Mechanisms, measurement and management of exertional dyspnoea in asthma

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ABSTRACT Asthma is a heterogeneous condition, with dyspnoea during exercise affecting individuals to a variable degree. This narrative review explores the mechanisms and measurement of exertional dyspnoea in asthma and summarises the available evidence for the efficacy of various interventions on exertional dyspnoea. Studies on the mechanisms of dyspnoea in asthma have largely utilised direct bronchoprovocation challenges, rather than exercise, which may invoke different physiological mechanisms. Thus, the description of dyspnoea during methacholine challenge can differ from what is experienced during daily activities, including exercise. Dyspnoea perception during exercise is influenced by many interacting variables, such as asthma severity and phenotype, bronchoconstriction, dynamic hyperinflation, respiratory drive and psychological factors. In addition to the intensity of dyspnoea, the qualitative description of dyspnoea may give important clues as to the underlying mechanism and may be an important endpoint for future interventional studies. There is currently little evidence demonstrating whether pharmacological or non-pharmacological interventions specifically improve exertional dyspnoea, which is an important area for future research.

Previous articles in this series: No. 1: Dubé B-P, Agostoni P, Laveneziana P. Exertional dyspnoea in chronic heart failure: the role of the lung and respiratory mechanical factors. *Eur Respir Rev* 2016; 25: 317–332. **No. 2:** O'Donnell DE, Elbehairy AF, Faisal A, *et al.* Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing. *Eur Respir Rev* 2016; 25: 333–347. **No. 3:** Bernhardt V, Babb TG. Exertional dyspnoea in obesity. *Eur Respir Rev* 2016; 25: 487–495. **No. 4:** Bonini M, Fiorenzano G. Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing. *Eur Respir Rev* 2017; 26: 160099.

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Introduction

Dyspnoea is a complex symptom experienced by many patients with chronic lung diseases and may occur at rest or with exertion. It is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. The sensation of breathing discomfort results from incompletely understood interactions between physiological, psychological, social and environmental factors [1, 2]. The mechanisms of dyspnoea in asthma have been extensively researched and reviewed [3–7].

Dyspnoea is a common symptom in asthma and can be captured under various other symptoms, including chest tightness, or can be interpreted and expressed as activity limitation. Symptoms are used to assess asthma control, and resting lung function is used to assess risk for future exacerbations [8]; however, the relationship between dyspnoea and objective measures of resting lung function in asthma is poor [9, 10]. Asthma is a heterogeneous condition with many different and overlapping clinical phenotypes and endotypes, including eosinophilic *versus* non-eosinophilic, allergic *versus* non-allergic and high *versus* poor symptom perceivers [11–14]. Many patients with severe or near fatal asthma, for example, have poor perception of dyspnoea symptoms [15–17].

Exertional dyspnoea may contribute to activity limitation and impaired quality of life, but it is a highly variable symptom in asthma [18]. For example, many individuals, particularly those with poor dyspnoea perception, are more limited by leg fatigue than dyspnoea during exercise [19], whereas others may have no limitations whatsoever, even during strenuous exercise. The exact mechanisms of exertional dyspnoea have been poorly explored compared with dyspnoea experienced during direct bronchoprovocation or under resistive loads. While exercise itself is an indirect bronchoprovocation challenge (as are eucapnic voluntary hyperventilation or mannitol), the intensity and quality of dyspnoea experienced during direct bronchoprovocation (*i.e.* with methacholine) may not reflect the experience of dyspnoea during exercise or activities in daily life. Recent evidence suggests that exertional dyspnoea in asthma is qualitatively different from that during methacholine testing [20] and results from bronchoconstriction, mechanical limitations due to dynamic lung hyperinflation [21], ventilatory effort [20] and psychological factors [22]. Importantly, resting measures of lung function, such as forced expiratory volume in 1 s (FEV_1), and results of direct bronchoprovocation testing do not predict exertional symptoms or physiological adaptations during exercise in asthma.

Understanding the various contributing factors and the impact of exertional dyspnoea for an individual with asthma can be difficult given the variable and heterogeneous nature of asthma. In many clinical studies, multidimensional symptom scores are used to measure asthma symptoms and their burden or impact, but exertional dyspnoea is not universally addressed within these scores. There are relatively few studies specifically addressing exertional dyspnoea in asthma, and those available are limited by high inter-individual variability in dyspnoea perception, heterogeneity in patient severity, the type of exercise used, and inconsistent assessment of dyspnoea intensity and quality. The objectives of this review are to 1) describe the pathophysiological mechanisms contributing to exertional dyspnoea in asthma, 2) explore the description and quantification of exertional dyspnoea in asthma, and 3) describe the effect of interventions on exertional dyspnoea in asthma.

Mechanisms of exertional dyspnoea in asthma

The mechanisms of exercise limitation and exertional dyspnoea are complex and are incompletely understood. In general, dyspnoea emerges from two interrelated neurophysiological mechanisms, a sensory component that identifies afferent respiratory information and an affective component, which identifies this information as disturbing or unpleasant [23, 24]. Many factors contribute to exercise limitation in asthma, including bronchoconstriction, dynamic hyperinflation (DH), respiratory muscle strength, psychological factors and others.

Bronchoconstriction and small airways disease

The importance of bronchoconstriction in exertional dyspnoea is complex, as most individuals with asthma do not develop a decrease in FEV_1 during short exercise sessions, and those with exercise-induced bronchoconstriction (EIB) usually develop a reduction in FEV_1 post-exercise [25, 26]. Importantly, EIB can occur without symptoms, whereas EIB in association with asthma symptoms is considered as exercise-induced asthma (EIA) [27]. Some individuals with EIA do develop a reduction in FEV_1 during exercise [28]. The type and duration of exercise may be important in EIA, as SUMAN *et al.* [29] demonstrated that, while FEV_1 and peak expiratory flow did not decrease during a 6-min progressive treadmill exercise test, there were 20% and 26% decreases in peak expiratory flow and FEV_1, respectively, during a 20-min test.

Many studies have examined the relationship between dyspnoea and the degree of decline in FEV_1 after methacholine. While methacholine accurately mimics the physiological derangements and quality of dyspnoea experienced during acute asthma exacerbations [30], it may not mimic the sensations experienced during exercise. Bronchoconstriction induced prior to exercise may modulate dyspnoea intensity, however. In a study of 15 asthmatic patients of varying severity by MAHLER *et al.* [31], either methacholine or a bronchodilator was given prior to cardiopulmonary exercise testing (CPET). When given prior to exercise, methacholine resulted in a 36% decline in pre-exercise FEV_1, a 20% decline in post-exercise FEV_1, a slight decrease in peak exercise work rate, and higher dyspnoea intensity compared to a baseline CPET or when a bronchodilator was given prior to CPET [31].

Small airway disease probably contributes to exertional dyspnoea. Although no gold standard exists, dysfunction of the small airways can be assessed by various techniques, including impulse oscillometry or with the forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25–75\%}$). Small airway disease is associated with more severe EIB [32] and more severe bronchial hyperresponsiveness to methacholine [33] but it is inconsistently associated with exertional breathlessness [33–35].

Mechanical factors: dynamic hyperinflation

DH is a recognised consequence of spontaneous and induced bronchoconstriction, but controversy exists regarding the mechanism. Although there is some evidence that DH is an "active" phenomenon due to persistent inspiratory muscle activity throughout expiration (often termed inspiratory muscle "braking") [36, 37], it is likely that DH is largely a passive consequence of expiratory flow limitation [30, 38, 39]. The differences between static hyperinflation and DH at rest, or DH provoked during exercise, are important, because the sensory consequences are different: DH is related to the degree of exertional dyspnoea whereas static hyperinflation is not [40]. DH occurs when end-expiratory lung volume progressively increases during bronchoconstriction or exercise, forcing tidal volume (V_T) to the non-compliant portion of the respiratory system pressure–volume relationship. End-expiratory lung volume necessarily increases when there is a discrepancy between the volume to exhale, the time needed to completely exhale and the time between inspirations (the respiratory frequency) [40]. DH results in excessive elastic loading of the inspiratory muscles, which must overcome both an inspiratory threshold from positive end-expiratory pressure and work against the inward recoil of the lung and chest wall [38, 41]. During exercise, DH is indicated by a decrease in the inspiratory capacity (IC), which reflects an increase in end-expiratory lung volume as long as total lung capacity (TLC) remains constant and there is no respiratory muscle weakness. The mechanical consequence of DH is that further increases in V_T are constrained by reduced dynamic compliance and increased elastic load, leading to increasing dyspnoea intensity (figure 1) [38, 39, 42]. The neuromechanical uncoupling that ensues probably explains the quality and intensity of dyspnoea experienced during DH. As thoracic volume approaches the TLC, the inspiratory muscles become functionally weak due to disadvantageous length–tension relationships, yet the muscles must still work against higher inspiratory and elastic loads. Inspiratory effort and respiratory drive must therefore be substantially higher to produce a given change in V_T, which is perceived as unsatisfied inspiration and dyspnoea [6, 30, 38].

In asthma, DH occurs during bronchoconstriction provoked by methacholine, but DH only occurs in 36–65% of subjects during exercise and, therefore, is not the dominant mechanism of exertional dyspnoea in many individuals [20, 21, 43]. Those individuals with asthma who develop EIB more frequently develop DH during exercise than asthmatics without EIB [44]. Expiratory flow limitation during normal resting tidal breathing and a reduced resting IC are associated with exercise limitation and DH in chronic obstructive pulmonary disease (COPD) [45, 46], but this finding is infrequently present in asthmatics at rest [43, 46, 47]. However, in one study, the 15% of asthmatic individuals who had more pronounced airflow obstruction at rest (FEV_1 <80% predicted) developed expiratory flow limitation and DH early during exercise, and these individuals reported greater exertional dyspnoea than those not developing expiratory flow limitation and DH during exercise (figure 2) [43]. Therefore, when a reduction in IC does occur during exercise, it is an important determinant of maximal exercise capacity in both COPD and asthma [43, 45, 48]. Furthermore, changes in IC better explain dyspnoea than changes in FEV_1 in most [39, 42], but not all, studies [49].

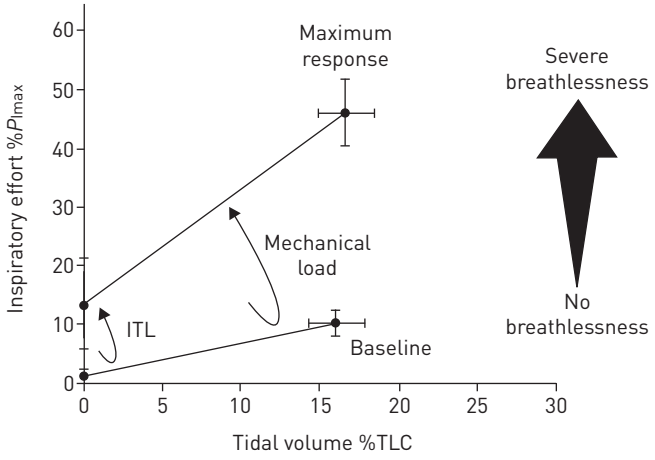

FIGURE 1 Neuromechanical dissociation in asthma. For a given breath in the absence of expiratory airflow limitation (baseline), there is a harmonious relationship between inspiratory effort (oesophageal pressure/maximal inspiratory pressure (P_{Imax})) and instantaneous change in volume (neuromechanical coupling). During bronchoconstriction (maximum response), intrinsic mechanical loading and functional muscle weakness disrupt this relationship (neuromechanical dissociation), and greater levels of inspiratory difficulty or breathlessness are experienced. ITL: inspiratory threshold load; TLC: total lung capacity. Reproduced and modified from [38] with permission.

Respiratory muscle function

There are conflicting data on the importance of respiratory muscle strength in relation to dyspnoea in asthma. Some authors have found reduced inspiratory muscle strength in asthmatic individuals [50], while others have found that respiratory muscle strength was similar to controls [42, 51]. Two studies have found no effect of corticosteroids on respiratory muscle strength [51, 52]; however, the study by Perez *et al.* [51] found that respiratory muscle endurance was reduced only in steroid-dependent asthma, and this best correlated with the degree of hyperinflation (as measured by functional residual capacity/TLC). In contrast, in another group of steroid-dependent asthmatics, Picado *et al.* [53] found that muscular endurance was not related to steroid treatment. A study by Weiner *et al.* [54] suggested that respiratory muscle weakness and reduced efficiency were correlated with hyperinflation, and improvements in muscle function following administration of a bronchodilator were related to the reduction in hyperinflation, not the improvement in FEV1. This suggests that respiratory muscle dysfunction in asthma is a consequence of altered muscle length–tension relationships from hyperinflation and not a primary problem. Respiratory muscle strength correlates poorly with exercise capacity whether measured by peak oxygen consumption ($V'O_2$) or peak work rate during CPET [55]. Furthermore, the relationship between respiratory muscle strength and exertional dyspnoea is not clear, with no significant correlation found in several studies [55, 56].

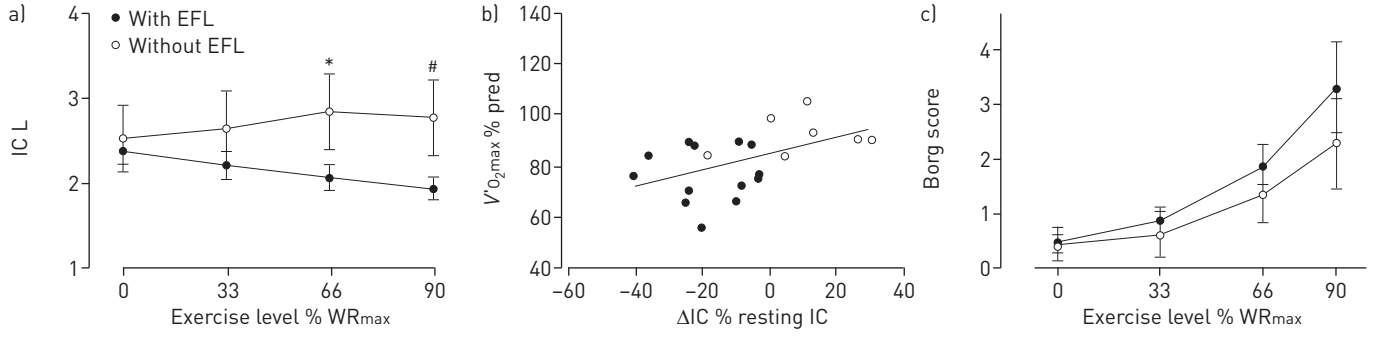

FIGURE 2 a) Inspiratory capacity (IC) in asthmatics with (n=13) and without (n=7) expiratory flow limitation (EFL) at various levels of exercise, expressed as a percentage of maximal work rate (WR_{max}). Patients with EFL developed a progressive decline in IC with increasing work rate. Data are presented as mean±SD. *: p=0.05; #: p=0.03. b) Relationship between maximal oxygen uptake ($V'O_{2max}$) and change in IC (ΔIC) from rest to 90% of WR_{max}. Each data-point represents a single patient. The regression equation is y=84+0.3x±11 (SE), r=0.48, p=0.03. c) Asthmatic patients with EFL during exercise tended to have a higher Borg dyspnoea score throughout exercise compared to non-EFL asthmatics. EFL patients started to experience higher dyspnoea at 66% WR_{max}, while those without EFL experienced higher dyspnoea scores at 90% WR_{max}. Data are presented as mean±SD. Reproduced and modified from [43] with permission.

Emotional and affective factors

Mood and psychological factors undoubtedly influence the reporting and perception of dyspnoea [57] and activity limitation [18]. Negative emotions affect the perceived unpleasantness of dyspnoea [58]. Anxiety and depression are common in asthma and can increase the perception of dyspnoea [58]; however, data are conflicting as to the exact relationship between dyspnoea and anxiety. Unpleasant emotional stimuli increase airway resistance and perceived dyspnoea at rest in asthma, which is probably mediated by cholinergic pathways [59, 60]. A study of 715 subjects by Janson *et al.* [57] reported correlations between depression/anxiety and asthma-related symptoms, such as breathlessness at rest and during activity. However, they did not find any correlation between anxiety or depression and a self-reported asthma diagnosis, or any objective measures of bronchial hyperresponsiveness such as FEV_1, peak expiratory flow variability or blood eosinophils. Existing data support the importance of emotional states, particularly anxiety, on dyspnoea at rest and during direct bronchoprovocation challenge [61, 62]. However, no studies have examined the effect of emotional and affective factors on exertional dyspnoea during exercise. In a study of moderate-to-severe Brazilian asthma subjects by Mendes *et al.* [63], lower aerobic capacity during CPET was associated with reduced health-related quality of life and depressive symptoms independent of body mass index, age and FEV_1; however, they did not report any data with regard to dyspnoea during or after exercise.

Comorbidities, differential diagnoses and other modifying factors

Several other characteristics, including obesity, concurrent laryngeal dysfunction or hyperventilation disorders, may influence dyspnoea on exertion. There can also be explanations for dyspnoea unrelated to asthma or EIB, which may be uncovered by using CPET. For example, in a retrospective analysis of 39 patients with difficult asthma complaining of exertional dyspnoea, 14 patients had a hyperventilation disorder, two had deconditioning, one had cardiac ischaemia and nine individuals had two simultaneous explanatory features diagnosed by CPET [64]. Nasal obstruction and other chronic nasal symptoms, which are common in asthma, have been reported to be associated with dyspnoea in COPD [65]. However, whether nasal disease contributes to dyspnoea in asthma has not been investigated.

Obese individuals are frequently misdiagnosed as having asthma, possibly due to their increased prevalence of respiratory symptoms compared to non-obese individuals, which could be related to deconditioning or an altered perception of dyspnoea. In a recent study, the main difference between obese individuals misdiagnosed with asthma and obese individuals with asthma was that misdiagnosed individuals had higher perceptions of dyspnoea during methacholine challenge or exercise testing, despite the absence of airflow obstruction or bronchial hyperreactivity and higher peak V'_{O_2} in comparison to obese asthmatics [66]. Is dyspnoea perception different in obese compared with non-obese asthmatics? Cortés-Télles *et al.* [67] found that there were no differences between well-controlled obese asthmatic subjects and normal-weight asthmatics in terms of ventilatory responses to exercise or exercise-related dyspnoea scores for a given work rate, but they did find significantly higher leg fatigue in the obese patients.

An important mimic of EIB is exercise-induced laryngeal obstruction (EILO), which usually results from supraglottic narrowing during exercise and may contribute to exertional dyspnoea. EILO can mimic asthma symptoms in individuals without asthma and is concurrently present in 4.8–14% of individuals with asthma, particularly in females [68, 69]. Importantly, the description of dyspnoea (difficulty on inspiration), methacholine challenge and inspiratory obstruction on flow–volume loops do not accurately identify those with EILO from those without EILO, and this condition is ideally diagnosed with laryngoscopy during exercise [69].

Dysfunctional breathing, particularly hyperventilation, is present in 17–29% of individuals with asthma and is associated with psychiatric comorbidity (anxiety and panic disorder), poor asthma control and frequent exacerbations [70, 71]. An excessively high respiratory rate due to dysfunctional breathing patterns can exacerbate DH during exercise or induce bronchoconstriction (similar to a eucapnic voluntary hyperventilation challenge) [72]. Furthermore, the frequent association of dysfunctional breathing with anxiety disorders could influence the perception of dyspnoea for a given degree of effort. The prevalence of a hyperventilation syndrome in uncontrolled asthma is probably underestimated. This diagnosis should be considered in patients who have disproportionate respiratory symptoms or an inappropriate level of ventilation during exercise without any other organic cause. It is important to consider the diagnosis of hyperventilation syndrome, as it may interfere with obtaining control of asthma symptoms.

Measurement of dyspnoea quality and intensity

Tools for measuring dyspnoea in asthma

In asthma, the language used to describe dyspnoea can vary, with different descriptive terms chosen during acute exacerbations compared to during methacholine challenge or exercise [20, 73, 74]. Bronchoconstriction and increased mechanical loading due hyperinflation, whether during acute

bronchoconstriction or exercise, are associated with different descriptions of dyspnoea [20, 30, 74]. Furthermore, because the severity of bronchoconstriction affects the quality of dyspnoea [20, 39], qualitative descriptors may be as relevant as the magnitude or intensity of dyspnoea [73].

Common descriptors of dyspnoea reported in clinical studies are shown in table 1 [20, 30, 73–75]. Across a variety of clinical and experimental settings, three dominant descriptive symptom clusters emerge: 1) chest tightness and/or constriction, 2) increased work and/or effort to breathe, and 3) unsatisfactory inspiration or "inability to take a deep breath in" [20, 30, 39, 75–77]. The intensity of dyspnoea is most often assessed according to a symptom scale, with the modified Borg scale [78], which measures dyspnoea on a scale of 0–10 arbitrary units, being used most frequently. The Borg scale is useful to assess exertional dyspnoea intensity in asthmatic individuals during exercise, is reproducible and responsive to treatment changes, and relates to physiological parameters such as 1) peak inspiratory flow rate, 2) V_T to forced vital capacity ratio, 3) respiratory frequency, and 4) peak inspiratory mouth pressure [31]. The Visual Analogue Scale (VAS) is also a reliable, reproducible measurement of dyspnoea intensity during exercise that correlates with Borg scale measurements of dyspnoea and with minute ventilation (V'_E) [79]. Other methods of measuring dyspnoea, such as the Baseline Dyspnea Index, the Medical Research Council dyspnoea scale and St George's Respiratory Questionnaire, have been used in asthma studies, although less frequently than Borg and VAS [80, 81].

In clinical practice and clinical trials, composite scores are frequently used to assess asthma symptoms, control and quality of life. Among the most frequently used scores are the Asthma Control Questionnaire (ACQ), the Asthma Control Test (ACT) and the Asthma Quality of Life Questionnaire (AQLQ) [82–85]. All of these questionnaires contain questions on patient-reported dyspnoea frequency and activity limitation, but do not explicitly distinguish between dyspnoea at rest, after exposures to irritants/triggers or during exercise/activity. Recently, two questionnaires have been developed to measure the emotional and affective component of dyspnoea in respiratory diseases: the Dyspnea-12 [86] and the Multidimensional Dyspnea Profile [87, 88]. These tools have been validated in asthma patients, but only the Dyspnea-12 assessed the correlation of components with objective exercise capacity (6-min walking distance). These brief questionnaires, which include some of the descriptors of dyspnoea found in table 1 and their emotional consequences, could be useful in future studies to assess the physiological and mechanistic correlates of the emotional and affective components of exertional dyspnoea.

Measuring dyspnoea perception during bronchoconstriction

Although our understanding of the relationship between dyspnoea labelling and mechanism is incomplete, current evidence suggests that a description of chest tightness is more closely linked to mild bronchoconstriction [30], and a sensation of increased work/effort is more closely linked to more severe bronchoconstriction or DH [21, 30, 38, 39]. Dyspnoea intensity varies widely between patients at a given degree of physiological impairment, and the correlations between changes in Borg score and changes in FEV_1 or IC vary widely across studies. In patients being treated with albuterol in an emergency department for acute asthma exacerbations, the "chest tightness" label predominated before treatment, which rapidly improved after albuterol, while the perceived ability to "breathe more" also improved with treatment [75]. The sensation of increased "work and effort" to breathe was less common than chest tightness, however, and did not change significantly with treatment. Dyspnoea intensity varied greatly between patients at any given degree of FEV_1 reduction and, although Borg scores decreased with

TABLE 1 List of dyspnoea descriptors commonly used in clinical studies

Symptom cluster	Descriptor
Chest tightness	My chest is constricted
	My chest feels tight
Unsatisfactory inspiration	I cannot get enough air
	My breathing does not go all the way in
	I cannot take a deep breath in
Increased work or effort	My breathing requires more work
	My breathing requires more effort
	My breathing is heavy
	I feel that I am breathing more

Adapted from [20, 21, 67, 75].

treatment, changes in dyspnoea were only weakly correlated with changes in FEV_1 in the acute exacerbation setting [75].

Similarly, in most studies using methacholine to provoke bronchoconstriction, descriptors of chest tightness predominate over symptoms of work/effort, "air hunger" or unsatisfactory inspiration [20, 76]. This finding is not consistent in the literature, however. In one study by Lougheed *et al.* [39], in which methacholine provoked a large degree of decline in FEV_1 (>50% baseline), "difficulty taking a deep breath" and increased "work/effort" descriptions were more common than "chest tightness", suggesting that the severity of bronchoconstriction and attendant dynamic mechanical responses influence the character of dyspnoea. The intensity of dyspnoea after methacholine was highly correlated with the degree of DH (r=0.74), and a change in IC back to baseline was the most important correlate of improved breathlessness during recovery [39]. In another study by Killian *et al.* [76], in which only 13.7% of patients experienced a >30% reduction in FEV_1 with methacholine, chest tightness was the most prevalent and most intense dyspnoea descriptor. The differences in the quality of dyspnoea between these studies are related to the degree of bronchoconstriction provoked: chest tightness is more prominent during mild bronchoconstriction [20, 30, 76], with work/effort descriptors becoming dominant with more severe bronchoconstriction as it results in lung hyperinflation, which augments the mechanical load on the respiratory muscles [39, 73].

As in the acute exacerbation setting, dyspnoea intensity during methacholine challenge varies widely between patients, with poor symptom perceivers and normal or high symptom perceivers. Inter-individual variability in dyspnoea intensity for a given change in FEV_1 is largely attributable to the degree of DH, as measured by change in IC [38, 39]. In a study that used both methacholine challenge and exercise testing, Borg scores varied from 0 to 9 (10 being maximal) following a 20% drop in FEV_1 from methacholine, and dyspnoea intensity correlated weakly with FEV_1 during bronchoconstriction (r=0.31) [9]. The group of patients who reported high symptom intensity after a methacholine-induced decline in FEV_1 of 20% also reported higher Borg scores during exercise testing, whereas the low symptom perceivers from methacholine reported Borg scores during exercise that were similar to the normal expected range [9]. In that study, however, there were no data on qualitative dyspnoea descriptors, so it was uncertain whether dyspnoea quality differed between patients who perceive low, moderate or high symptom intensity. Coli *et al.* [77] addressed this question by assessing changes in IC, FEV_1 and Borg score, as well as assessing dyspnoea descriptors after a methacholine challenge. They confirmed that most patients describe chest tightness to a greater extent than work/effort, and that these language descriptors were similarly distributed between "normoperceivers", "hyperperceivers" and "hypoperceivers". It is important to highlight the clinical importance of these so-called "hypoperceivers". Individuals with near-fatal asthma exhibit reduced dyspnoea intensity in response to various challenges, including hypoxia, hypercapnia [15] and exercise [19]. In one study, the presence of a Borg dyspnoea score $\leqslant 6$ at maximal exercise had a sensitivity of 100% for discriminating patients with near-fatal asthma from those without an episode of near-fatal asthma [19]. Furthermore, individuals with asthma and blunted dyspnoea perception have a higher rate of emergency department visits, hospitalisations, near-fatal exacerbations and deaths [89].

Measuring dyspnoea perception during exercise

Given the contrasting effects of airflow obstruction severity and DH on the qualitative description of dyspnoea during methacholine inhalation, Laveneziana *et al.* [20] investigated whether dyspnoea intensity and quality differed after methacholine compared with a short exercise session in patients with stable asthma. Hyperinflation occurred in 18 out of 19 individuals following the methacholine challenge, and most of the variability in dyspnoea intensity was explained by hyperinflation (as indicated by the decrease in IC) and the change in FEV_1 [20], consistent with previous studies [38, 39]. In this study, 68% of patients reported chest tightness as opposed to 18% describing inspiratory effort after methacholine [20], which may be explained by the use of low-dose methacholine and relatively small decreases in FEV_1 compared to studies that found that >30% decreases in FEV_1 provoke sensations of inspiratory difficulty [39].

During CPET, the predominant symptom description was that of increased inspiratory effort (72%) rather than chest tightness (figure 3) [20]. Unlike with methacholine, the main correlate of dyspnoea intensity during CPET was V'_E, not DH. A minority of asthmatic subjects exhibited hyperinflation during exercise, but those who did reported a higher intensity of dyspnoea, reflecting increased demand on the respiratory muscles [20]. This study from Laveneziana *et al.* [20], along with previous studies of exertional dyspnoea in asthma [19, 29], confirmed that significant airflow obstruction and DH are not very common during brief exercise sessions. Thus, work/effort descriptors of dyspnoea are associated with severe airflow obstruction and hyperinflation during methacholine inhalation, but these same descriptors predominate during exercise, even in the absence of hyperinflation, suggesting that increased central respiratory drive (higher V'_E) provokes the sensation of work/effort during exercise.

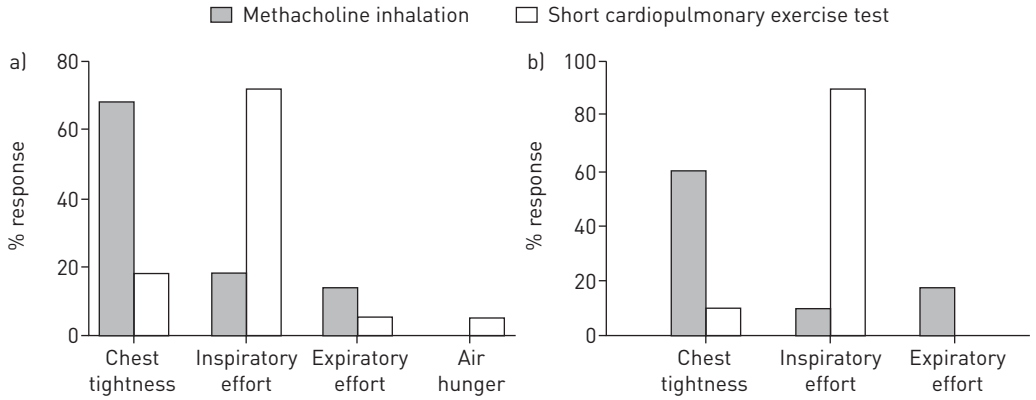

FIGURE 3 a) Percent responses of descriptors selected after methacholine inhalation and short cardiopulmonary exercise test. b) Percent responses of descriptors selected by the eight subjects who similarly hyperinflated at the end of both tests. Reproduced and modified from [20] with permission.

Nevertheless, individuals with mild asthma can develop hyperinflation during exercise, and their description of dyspnoea evolves over the course of exertion. During cycle exercise at a constant work rate, a change in the qualitative description of dyspnoea was related to important inflection points in the V_T/V'_E relationship [21]. When plotting V_T as a function of V'_E during exercise, V_T increases until an inflection point or plateau occurs (figure 4). In most individuals with asthma, this inflection point occurs near peak exercise and at a preserved inspiratory reserve volume (IRV), *i.e.* without hyperinflation, similar to healthy individuals. In those with a preserved IRV at the inflection point, the work/effort descriptor predominated, even after the V_T/V'_E inflection point, and the intensity of dyspnoea increased linearly. However, in some individuals who developed a critical reduction in IRV, the V_T/V'_E inflection point occurred at a lower V_T and at a reduced IRV, reflecting hyperinflation. At this point, mechanical constraints to V_T expansion imposed an increased load on the respiratory system, and the dominant dyspnoea descriptor changed from work/effort to "difficult/unsatisfied inspiration". These results suggested that the quality of dyspnoea during exercise could inform the clinician whether a critically reduced IRV is reached (with the description of difficult or unsatisfied inspiration as opposed to work/effort); however, this cannot yet be incorporated into clinical practice until replicated in larger studies, using different languages and in more severe patients [21]. Pharmacological or non-pharmacological interventions that delay the onset of this inflection point and critical reduction in IRV could potentially reduce exertional dyspnoea, but this has yet to be demonstrated. Although all patients in this study had mild asthma, those

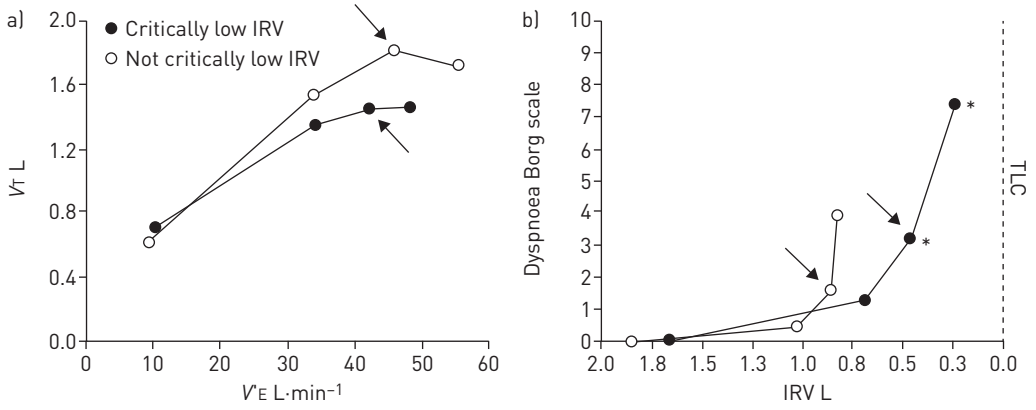

FIGURE 4 a) Tidal volume (V_T) plotted as a function of ventilation (V'_E), and b) exertional dyspnoea intensity (in Borg scale units) plotted as a function of inspiratory reserve volume (IRV), expressed in absolute value, during symptom-limited constant work rate cycle exercise. Patients who reached a critically low IRV at the V_T inflection point (n=6) were compared with those who did not (n=10). Arrows indicate the V_T inflection points. Patients who reached a critically low IRV had dynamic hyperinflation with lower inspiratory capacity at peak exercise, which translated to markedly higher dyspnoea intensity (mean Borg rating 7 "very severe") in this group after the V_T inflection point. The dashed vertical line indicates the total lung capacity (TLC). Graphs represent mean values at rest, at isotime, at V_T inflection point, and at peak exercise. *: p<0.05 between groups at the same measurement point. Reproduced and modified from [21] with permission.

with hyperinflation and a critical reduction in IRV had greater resting and exercise expiratory flow limitation and a trend to lower $FEF_{25–75\%}$ (46±13% *versus* 61±18% predicted; p=0.06). This suggests that a small airway obstruction could be a cause or predisposition for air trapping and DH during exercise in mild asthmatics and therefore could explain the perceptual differences in exertional dyspnoea quality observed in mild asthmatics with otherwise normal resting lung function [21]. The evolution of dyspnoea quality and its mechanistic correlates in moderate or severe asthmatic patients has not yet been studied.

Limitations in exertional dyspnoea measurement

Linguistic and cultural variations in descriptors presented to subjects and linguistic differences in dyspnoea labelling could also explain differences between the Italian study by Laveneziana *et al.* [20] and the Canadian study by Lougheed *et al.* [39], in which inspiratory difficulty predominated during methacholine challenge. It is also important to recognise that the studies discussed above provided no data on the reproducibility or consistency of dyspnoea descriptors in individual patients for a given stimulus. Furthermore, these dyspnoea descriptors may not be specific for asthma and could reflect concurrent laryngeal dysfunction, hyperventilation or dysfunctional breathing [69, 72]. Dyspnoea quantification (using the Borg or VAS) during incremental or constant work rate cycle exercise testing may not reproduce the type of effort or correlate with symptoms encountered during activities in daily life.

Effects of pharmacological and non-pharmacological interventions on exertional dyspnoea

Bronchodilators and exertional dyspnoea

Bronchodilator-induced changes to dyspnoea at rest may be related to the dilation of larger central airways based on measures of airway conductance [90], as there is no relation between dyspnoea while breathing against a respiratory load and decrease in FEV_1 following bronchoconstriction [91]. Supporting this notion is a randomised, double-blind crossover study by Schermer *et al.* [92], which showed that immediate changes in FEV_1 after a long-acting β_2-agonist (LABA) did not lead to a simultaneous improvement in perceived dyspnoea, but that dyspnoea improvement took 10–30 min. In the study by Mahler *et al.* [31], acute bronchoconstriction before exercise increased the intensity of exertional dyspnoea, but there was no effect of bronchodilation with a β_2-agonist before exercise on dyspnoea during the effort. Although albuterol rapidly changes the quality of dyspnoea in asthmatic patients suffering acute exacerbations, it is not known whether bronchodilators taken before exercise affect the descriptive character of exertional dyspnoea [75].

There are surprisingly few studies reporting the effects of long-acting bronchodilators on exertional dyspnoea. Long-acting anti-cholinergic medications (LAACs), such as tiotropium, in addition to inhaled corticosteroid (ICS) or ICS/LABA therapy, may improve lung function and asthma control but minimally improve asthma symptom scores (such as ACQ, ACT and AQLQ) and there are no studies investigating the effects of LAACs on exercise performance or exertional dyspnoea in asthmatics [93–96]. There are conflicting data regarding the effects of LABAs on exertional dyspnoea over and above the effects of ICSs and short-acting bronchodilators [97, 98].

Inhaled corticosteroids and dyspnoea

The effect of ICSs on dyspnoea *per se* is controversial. Some studies have shown that ICSs increase the perception of dyspnoea after various bronchoprovocation challenges in asthma, but the methods of quantifying asthma symptoms differed across these studies [99, 100]. Others have found individuals with severe asthma and who are taking ICSs had blunted dyspnoea perception [101–103]. Dyspnoea perception was inversely related to the degree of sputum eosinophilia in one study [101], so the disparate results between studies could be explained by heterogeneity in the type of airway inflammation and severity of included patients, differences in duration of ICS treatment, or concurrent use of LABAs. Indeed, the potential modulating effect of concurrent use of a LABA with ICS was demonstrated by Nathan *et al.* [98], who found that fluticasone/salmeterol significantly improved strenuous activity symptoms on the AQLQ compared to fluticasone alone and placebo, whereas salmeterol alone was no better than placebo. None of these studies used exercise challenge or evaluated exercise-related symptoms in relation to ICS initiation or withdrawal. One recent study of 14 individuals with well-controlled mild asthma, all of whom were receiving ICS or an ICS/LABA combination, found small but nonsignificantly higher Borg scores at a given work rate during CPET, but otherwise identical ventilatory and cardiovascular responses compared with controls [104].

Non-pharmacological interventions for exertional dyspnoea

Interestingly, exercise training itself may help improve exertional dyspnoea in asthma. A small prospective cohort of mild intermittent asthmatics found that aerobic training improves exercise capacity but also

reduces dyspnoea levels at submaximal and maximal exercise in asthmatics compared to control subjects, probably by reducing the required level of ventilation (V'_E) at each work rate [105]. A 3-month randomised trial compared aerobic exercise training plus education and breathing exercises to a control group receiving education and breathing exercises alone [106]. They demonstrated improvements in physical limitation, frequency of symptoms and psychosocial distress as well as a reduction in asthma symptoms, anxiety and depression scores in the aerobic training group. Although there was an improvement in peak V'_{O_2} with exercise training, they did not report any change in dyspnoea score at an iso-work rate or iso-V'_E during post-intervention CPET in this study, in contrast to the previously discussed cohort study [105, 106]. Turner *et al.* [107] found similar results in a group of older (mean age 65 years) moderate-to-severe asthmatics who were randomised to a 6-week course of exercise classes compared to standard medical care. All domains on the AQLQ improved in the exercise group compared to the control group, in addition to a significant increase in the 6-min walk distance. However, Borg dyspnoea score at the end of the 6-min walk distance did not improve in either group post-intervention [107]. A Cochrane review in 2013 summarised the evidence for exercise training in asthma, and concluded that exercise training is well tolerated and improves asthma symptoms, cardiovascular fitness and health-related quality of life but has no effects on lung function [108]. However, with regards to asthma symptoms, exertional dyspnoea was not specifically reported, and the heterogeneity of symptom assessment instruments in the nine included studies did not allow pooling of data. Three of the included studies reported fewer days of symptoms, five reported no changes and one study reported improvement [108]. The mechanisms through which exercise training improves exertional symptoms could relate to improving peripheral muscle conditioning, improved emotional wellbeing, modification of dyspnoea perception, or a disease-modifying effect of exercise on asthma. For example, a more recent trial found that 12 weeks of aerobic training improved bronchial hyperresponsiveness, inflammatory markers and patient-reported asthma control and quality of life, with particular improvement in the Activity Limitation domain on the AQLQ [109].

Inspiratory muscle training (IMT) has also been studied in relation to exertional dyspnoea [110]. A Cochrane review including five randomised controlled trials involving a total of 113 patients found that IMT improves respiratory muscle strength as measured by maximal mouth pressures (mean increase 13.34 cmH_2O), but concluded that there was inadequate evidence to support or refute a role for IMT for asthma [111]. Of the included studies, only one addressed exertional dyspnoea using an incremental cycle ergometer [112]. In this study, Turner *et al.* [112] found improved peak V'_{O_2} and reduced dyspnoea ratings at minute 4 and at peak exercise in the IMT group, whereas no change in Borg score at peak exercise was observed in the placebo group. However, the change in peak exercise Borg dyspnoea score with IMT was −0.8 arbitrary units, below the minimally important difference threshold of 1.0 unit established for patients with other chronic cardiorespiratory diseases [113, 114]. Therefore, although IMT cannot be recommended at the present time, the existing data warrant further studies to clarify the effect of IMT on dyspnoea intensity and quality.

Conclusions

Asthma is a heterogeneous condition with exertional dyspnoea manifesting as a common but highly variable symptom that is not well captured in asthma control tests or scores. In contrast to dyspnoea during provoked bronchoconstriction, the mechanisms leading to exertional dyspnoea are incompletely understood. The available evidence suggests that the pathophysiology of exertional dyspnoea is different from that during direct bronchoprovocation and cannot be reliably predicted from resting lung function tests. Hence, the language used to describe dyspnoea during exercise can be categorically different from that during methacholine challenge or acute exacerbations. When available, exercise testing with quantification of dyspnoea intensity using a validated score and measurement of qualitative dyspnoea descriptors can be useful to elucidate the reasons for exertional dyspnoea. A comprehensive evaluation is necessary to consider and to rule out differential diagnoses, comorbidities and contributory factors such as laryngeal dysfunction or hyperventilation. The magnitude of EIB and DH, as well as mechanical ventilatory constraints, may modulate exertional dyspnoea in some patients, but many other factors probably contribute, including central respiratory drive, small airways disease, emotional and affective factors, and comorbidities. There are limited or conflicting data on the effects of long-acting bronchodilators and ICSs on exertional dyspnoea, but exercise training seems to improve exertional symptoms through several potential mechanisms.

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