were not statistically significant when comparisons were made with a sham-training control group. The authors suggested that the lack of difference in the training-induced change in dyspnoea between the two groups resulted, in part, from training-induced increases in inspiratory muscle performance in the control group.<sup>[83]</sup>

Collectively, the literature tends to support the theoretical rationale for IMT in patients with COPD. There is evidence that dyspnoea is ameliorated following inspiratory muscle strength training. The statistically significant correlations between increases in MIP and reductions in respiratory effort sensations observed in some studies<sup>[74,75]</sup> lend support to a link between these two factors.

### 3.3 Patients with Asthma

The mechanical abnormalities in patients with asthma closely mimic those described in COPD except that there is less reduction in static lung recoil pressure and more widespread intrathoracic airway narrowing in asthma.<sup>[84]</sup> In addition, the increased airway collapsibility in patients with COPD is not seen in patients with asthma.<sup>[84]</sup> Furthermore, the reversible nature of airways obstruction in asthma results in relatively short-lived periods of stress upon the inspiratory muscles, which undoubtedly in-

fluences their capacity to adapt, as they appear to in patients with COPD.<sup>[55,70]</sup>

As is the case in COPD, the major mechanical consequences of airway narrowing are increased flow resistive work, increased elastic work resulting from dynamic lung hyperinflation, and reduced dynamic lung compliance.<sup>[62,85]</sup> Dynamic hyperinflation contributes importantly to the dyspnoea experienced during acute bronchoconstriction in patients with asthma.<sup>[86]</sup> Loughheed et al.<sup>[86]</sup> found that during methacholine-induced bronchoconstriction, patients with mild, stable asthma reported increased inspiratory effort and described symptoms of 'inspiratory difficulty' and 'unrewarded inspiratory effort'. In a multiple regression analysis, the change in inspiratory capacity (an estimate of dynamic hyperinflation) was the most powerful predictor of dyspnoea during bronchoconstriction, accounting for 74% of the variance in perceptual ratings. A unique feature of hyperinflation in asthma is the persistence of inspiratory muscle activity during expiration,<sup>[85,87-89]</sup> which may compromise inspiratory muscle blood flow and exacerbate fatigue of these muscles.<sup>[90]</sup> As discussed in section 2.3, the uncoupling of motor outflow and inspiratory muscle tension with fatigue might increase the severity of respiratory effort.

Since bronchoconstriction is associated with hyperinflation,<sup>[85]</sup> it is reasonable to infer that functional weakness of the inspiratory muscles is present in asthma. Thus, it is likely that the intensity of dyspnoea is increased in patients with asthma via a mechanism linked to the greater motor outflow required for a given pressure generation by the inspiratory muscles.<sup>[62,91]</sup> In addition, there may be an independent contribution from the recruitment of inspiratory accessory muscles (see section 3.1),<sup>[33]</sup> which is greater than that of the diaphragm during histamine-induced bronchoconstriction.<sup>[92]</sup> As discussed in section 3.1, inspiratory accessory muscle recruitment may be important in the development of dyspnoea.<sup>[33]</sup>

As is the case in COPD, there is no clear consensus regarding the influence of asthma on absolute inspiratory muscle strength. Some studies have reported that the inspiratory muscles are weaker in

patients with asthma compared with healthy individuals,<sup>[93-95]</sup> whilst others have observed no strength deficit.<sup>[96-98]</sup> When it is present, inspiratory muscle weakness appears to be related to the mechanical consequences of lung hyperinflation.<sup>[95,98-100]</sup> However, there is some evidence of an inability to achieve full neural activation of the diaphragm during voluntary efforts,<sup>[94]</sup> which may be due to impaired reflex excitation of inspiratory motoneurons.<sup>[101]</sup> In some patients, moderate doses of corticosteroids may induce myopathy resulting in further absolute inspiratory muscle weakness.<sup>[99,100]</sup> Thus, a functional deficit in inspiratory muscle function is likely to exist in patients with asthma, particularly during episodes of bronchoconstriction, when hyperinflation is present.<sup>[85]</sup>

The interrelationship of inspiratory muscle strength and intensity of dyspnoea during bronchoconstriction and exercise has been examined. Patients with asthma reporting high levels of dyspnoea during methacholine-induced bronchoconstriction also report high ratings of dyspnoea during exercise.<sup>[102]</sup> Although the highest ratings of dyspnoea during exercise were made by patients with the weakest inspiratory muscles, this relationship did not exist for dyspnoea during methacholine-induced bronchoconstriction. The authors suggested that the discrepancy was due to the modest level of bronchoconstriction that was induced in their study,<sup>[102]</sup> rather than to a difference in the contribution of inspiratory muscle strength to the intensity of dyspnoea during bronchoconstriction. These findings hint at a negative relationship between inspiratory muscle strength (and hence the required level of motor outflow) and the intensity of dyspnoea during both bronchoconstriction and exercise.

There is some direct evidence that elevated levels of inspiratory motor outflow contribute importantly to dyspnoea during bronchoconstriction.<sup>[62,103,104]</sup> Bellofiore et al.<sup>[103]</sup> found that the strongest determinant of dyspnoea during methacholine-induced bronchoconstriction was inspiratory motor drive ( $P_{0.1}$ ), which explained 82% of the total variance. Most recently, Binks et al.<sup>[104]</sup> reported that institution of mechanical ventilation during methacholine-

induced bronchoconstriction and hyperinflation significantly reduced ratings of 'effort to breathe' in patients with mild asthma. It is likely that the decrease in mechanical load (and motor outflow) associated with respiratory muscle unloading was responsible for the reduced perceptual ratings. The specific contribution of PEEPi to the genesis of dyspnoea in patients with asthma has been examined by comparing the effects of two modes of mechanical ventilation (continuous and inspiratory positive airway pressure) upon dyspnoea during induced hyperinflation.<sup>[62]</sup> Although both modes of ventilation reduced the work of breathing to a similar extent, inspiratory positive airway pressure did not negate PEEPi and did not relieve dyspnoea to the same extent as continuous positive airway pressure. These data are consistent with similar observations in patients with COPD<sup>[60]</sup> and suggest that the inspiratory threshold load is an important independent contributor to dyspnoea in patients with both conditions.

Based on the aforementioned considerations, there appears to be a theoretical rationale for IMT in patients with asthma. Thus, strengthening the inspiratory muscles may reduce the level of motor outflow required to generate a given inspiratory muscle tension and thereby reduce the severity of dyspnoea. Although there is not an extensive literature on the influence of RMT upon dyspnoea in patients with asthma, recent studies have reported the interrelationship of dyspnoea and inspiratory muscle strength, as well as  $\beta_2$ -agonist consumption in patients with asthma.<sup>[105,106]</sup> Weiner et al.<sup>[105]</sup> showed that patients with mild bronchoconstriction (forced expiratory volume in 1 second [FEV<sub>1</sub>] >80% of predicted) and a high  $\beta_2$ -agonist consumption (2.7 puffs/day) have a significantly higher perception of dyspnoea during pressure-threshold loading compared with patients with mild bronchoconstriction and normal consumption ( $\leq 1$  puff/day). Furthermore, dyspnoea and  $\beta_2$ -agonist consumption in patients with high  $\beta_2$ -agonist consumption were decreased significantly after pressure-threshold IMT compared with a sham-training placebo group.<sup>[105]</sup>

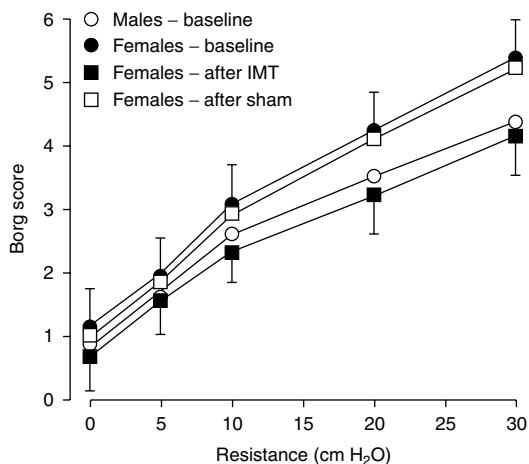
A notable feature of airway obstruction in asthma is the large inter-individual variation in the intensity of dyspnoea for a given fall in FEV<sub>1</sub>.<sup>[106]</sup> Weiner et al.<sup>[106]</sup> compared the inspiratory muscle strength, perception of dyspnoea to threshold loads, and bronchodilator consumption of 22 male and 22 female asthmatic patients with mild-to-moderate bronchoconstriction (FEV<sub>1</sub> >60% of predicted). For the same FEV<sub>1</sub> (% of predicted), the women had significantly weaker inspiratory muscles, whilst dyspnoea and  $\beta_2$ -agonist consumption were higher than in the men. The women were divided into two groups: half received pressure-threshold IMT, the remainder received sham-training. After 20 weeks of IMT that equalised their inspiratory muscle strength with that of the men (+42% MIP from pre-IMT), dyspnoea and  $\beta_2$ -agonist consumption of the women in the IMT group decreased compared with the placebo group and were no longer different compared with the men (see figure 6). These findings support a role for the absolute strength of the inspiratory muscles in determining dyspnoea.

Evidence from the limited number of IMT studies in patients with asthma appears to support the theoretical rationale for IMT in reducing dyspnoea. Although a decrease in the perception of dyspnoea with IMT could be beneficial in symptom relief, it

could be detrimental to patients who must use symptoms to manage their disease. However, available evidence suggests that patients do not become desensitised to bronchoconstriction following IMT. Weiner et al.<sup>[105]</sup> noted that IMT did not result in "exaggerated ablation of dyspnoea", and concluded that IMT was safe, at least for use in patients with mild asthma.

#### 4. Conclusions

Dyspnoea is a complex, multifaceted symptom, but one whose mechanistic underpinnings appear to be best encapsulated in Cambell's LTI paradigm. Based on this paradigm, an increase in the severity of dyspnoea during intense exercise in healthy volunteers is the result of uncoupling between motor outflow and respiratory muscle tension due to factors such as functional weakening and fatigue, and perhaps also the recruitment pattern of respiratory muscles. Similarly, intensification of dyspnoea in obstructive pulmonary disease can be explained mechanistically by alterations in respiratory mechanics, and the corresponding 'inappropriateness' of the respiratory motor outflow. Acute and chronic improvements in the contractile properties of the respiratory muscles lead to reductions in the severity of exertional dyspnoea in healthy, young adults, most likely by reducing the level of motor outflow. The mechanical and perceptual consequences of obstructive pulmonary disease provide a strong theoretical rationale for inspiratory muscle strengthening in patients with COPD and asthma. The available evidence supports the positive influence of RMT on dyspnoea in patients with COPD, although further research is required to determine the effects of RMT in patients with asthma. It is likely that many of the principles described here for patients with obstructive pulmonary disease also apply to other clinical populations (e.g. patients with cardiorespiratory and neuromuscular disorders). However, further research is required to understand the ventilatory limitations in these other medical conditions, and to determine the effects of specific RMT upon dyspnoea, exercise tolerance and overall quality of life.



**Fig. 6.** Baseline mean  $\pm$  standard error perception of dyspnoea during breathing against load in the female and male groups, and following inspiratory muscle training (IMT) in the female group (reproduced from Weiner et al.,<sup>[106]</sup> with permission).

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