

# Qualitative aspects of exertional dyspnea in patients with restrictive lung disease

## Aspetti qualitativi della dispnea da sforzo nei pazienti con patologie respiratorie restrittive

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### ABSTRACT

Restrictive lung disease is a broad term encompassing a number of conditions in which lung volumes are reduced. Dyspnea is a common clinical manifestation of restrictive lung disease and frequently becomes a prominent and disabling symptom that undermines patients' ability to function and engage in activities of daily living (especially in those with more advanced restriction). Effective management of this disabling symptom awaits a better understanding of its underlying physiology. In recent decades, our understanding of the mechanisms of dyspnea in restrictive lung disease has been improved by a small, but significant, body of research. One approach to the study of dyspnea is to identify the major qualitative dimensions of the symptom in an attempt to uncover different underlying neurophysiologic mechanisms. This article will review the existing literature on the intensity and qualitative dimensions of dyspnea during exercise in patients with restrictive lung disease. The main focus will be on interstitial lung disease (ILD), since it is the prototypical restrictive disease.

**Keywords:** Dynamic lung hyperinflation, dyspnea, respiratory mechanics, restrictive lung disease.

### RIASSUNTO

Il termine "patologia restrittiva" è generalmente usato per descrivere una varietà di condizioni patologiche caratterizzate da una riduzione dei volumi polmonari. La dispnea è una comune manifestazione clinica della patologia restrittiva e frequentemente diventa un sintomo prominente ed invalidante che porta i pazienti, specialmente quelli in stadio avanzato, ad una ridotta capacità funzionale e ad una riduzione delle atti-

vità della vita quotidiana. La gestione effettiva di questo sintomo invalidante necessita di una migliore comprensione dei meccanismi fisiologici sottostanti. Negli ultimi anni, la ricerca ha permesso di approfondire notevolmente la nostra conoscenza dei meccanismi della dispnea nella patologia restrittiva. Un approccio allo studio della dispnea è quello di identificare gli aspetti qualitativi di questo sintomo (descrittori della dispnea) nel tentativo di smascherare i possibili e differenti meccanismi neurofisiologici sottostanti. Il presente capitolo di questa serie si occuperà di revisionare la letteratura scientifica su intensità e qualità (descrittori della dispnea) della dispnea durante esercizio fisico nei pazienti con patologia restrittiva. Nel presente capitolo l'attenzione sarà rivolta esclusivamente alla malattia interstiziale polmonare, dal momento che questa può essere considerata il prototipo della patologia restrittiva.

**Parole chiave:** Dispnea, iperinsufflazione polmonare dinamica, meccanica respiratoria, patologia restrittiva.

### INTRODUCTION

Dyspnea is a respiratory symptom which can be defined as "the perception of respiratory discomfort occurring for an activity level that does not normally lead to breathing difficulty" [1]. Dyspnea is a complex multifaceted and highly personalized sensory experience, the source and mechanisms of which are incompletely understood. Activity-related dyspnea appears to be the earliest and dominant symptom limiting exercise in the majority of

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patients afflicted by interstitial lung disease (ILD). This symptom progresses relentlessly with time leading invariably to avoidance of activity with consequent skeletal muscle deconditioning and poor perceived quality of life. The mechanisms of exertional dyspnea in patients with ILD remain obscure and there are multiple potential sources of respiratory discomfort. Possible components of dyspnea include: perception of heightened inspiratory effort, awareness of unrewarded effort, and perceptions arising from dyspneogenic afferent inputs from chemoreceptors and a multitude of mechanosensors in the airway, lung and chest wall. To better understand the mechanisms of exertional dyspnea in patients with ILD, one should: 1) evaluate the ventilatory response and respiratory mechanics derangements that characterize ILD during exercise, and 2) identify the major qualitative dimensions of this respiratory symptom in an attempt to uncover different underlying neurophysiologic mechanisms. This article will focus on the potential contributory factors to the intensity and quality of dyspnea during exercise in patients with ILD.

## PHYSIOLOGICAL RESPONSES TO EXERCISE IN ILD

### Ventilatory response

In all cardiopulmonary disorders, dyspnea intensity rises during exercise as minute ventilation ( $V_E$ ) increases as a fraction of maximal ventilatory capacity (MVC). As in other cardiopulmonary disorders, dyspnea intensity is increased at any given  $V_E$  during exercise in patients with ILD compared to age-matched healthy individuals [2]. It follows that any factor that increases ventilatory demand during physical activity would be expected to contribute to dyspnea in ILD. The typical ventilatory response pattern in ILD is characterized by low peak  $V_E$ , high peak  $V_E$ /MVC ratio and high submaximal  $V_E$  [2,3]. The breathing pattern is usually more rapid and shallow throughout exercise than in health [2,3]. Increases in submaximal  $V_E$  in ILD reflect ventilatory inefficiency secondary to high physiological dead space, arterial hypoxemia, and early metabolic acidosis [4,5]. Other potential, but less well studied, contributory factors to excessive submaximal  $V_E$  in ILD include increased pulmonary vascular pressures, altered vagal afferent activity, increased sympathetic nervous system activation and increased peripheral muscle mechanoreceptor/metaboreceptor activation [6-8].

### Dynamic respiratory mechanics

As in chronic obstructive pulmonary disease (COPD), restrictive dynamic respiratory mechanics limits the ability of patients with ILD to increase  $V_E$  in response to increased metabolic demands of exercise. The pressure-volume relationship of the entire respiratory system maintains its sigmoid shape, but is contracted along its volume axis in ILD [9,10]. Lung compliance is reduced and, therefore, greater pressure generation is required by the inspiratory muscles for a given tidal volume ( $V_T$ ) [9,10].

The resting inspiratory capacity (IC) and inspiratory reserve volume (IRV) are often diminished in ILD compared with health [2]. Therefore,  $V_T$  expansion is seriously constrained early in exercise with a greater reliance on increasing breathing frequency to increase  $V_E$  [2]. As a result,  $V_T$  increases during exercise so that the dynamic end-inspiratory lung volume (EILV) encroaches on the upper alinear extreme of the contracted pressure-volume relationship where there is substantial elastic loading of the inspiratory muscles. However, although ventilatory and respiratory mechanics responses to exercise are remarkably similar in COPD and ILD, the behaviour of the operating lung volumes during exercise is different; in COPD  $V_T$  is restricted from below by the effects of dynamic lung hyperinflation, whereas in ILD the restriction is from above, reflecting the reduced total lung capacity (TLC) and IRV. Regardless of the mechanism of restriction, the inability to expand  $V_T$  in response to the increasing respiratory drive (or inspired effort) of exercise contributes importantly to low ventilatory capacity in both diseases.

As a result of this restrictive mechanics, the work and oxygen cost of breathing are consistently elevated, and the ratio of inspiratory muscle effort (esophageal inspiratory pressure expressed as a fraction of maximal inspiratory pressure, i.e.  $P_{es}/P_{I_{max}}$ ) to  $V_T$  (relative to vital capacity, i.e. VC) is consistently increased at any given  $V_E$  compared with health [2]. Despite the increased work and oxygen cost of the muscles of breathing, patients with ILD often exhibit a preserved force-generating capacity of the inspiratory muscles, reflecting their mechanical advantage at the lower operating lung volumes as well as the absence of inspiratory threshold and resistive loading to contend with [2,11]. However, even in clinically stable ILD patients, the derangements of respiratory mechanics and gas exchange during exercise along with the underlying systemic inflammatory process, the effects of oral steroids at high dose, malnutrition, and electrolytic abnormalities may have a deleterious impact on ventilatory muscle function [12]. Some studies have pointed out that dynamic lung hyperinflation does not occur throughout exercise (i.e. IC remains largely preserved), even in patients who exhibit expiratory flow limitation [2,13]. This may reflect the already diminished IC at rest; patients may, therefore, reach a critically reduced IRV and terminate exercise before air trapping occurs [2,13]. In ILD, dyspnea intensity has been shown to correlate with the increasing  $V_T$ /IC ratio during exercise and with the increased inspiratory effort/displacement ratio [2,13], a crude index of neuromechanical dissociation (see below).

## QUALITATIVE DIMENSIONS OF DYSPNEA IN ILD

One approach to the study of dyspnea is to identify the major qualitative dimensions of the symptom in an attempt to uncover different underlying neurophysiologic mechanisms. Both healthy individuals

and ILD patients commonly select descriptors denoting increased ‘work/effort’ and ‘heaviness’ of breathing to describe their dyspnea at peak symptom-limited exercise [2]. However, only patients with ILD select descriptors relating to ‘unsatisfied inspiratory effort’, ‘increased inspiratory difficulty’ and ‘rapid breathing’ [2]. Current unitary concepts of the origins of dyspnea emphasize the importance of central mechanisms such as increased respiratory motor command output and a mismatch in the relationship between motor command (or efferent) output and multiple afferent inputs from activated peripheral mechanoreceptors throughout the respiratory system. The latter disparity of motor command output to the mechanical response has been termed ‘neuromechanical dissociation’. Several recent studies suggest a potential basis for the conscious appreciation of central motor command output (via corollary discharge) and of afferent information from mechanoreceptors in the muscles, chest wall, airways, and lung. In patients with ILD it is reasonable to postulate that the dominant qualitative respiratory sensations, which allude to unsatisfied inspiration, ultimately have their neurophysiological basis in the conscious awareness of a disparity between the increased drive to breathe and the restricted mechanical response of the respiratory system.

#### **Perceived increased effort and dyspnea**

Recent theories on the mechanisms of dyspnea in human beings have emphasized the central importance of the perception of increased contractile inspiratory muscle effort [14-21]. When respiratory muscles are mechanically loaded, weakened or fatigued, increased electrical activation of the muscles is required to generate a given force, and central motor output to these muscles is amplified. It is hypothesized that increased central motor output is accompanied by increased central corollary discharge which provides an efferent copy of information from the brainstem respiratory centers to the somatosensory cortex where it is directly perceived as a heightened sense of effort [19-23]. In health, if the sensory information related to the motor act of breathing is attended to, a conscious determination will generally be made that perceived breathing effort is appropriate for the specific physical task being undertaken. Increased respiratory muscular effort in health is appropriately rewarded by increased ventilatory output, even at high exercise intensities. Thus, this perception of increased effort or work of breathing needs not be unpleasant and, therefore, needs not elicit an affective ‘distress’ response (limbic system activation) to perceived threat with corresponding behavioral compensation [24]. Beyond a certain threshold, the increased effort may be consciously registered as respiratory discomfort [14-19]. Perceived heightened inspiratory effort is common in ILD but is more intense and occurs at lower levels of exercise than in health [2]. In ILD, as in COPD, inspiratory muscle contractile effort (relative to maximal possible effort) is substan-

tially increased, reflecting increased ventilatory demand imposed by the physical task [2]. Moreover, inspiratory muscle contractile effort is increased for any given  $V_E$  compared with health as a result of increased elastic load [2]. In ILD, strong statistical correlations have been demonstrated between ratings of dyspnea intensity during exercise and physiologic indices of motor command output, such as Pes/PI<sub>max</sub> [2,25]. It is reasonable to suggest that dyspnea intensity, which is known to rise as  $V_E$  increases during exercise, is a function of the amplitude of central motor command output that originates in the brainstem (automatic) and/or in cortical (voluntary) motor areas in the brain. Increased corollary discharge remains a plausible mechanistic explanation for the qualitative descriptors that allude to increased effort or work of breathing selected by ILD patients at the break-point of cycle exercise [2].

#### **Unsatisfied inspiration and dyspnea**

In many respects, the sensory experience in ILD differs fundamentally from that of age-matched healthy individuals at peak symptom-limited cycle exercise [2]. While the sense of increased effort, work or heaviness of breathing is pervasive in both groups, only ILD patients consistently select descriptors that allude to ‘unsatisfied inspiratory effort’, ‘increased inspiratory difficulty’ and ‘rapid breathing’ at the break-point of exercise. In patients with ILD, it is reasonable to postulate that these dominant qualitative respiratory sensations, which allude to unsatisfied inspiration, ultimately have their neurophysiological basis in the conscious awareness of a disparity between the increased drive to breathe and the restricted mechanical response of the respiratory system (i.e. neuro-mechanical dissociation).

As outlined above, during resting spontaneous breathing and during exercise, the mechanical output of the respiratory system, measured as  $V_E$ , changes in accordance with the level of central neural drive in healthy subjects. Complex proprioceptive information (obtained from muscle spindles, Golgi tendon organs, and joint receptors), as well as sensory information pertaining to respired airflows and volume displacement (from mechanosensors located in the lung parenchyma and airways), provide simultaneous feedback to the central nervous system that ventilatory output is appropriate for the prevailing drive [22,23,26-30]. Physiological adaptations during exercise, which include precise control of operating lung volumes and airway (intra- and extra-thoracic) resistance together with breathing pattern adjustments, ensure harmonious neuro-mechanical coupling of the respiratory system and avoidance of respiratory discomfort [1]. The relationship between effort (measured as Pes/PI<sub>max</sub>) and the mechanical response/volume displacement (i.e. extent of inspiratory muscle shortening as expressed by  $V_T$  as a fraction of VC or IC) remains remarkably constant throughout exercise in health given that  $V_T$  is positioned on the lin-

ear portion of the respiratory system's pressure-volume relation. As outlined above, when the relationship between central motor command output (and corollary efferent signals) to the respiratory muscles and afferent feedback from a multiple sensory receptors throughout the respiratory system is altered, the sensation of dyspnea is produced [1]. Although the perceived effort of breathing may increase as  $\dot{V}_E$  increases during exercise, medullary output remains appropriately rewarded, and healthy subjects generally do not describe inspiratory difficulty or unsatisfied respiratory effort, even at peak exercise.

The situation is markedly different in patients with ILD, where the relationship between  $P_{es}/P_{I_{max}}$  and  $V_T/VC$  or  $V_T/IC$  becomes increasingly disparate as exercise progresses. In ILD efferent drive is increased due to ventilation/perfusion ( $\dot{V}/Q$ ) mismatching and elastic loading.  $\dot{V}/Q$  mismatching increases physiologic deadspace, requiring a compensatory increase in  $\dot{V}_E$  (and efferent drive) in order to meet metabolic requirements imposed by the physical task. Reduced lung compliance also requires an increase in efferent signaling to the respiratory muscles in order to maintain a given level of  $\dot{V}_E$ . On the other hand the restriction in lung volume expansion due to marked reduction in resting IC and restriction of  $V_T$  from above also alters the afferent feedback; the  $V_T/IC$  ratio approaches unity, and the EILV increasingly encroaches on the upper nonlinear extreme of the contracted respiratory system's pressure-volume curve, where the elastic loading of the inspiratory muscles is substantial. It follows that further increases in neural output to the respiratory system are unrewarded in terms of increased mechanical output. The inability to expand  $V_T$  (mechanical/volume restriction) appropriately in the face of an increased drive to breathe would appear to substantially contribute to the intensity of exertional dyspnea and its dominant qualitative dimension of unsatisfied inspiration experienced in ILD [2]. Unsatisfied inspiratory effort may therefore have its psychophysical basis in the conscious awareness of a disparity between corollary discharge and afferent sensory feedback from a multitude of mechanoreceptors throughout the respiratory system. These mechanoreceptors, which provide precise proprioceptive information about muscle and chest wall displacement (muscle spindles and joint receptors), inspiratory muscle tension development (Golgi tendon organs), and changes in respiratory flow or volume (vagal airway and pulmonary receptors), collectively convey to a conscious level the information that the mechanical output achieved is inadequate for the prevailing respiratory drive. Respiratory mechanoreceptors are ideally placed to detect any disparity between the volume displacement achieved and that which is expected [2]. A plausible mechanistic explanation for the sensation that alludes to 'rapid breathing' selected by ILD patients at the break-point of cycle

exercise may also find its basis in the critical restriction of  $V_T$  expansion with a consequent greater reliance on increasing breathing frequency to increase  $\dot{V}_E$  [2].

It should be appreciated that, although the concept of neuromechanical dissociation may be appealing, it is also difficult to prove, in part because comprehensive measurements of efferent and afferent signals are not currently possible.

## CONCLUSIONS

Activity-related dyspnea appears to be the earliest and dominant symptom limiting exercise in the majority of patients afflicted by ILD. This symptom progresses relentlessly with time leading invariably to avoidance of activity with consequent skeletal muscle deconditioning and poor perceived quality of life. The conditions under which dyspnea occurs in the clinical setting are well established, but the precise mechanisms are not completely understood and have not been studied extensively in the population with ILD. Dyspnea occurs when ventilatory demand is increased relative to capacity, when the ventilatory muscles are impeded in their action, and when the ventilatory muscles are functionally weakened. All these conditions apply in the exercising patient with ILD. Thus, any therapeutic intervention that would reduce ventilatory demand, improve ventilatory capacity, reduce the mechanical load, or increase the functional strength of weakened ventilatory muscles, should alleviate dyspnea.

An evaluation of the qualitative dimensions of dyspnea at the break-point of exercise makes it possible to uncover different underlying neurophysiologic mechanisms. It emerges that the sensory experience in ILD differs fundamentally from that of age-matched healthy individuals at peak symptom-limited exercise. While the sense of increased effort, work or heaviness of breathing is pervasive in both groups, only ILD patients consistently select descriptors that allude to 'unsatisfied inspiratory effort', 'increased inspiratory difficulty' and 'rapid breathing' at the break-point of exercise. In patients with ILD, it is reasonable to postulate that these dominant qualitative respiratory sensations alluding to unsatisfied inspiration ultimately have their neurophysiological basis in the conscious awareness of a disparity between the increased drive to breathe and the restricted mechanical response of the respiratory system (i.e. neuromechanical dissociation).

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