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Does expiratory muscle activity influence dynamic hyperinflation and exertional dyspnea in COPD?

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ABSTRACT

Increased expiratory muscle activity is common during exercise in patients with COPD but its role in modulating operating lung volumes and dyspnea during incremental cycle ergometry is currently unknown. We compared gastric (Pga) and esophageal (Pes) pressures, operating lung volumes and qualitative descriptors of dyspnea during exercise in 12 COPD patients and 12 age- and sex-matched healthy controls. Pes- and Pga-derived measures of expiratory muscle activity were significantly ($p < 0.05$) greater in COPD than in health during exercise. End-expiratory lung volume (EELV) increased by 0.8 L, independent of increased expiratory muscle activity in COPD. Dynamic function of the diaphragm was not different in health and COPD throughout exercise. In both groups, dyspnea descriptors alluding to increased work and inspiratory difficulty predominated whereas expiratory difficulty was rarely reported, even at the limits of tolerance. In conclusion, increased expiratory muscle activity did not mitigate the rise in EELV, the relatively early respiratory mechanical constraints or the attendant perceived inspiratory difficulty during exercise in COPD.

1. Introduction

Activity-related dyspnea occurs in the majority of patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) and current treatments are only partially effective in providing relief (Parshall et al., 2012). Previous studies on mechanisms of dyspnea during exercise in COPD have largely focused on the role of the inspiratory muscles and the mechanical constraints imposed by resting and dynamic lung hyperinflation (Guenette et al., 2012; Kyroussis et al., 2000; Laveneziana et al., 2011; Leblanc et al., 1986; O'Donnell et al., 1997, 2012, 2006; Puente-Maestu et al., 2005). The influence of increased expiratory muscle activity on the intensity and quality of dyspnea is unknown and is the primary focus of the current study.

Expiratory muscle activity in more advanced COPD has been shown to be variable and, in the majority of mechanical studies, peak tidal expiratory esophageal pressure rose smoothly to ~20–25% of maximal expiratory pressure at end-exercise (Kyroussis et al., 2000; Marin et al., 1999; Montes de Oca and Celli, 2000). It has been proposed that increased expiratory muscle activity may convey a mechanical advantage in COPD by optimizing the length-tension characteristics of the diaphragm (Dodd et al., 1984), with possible attendant salutary effects on perceived dyspnea (Younes, 1991). A contrasting view is that excessive abdominal and internal intercostal muscle activation at higher levels of ventilation (V'_E) may contribute to the overall sense of dyspnea (Aliverti et al., 2004, 2008). Thus, the inability of patients with expiratory flow limitation to increase tidal expiratory flow rates and reduce end-expiratory lung volume (EELV) below the resting value, by increasing expiratory muscle activity, places the diaphragm under a mechanical disadvantage and excessive intra-thoracic expiratory pressures may also have negative cardio-circulatory consequences (Kyroussis et al., 2000; Potter et al., 1971). Moreover, it has recently been proposed based on optoelectronic plethysmography that a subset of patients with COPD may avoid dynamic lung

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hyperinflation during exercise ("euvolumics") by increasing expiratory muscle recruitment (Aliverti et al., 2004). However, the paucity of esophageal and gastric pressure measurements in that study precluded any definitive conclusion about the interaction between expiratory muscle activity and dynamic hyperinflation.

The purpose of the current study was therefore to examine the relationships between expiratory muscle activity, dynamic end-inspiratory and end-expiratory lung volumes, diaphragmatic function and perceived dyspnea during exercise in COPD. Accordingly, we compared detailed dynamic respiratory mechanics (including measurements of expiratory and inspiratory muscle function) and the intensity and quality of dyspnea in COPD and age-matched healthy controls during incremental cycle exercise.

2. Methods

2.1. Subjects

Twelve clinically stable patients with COPD ($FEV_1/FVC < 0.7$), a $FEV_1 \leq 80\%$predicted (Rabe et al., 2007), and a smoking history ≥10 pack-years were included. Twelve age- and sex-matched healthy controls with normal spirometry and a smoking history <10 pack-years were included for comparison. Exclusion criteria were as follows: a disease other than COPD that could contribute to dyspnea or exercise limitation; important contraindications to clinical exercise testing; or use of supplemental oxygen or desaturation below 85% during exercise.

2.2. Study design

This study received ethical approval from Queen's University and Affiliated Hospitals Health Sciences Human Research Ethics Board (DMED-906-05). After obtaining informed consent, subjects completed two visits conducted 7 days apart. Visit 1 included medical screening, evaluation of chronic activity-related dyspnea (Fletcher et al., 1959; Mahler et al., 1984), and familiarization with all testing procedures including all aspects of dyspnea evaluation, pulmonary function testing and symptom-limited incremental cardiopulmonary cycle exercise testing. Visit 2 included pulmonary function tests followed by an incremental cycle exercise test with detailed dynamic respiratory mechanical measurements. Prior to each visit, subjects used their respiratory medications as usual but withdrew short-acting inhaled bronchodilators for 6 h, avoided smoking ≥60 min, caffeine, alcohol and heavy meals ≥4 h, and strenuous physical exertion ≥12 h. Visits were conducted at the same time of day for each subject.

2.3. Procedures

Spirometry (Miller et al., 2005), body plethysmography (Wanger et al., 2005), diffusing capacity of the lung for carbon monoxide (MacIntyre et al., 2005) and maximal mouth pressures (American Thoracic Society/European Respiratory Society, 2002) were performed using automated equipment (Vmax 229d with Autobox 6200 D_L body plethysmograph; SensorMedics, Yorba Linda, CA). Measurements were expressed as percentages of predicted normal values (Black and Hyatt, 1969; Briscoe and Dubois, 1958; Burrows et al., 1961; Crapo et al., 1982; Hamilton et al., 1995; Morris et al., 1988); predicted inspiratory capacity (IC) was calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity (FRC).

Symptom-limited incremental exercise tests were conducted on an electrically-braked cycle ergometer (Ergometrics 800S; SensorMedics) with a cardiopulmonary exercise testing system (Vmax229d; SensorMedics) as previously described (O'Donnell et al., 2001). After a steady-state resting period, tests consisted of a 1-min warm-up of unloaded pedaling followed by stepwise increments of 10 W/min (COPD) or 20 W/min (Healthy) until a symptom-limited endpoint was reached. Breath-by-breath cardiopulmonary and metabolic data were collected at baseline and throughout exercise while subjects breathed through a mouthpiece with nasal passages occluded by a nose-clip; variables were evaluated as 30-s averages at rest, at each work rate and at peak exercise (the last 30 s of loaded pedaling). Exercise variables were compared with the predicted normal values of Jones (Jones, 1988). The onset of ventilatory mechanical constraints was evaluated using the inflection point of the tidal volume (V_T) and V'_E relationship; this point was determined by two different observers for each subject during exercise by examining individual Hey plots (Hey et al., 1966). The IC was measured at rest, every second minute during exercise and at end-exercise (O'Donnell et al., 2001).

2.3.1. Dyspnea evaluation

Intensity of dyspnea ("How strong/intense is your breathing discomfort?") and leg discomfort was rated using the modified 10-point Borg scale at rest, every minute during exercise and at peak exercise (Borg, 1982). The endpoints of this scale were anchored such that zero represented "no breathing/leg discomfort" and 10 was "the most severe breathing/leg discomfort that they could imagine experiencing." Three dyspnea descriptor phrases were chosen for evaluation during exercise: (1) "my breathing requires more work/effort" (*work/effort*); (2) "I cannot get enough air in" (*unsatisfied inspiration*); and (3) "I cannot get enough air out" (*unsatisfied expiration*), as previously described (Laveneziana et al., 2011). Every minute during exercise just before intensity ratings, subjects were asked to select the phrase(s) from this list that described their sensation of breathing discomfort: none to all three phrases could be chosen at any one time. At end-exercise, subjects were also asked to select applicable descriptor phrases from a more comprehensive questionnaire (Simon et al., 1990).

2.3.2. Pressure-derived respiratory mechanical measurements

Esophageal pressure (Pes)- and gastric pressure (Pga) measurements were collected continuously throughout exercise testing with an integrated data-acquisition setup (O'Donnell et al., 2006) and analyzed as previously reported (Ora et al., 2011). Transdiaphragmatic pressure (Pdi) was calculated by electronic subtraction of Pes from Pga (American Thoracic Society/European Respiratory Society, 2002). Inspiratory sniff and expiratory cough manoeuvres were performed pre-exercise at rest and immediately at end-exercise to obtain maximum values for Pes (Pes,sn and Pes,co), Pdi (Pdi,sn) and Pga (Pga,co) (American Thoracic Society/European Respiratory Society, 2002). During the IC manoeuvres performed throughout exercise testing, dynamic peak inspiratory Pes (Pes,IC) and Pdi (Pes,IC) were recorded. Pre- and post-exercise FVC manoeuvres were conducted to obtain dynamic peak expiratory Pes (Pes,FVC) and Pga (Pga,FVC); values for work rates between were calculated by linear interpolation. The maximal dynamic Pes (Pes,max) for tidal swings of Pes to operate within was calculated as the difference between Pes,IC and Pes,FVC. Pes-, Pdi- and Pga-derived respiratory mechanical measurements are described in greater detail in the *online supplement*.

Inspiratory (Pes,insp) and expiratory (Pes,exp) Pes were evaluated as the most negative and positive values during tidal breathing, while the tidal swing (Pes,tid) was the difference between these. Similarly, inspiratory Pdi (Pdi,insp) and expiratory Pga (Pga,exp) were the most positive values during inspiration and expiration, respectively. The amplitude of the Pdi rise (Pdi,insp.rise) from its lowest point after end-expiration to the peak value during inspiration was used to reflect inspiratory muscle activity. Activation of the expiratory muscles during expiration was assessed using the expiratory Pga rise (Pga,exp.rise) and Pga,exp (Yan et al.,