Effects of dead space loading on neuro-muscular and neuro-ventilatory coupling of the respiratory system during exercise in healthy adults: Implications for dyspnea and exercise tolerance

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A B S T R A C T

We examined the effects of dead space loading (DSL) on ventilation (VE), neural respiratory drive (EMGdi%max, diaphragm EMG expressed as a % of maximal EMGdi), contractile respiratory muscle effort (Pes,tidal%PImax, tidal esophageal pressure swing expressed as a % of maximal inspiratory Pes) and exertional dyspnea intensity ratings in 11 healthy adults with normal spirometry. Subjects completed, in random order, symptom-limited incremental cycle exercise tests under control (CTRL) and DSL (500 ml) conditions. Compared with CTRL, DSL decreased exercise tolerance by 20–25%; increased exertional dyspnea intensity ratings in direct proportion to concurrent increases in EMGdi%max, Pes,tidal%PImax and VE; and had little/no effect on the inter-relationships between EMGdi%max, Pes,tidal%PImax and VE during exercise. In conclusion, DSL was associated with an earlier onset of intolerable dyspnea; however, neuro-muscular and neuro-ventilatory coupling of the respiratory system remained relatively preserved during exercise in the presence of an increased external dead space. Under these circumstances, DSL-induced increases in exertional dyspnea intensity ratings reflected, at least in part, the awareness of increased neural respiratory drive, contractile respiratory muscle effort and ventilatory output.

1. Introduction

Dyspnea (respiratory discomfort) on exertion is the dominant symptom of patients with chronic cardiorespiratory disease (e.g., obstructive and restrictive pulmonary disease, pulmonary vascular disease, congestive heart failure) and contributes importantly to exercise intolerance and an impoverished health-related quality-of-life in these patients (O’Donnell et al., 2006, 2007, 2009; Sajkov et al., 2010). There is increasing evidence that troublesome activity-related dyspnea and progressive reductions in aerobic working capacity also arises as a consequence of normative aging (Ofir et al., 2008; Jensen et al., 2009). In all cases, the increase in dyspnea and decrease in exercise tolerance is associated with concurrent increases in central (neural) respiratory motor command output, primarily as a result of increases in physiological dead space and/or ventilation-perfusion mismatching (Ofir et al., 2008; Jensen et al., 2009; O’Donnell et al., 2009; Van der Plas et al., 2010). However, the specific inter-relationships between increased neural respiratory drive, exertional dyspnea and activity-limitation are not completely understood and represent the primary focus of this study.

Increases in central motor command output to the respiratory muscles have the potential to curtail exercise performance by (i) accelerating the rise in exertional dyspnea intensity ratings thereby leading to an earlier onset of intolerable dyspnea, (ii) hastening or shortening the time to reach a critical mechanical constraint on thoracic volume displacement with attendant uncoupling of the inter-relationships between neural respiratory drive, contractile respiratory muscle pressure/force generation and ventilatory output or (iii) a combination of these factors. The purpose of the present study, therefore, was to examine the acute effects of dead space loading (DSL) on ventilation (VE), breathing pattern, multipair esophageal electrode catheter-derived measures of the diaphragm electromyogram (EMGdi), esophageal pressure (Pes)-derived measures of contractile respiratory muscle effort, exertional dyspnea intensity ratings and exercise performance in healthy, older adults. Briefly, increased external physiological dead space stresses the ventilatory control system such that a greater VE is required to affect the same arterial Pco2 (PaCO2) and H+ regulation at any given metabolic rate, in accordance with the alveolar gas equation for CO2: VE = (VCO2 × 863)/(PaCO2 × [1 – VT/VE]), where VCO2 and VT/VE represent the metabolic rate of CO2 production and
the physiological dead space-to-tidal volume ratio, respectively. We postulated that if significant dynamic respiratory mechanical constraints exist at peak exercise in this population (Ofr et al., 2008), then the otherwise harmonious inter-relationships between increased neural activation of the diaphragm, contractile respiratory muscle effort and ventilatory output will be disrupted, with attendant intensification of dyspnea at any given VE near end-exercise. Alternatively, if healthy adults possess large ventilatory reserve, as some previous studies suggest (Leblanc et al., 1988; Dempsey et al., 1990; Johnson & Dempsey, 1991; Johnson et al., 1991; O’Donnell et al., 2000), then indices of neuro-muscular and neuro-ventilatory coupling of the respiratory system will remain intact throughout exercise, even in the presence of an increased external dead space. Under these circumstances, DSL will be associated with an accelerated rise in exertional dyspnea intensity ratings and an earlier onset of intolerable dyspnea; however, dyspnea intensity ratings will not increase at any given VE during exercise near the limits of tolerance.

2. Methods

2.1. Ethical approval

The study protocol and consent form were approved by the First Affiliated Hospital of Guangzhou Medical College Ethics Committee in accordance with the standards set by the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study participation.

2.2. Experimental design

This was a controlled, randomized, cross-over study in which subjects visited the laboratory on 3 separate occasions over a period of <2 weeks. Visit 1 included screening for eligibility, anthropometric measurements, pulmonary function testing and a symptom-limited incremental cardiopulmonary exercise test (CPET) for familiarization purposes. Visits 2 and 3 included CPET with added measurements of EMGdi and Pes under one of two conditions, randomized to order: unloaded control (CTRL) or increased external dead space (DSL). Each visit was separated by ≥24 hrs and all visits were conducted at approximately the same time of day (±1 h) for each subject. Subjects avoided caffeine, heavy meals, alcohol and major physical exertion entirely on the day of each test.

2.3. Subjects

Subjects included 11 healthy, non-smoking, normal weight, Chinese men (n = 3) and women (n = 8) between 49 and 67 years of age (mean ± SEM 56.5 ± 1.6 years) with normal spirometry (forced expiratory volume in 1 s (FEV1) >80%predicted; FEV1/FVC >70%) and no history of respiratory, cardiovascular, neuromuscular, metabolic and/or musculoskeletal disease.

2.4. Pulmonary function testing

Routine spirometry and constant-volume body plethysmography were performed (Miller et al., 2005a, 2005b; Wang et al., 2005) using automated equipment (Q-Box, COSMED, Italy) and expressed as percentages of predicted normal values (Hou et al., 1990). A 12-s maximal voluntary ventilation maneuver was also performed (Miller et al., 2005b).

2.5. Cardiopulmonary exercise testing

Exercise tests were conducted on an electronically braked cycle ergometer (Ergoline 100P, COSMED, Italy) using an automated CPET system (ML870B80 Exercise Physiology System, ADInstruments, Castle Hill, Australia) and consisted of a steady-state resting period of >6 min, followed by 20 W increases in cycle work rate every 2-min to the point of symptom-limitation. At rest and during exercise, subjects breathed through a mouthpiece (with nasal passages occluded by noseclip) that was connected, in series, to a 2-way non-rebreathing valve and a pneumotachograph (apparatus dead space [VDapp] = 545 ml) to continuously measure inspiratory and expiratory airflow, which was then integrated to obtain volume. Mixed expired gases were measured at a port located in a mixing chamber using a calibrated O2/CO2 analyzer. Oxymoglobin saturation and end-tidal P CO2 (PET CO2) were measured continuously by finger pulse oximetry and capnography (Capnocheck Plus, model 9004–001, BCI, Waukesha, WI, USA), respectively. Changes in end-expiratory lung volume (EELV) were estimated from inspiratory capacity (IC) maneuvers performed at rest, at the end of every 2-min interval during exercise and at end-exercise. Assuming that total lung capacity does not change during exercise (Stubbings et al., 1980), changes in IC reflect changes in dynamic EELV. Pedaling cadence was maintained between 50 and 70 rpm, and subjects were verbally encouraged to cycle to the point of symptom-limitation. Signals were sampled at a rate of 200 Hz using a PowerLab 16/30 analog-to-digital converter running LabChart Pro Version 5.4 software (ADInstruments, Castle Hill, Australia); and were displayed in real time and saved for further off-line analysis.

2.6. Dead space loading

A dead space of 500 ml was added to the breathing apparatus using a length of 35-mm tubing placed between the mouthpiece and the pneumotachograph (VDapp = 1045 ml).

2.7. Electromyogram of the diaphragm: measurement and analysis

The electromyogram of the crural diaphragm (EMGdi) was recorded from a multipair esophageal electrode catheter and used as an index of neural respiratory drive (Luo et al., 2008). As illustrated in Fig. 1 of Luo et al. (2009), the catheter was 90 cm in length. 2.6 mm in diameter, and consisted of 10 cm silver coils and a latex balloon. The esophageal balloon was 7 cm in length and 2.4 cm in diameter with a 1 cm gap between it and the ground electrode (coil 0). The diameter of the inner lumen of the tube used for esophageal pressure measurement was 1 mm. The most proximal coil (coil 0) was connected to the ground and was 2 cm away from coil 1. Coils 1–9 were used for recording and were 1 cm in length with a gap of 1 mm between adjacent coils. Five consecutive recording pairs were formed with an inter-electrode distance of 3.4 cm within a pair.

The combined electrode-balloon catheter was passed through the nose and carefully positioned based on the strength of EMGdi recorded simultaneously from different pairs of electrodes during spontaneous breathing. Briefly, the position of the electrode catheter was known to be optimal (that is, electrode 5 positioned at the electrically active center of the diaphragm) when the amplitude of EMGdi during inspiration was greatest in electrode pairs 1 and 5, and lowest in electrode pair 3. The placement and position of the catheter was the same under CTRL and DSL conditions. The EMGdi signals were sampled at a rate of 2000 Hz using a PowerLab 16/30 analog-to-digital converter running LabChart Pro Version 5.4 software; amplified and band-pass filtered between 20 and 1000 Hz (bio-amplifier model RA-8, Guangzhou Yinhui Medical Equipment...
was esophageal, Inc., San Jose, CA). A p < 0.05 level of statistical significance was used for all analyses. The results are reported as mean ± SEM.

3. Results

3.1. Subjects

Physical characteristics and pulmonary function test parameters are presented in Table 1. Spirometric parameters and plethysmographic lung volumes were within normal age, sex and height predicted limits.

3.2. Symptom-limited incremental cycle exercise

Compared to CTRL, DSL significantly decreased aerobic working capacity; peak work rate, peak VO₂, and the duration of loaded pedaling decreased by 24 ± 7 W (−22%), 4.8 ± 1.4 ml/kg/min (−20%) and 2.5 ± 0.7 min (−25%), respectively (Table 2). However, VO₂/工作 rate (10.6 ± 0.7 vs. 10.3 ± 0.8 ml/min/W, p = 0.634) and VCO₂/工作 rate (12.4 ± 0.7 vs. 11.0 ± 0.9 ml/min/W, p = 0.096) slopes were not significantly different during incremental cycle exercise under CTRL and DSL conditions.

Values of P_{max} (−62.5 ± 6.4 vs. −63.7 ± 5.8 cmH₂O, p = 0.706) and EMGd_{max} (225.4 ± 17.9 vs. 212.3 ± 13.9 μV, p = 0.262) were similar under DSL vs. CTRL conditions. Compared with CTRL, DSL was associated with consistent increases in PETCO₂, VE, tidal volume (VT), breathing frequency (f), Pes, tidal % P_{max} and EMGd_{max} at rest and at any given submaximal work rate during exercise (Fig. 1, Table 2); an increase in the slope of the VE – VCO₂ relationship during exercise (41.0 ± 3.0 vs. 57.5 ± 5.7, p = 0.005); no change in the behavior of dynamic IC (or EELV) during exercise (Table 2); a discernible plateau in VT expansion

**Table 1**

Subject characteristics and pulmonary function test parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.5 ± 1.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>158.2 ± 1.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.4 ± 0.8</td>
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</tbody>
</table>

**Pulmonary function test parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>FEV₁, l [% predicted]</td>
<td>2.22 ± 0.09 [102 ± 5]</td>
</tr>
<tr>
<td>FEV₁/FVC, % [% predicted]</td>
<td>79.8 ± 1.4 [102 ± 2]</td>
</tr>
<tr>
<td>FVC, l [% predicted]</td>
<td>2.79 ± 0.12 [107 ± 5]</td>
</tr>
<tr>
<td>PEFR, l/s [% predicted]</td>
<td>6.06 ± 0.31 [103 ± 4]</td>
</tr>
<tr>
<td>FEF_{25–75}, l/s [% predicted]</td>
<td>2.17 ± 0.16 [75 ± 5]</td>
</tr>
<tr>
<td>MVV, l/min</td>
<td>97.1 ± 5.3</td>
</tr>
<tr>
<td>TLC, l [% predicted]</td>
<td>5.21 ± 0.29 [107 ± 4]</td>
</tr>
<tr>
<td>SVC, l [% predicted]</td>
<td>3.22 ± 0.15 [116 ± 6]</td>
</tr>
<tr>
<td>IC, l [% predicted]</td>
<td>2.06 ± 0.14 [126 ± 10]</td>
</tr>
<tr>
<td>FRC, l [% predicted]</td>
<td>3.20 ± 0.17 [116 ± 4]</td>
</tr>
<tr>
<td>RV, l [% predicted]</td>
<td>2.15 ± 0.20 [116 ± 10]</td>
</tr>
</tbody>
</table>

Values are means ± SEM. BMI, body mass index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; FEF_{25–75}, forced expiratory flow between 25 and 75% of the FVC manoeuvre; MVV, maximal voluntary ventilation; TLC, total lung capacity; SVC, slow vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume. linear regression analysis using dyspnea intensity ratings ≥0.5 Borg units. Similarly, the slope of the relationship between increasing VE and VCO₂ was calculated for each subject under CTRL and DSL conditions by linear regression analysis using the 30-s averaged data from rest through to end-exercise.

2.11. Statistical analysis

Paired t-tests were used to examine the effects of DSL vs. CTRL on measured parameters at rest, at standardized submaximal work rates during exercise, and at end-exercise (SigmaStat for Windows Version 3.10, Systat Software, Inc., San Jose, CA). A p < 0.05 level of statistical significance was used for all analyses. The results are reported as mean ± SEM.
between iso-work and peak exercise (Fig. 1, Table 2); and a significantly greater (~2-fold) mean change in PETCO₂ from rest to end-exercise (Fig. 1, Table 2). Mean values of VE, Pes,tidal×PImax, and EMGdi%max at end-exercise under DSL vs. CTRL conditions were increased by 3.7 ± 2.01/min (p = 0.088), 10.7 ± 5.3% PImax (p = 0.071) and 8.6 ± 4.3% EMGdi,max (p = 0.073), respectively; however, these differences were not statistically significant (Fig. 1, Table 2).

Compared with CTRL, DSL had little/no effect on the inter-relationships between EMGdi%max, Pes,tidal×PImax and VE during symptom-limited incremental exercise (Fig. 2), indicating relative preservation of neuro-muscular and neuro-ventilatory coupling of the respiratory system.

Dyspnea was identified as the primary symptom limiting exercise in 9 vs. 4 subjects under DSL vs. CTRL conditions, respectively. The intensity of perceived dyspnea and leg discomfort was similar at end-exercise under DSL vs. CTRL conditions (Fig. 3, Table 2). Compared with CTRL, DSL was associated with significant increases in Borg ratings of perceived dyspnea (Fig. 3, Table 2) and leg discomfort (Table 2) at any given submaximal work rate. As illustrated in Fig. 3, however, DSL had no statistical effect on the slope of the relationship between increasing dyspnea intensity ratings and each of EMGdi%max (CTRL, 0.16 ± 0.02 vs. DSL, 0.21 ± 0.04; p = 0.292); Pes,tidal×PImax (CTRL, 0.23 ± 0.04 vs. DSL, 0.25 ± 0.07; p = 0.839); and VE (CTRL, 0.22 ± 0.06 vs. DSL, 0.18 ± 0.02; p = 0.377) during symptom-limited incremental exercise.

### 4. Discussion

To our knowledge, the present study is the first to investigate specifically whether stressing the ventilatory control system via DSL affects exertional dyspnea and exercise tolerance by disrupting the otherwise harmonious inter-relationships between increased neural activation of the diaphragm (EMGdi%max), contractile respiratory muscle effort (Pes,tidal×PImax) and ventilatory output (VE) during incremental cycle exercise in healthy adults. The main findings of this study are as follows: (1) DSL provoked an earlier onset of intolerable dyspnea (with concomitant reductions in exercise tolerance) by accelerating the rise in exertional dyspnea intensity ratings; (2) DSL-induced increases in exertional dyspnea intensity ratings rose linearly with increases in neural respiratory drive, contractile respiratory muscle effort and ventilatory output; and (3) neuro-muscular and neuro-ventilatory coupling of the respiratory system was relatively preserved during DSL vs. CTRL exercise. These findings are consistent with the hypothesis that healthy adults possess large ventilatory reserve and that significant dynamic respiratory mechanical constraints do not exist during exercise in this population.

### 4.1. Increased neural respiratory drive, exertional dyspnea and activity-limitation

DSL-induced reductions in aerobic working capacity (by 20–25%) occurred in tandem with an accelerated rise in exertional dyspnea intensity ratings and an earlier onset of intolerable dyspnea: dyspnea intensity ratings were uniformly increased at any given submaximal work rate during DSL vs. CTRL exercise (e.g., by 2.2 ± 0.3 Borg scale units at iso-work); and subjects reached their symptom-limited peak at an earlier time and at a relatively reduced Vco₂ and work rate under DSL vs. CTRL conditions. In keeping with the results of previous studies (Jones et al., 1971; Ward & Whipp, 1980; Poon, 1992; McClaren et al., 1999; O'Donnell et al., 2000; Wood et al., 2008, 2010), we also found that, compared with CTRL, DSL significantly increased VE, EMGdi%max and Pes,tidal×PImax at any given work rate during exercise (e.g., by 17.2 ± 2.1/min, 19.2 ± 3.0%EMGdi,max and 17.2 ± 4.5%PImax at iso-work, respectively). By contrast, increased external dead space had little/no effect on the behavior of dynamic IC (or EELV) or on the inter-relationships between EMGdi%max, Pes,tidal×PImax and VE during symptom-limited incremental exercise. These findings corroborate and extend those of O’Donnell et al. (2000), and provide evidence to suggest that, in healthy adults with normal pulmonary function, the increased ventilatory requirements...
during exercise in the setting of an increased external dead space were accommodated within the most compliant (linear) portion of the respiratory system’s sigmoid pressure-volume relation, where neuro-muscular and neuro-ventilatory coupling of the respiratory system is harmoniously preserved. Based on our current understanding of the neurophysiology of exertional dyspnea (ATS, 1999; O’Donnell et al., 2006, 2009; Jensen et al., 2009), it is reasonable to conclude that, under these circumstances, DSL-induced increases in exertional dyspnea intensity ratings likely reflect the awareness of (i) increased central motor command output to the respiratory muscles, as sensed by increased central corollary discharge to the somatosensory cortex; (ii) increased feedback information from sensory afferent nerves located in the lungs, airways and respiratory musculature, secondary to increased ventilatory output and/or contractile (global) respiratory muscle force/pressure generation; or (iii) some combination thereof. Indeed, as illustrated in Fig. 3, the slope of the linear relationship between increasing dyspnea intensity ratings and each of EMGdi\%max, Pes,tidal\%PImax and VE was similar throughout exercise under DSL vs. CTRL conditions. Thus, dyspnea intensity ratings rose linearly (and to a similar symptom-limited peak compared with CTRL) in association with concomitant increases in neural respiratory drive, contractile respiratory muscle effort and ventilatory output during exercise in the setting of an increased external dead space. Unfortunately, the relative contribution of these dyspneogenic stimuli could not be ascertained.

Based on the collective results of previous studies (Harms et al., 1997, 1998, 2000; Wetter et al., 1999; Romer et al., 2006), it is reasonable to speculate that DSL-induced increases in contractile respiratory muscle effort (and presumably, therefore, the work and O₂ cost of breathing) may have contributed, at least in part, to (i) increases in the intensity of perceived leg discomfort (Table 2) and (ii) reductions in exercise performance by causing a redistribution of total blood flow and O₂ from the legs to the respiratory muscles (i.e., the ‘respiratory muscle steal’ hypothesis), particularly toward the higher intensities of incremental exercise. This possibility requires further investigation.
alveolar $P_{CO_2}$ during the respiratory cycle, increases above resting levels during exercise. In the present study, exercise-induced increases in $V_{CO_2}$ (and presumably, therefore, mixed-venous $P_{CO_2}$) were similar under DSL vs. CTRL conditions; however, VT was consistently increased at rest and during exercise in the former (Fig. 2, Table 2). These differences in breathing pattern may explain, at least in part, the greater ($\sim 2$-fold) mean change in PET$_{CO_2}$ from rest to end-exercise in the presence of an increased external dead space (Fig. 1, Table 2).

From a methodological standpoint, the relative preservation of $VE$-EMGdi%max and $VE$-Pes,tidal%Pmax relationships during DSL vs. CTRL exercise (Fig. 2) provides evidence to suggest that simple, routine and non-invasive assessment of $VE$ may be used as a valid and reliable index of neural respiratory drive and contractile respiratory muscle effort during incremental cycle exercise, at least in healthy, normal weight adults with normal respiratory mechanical/muscular function. However, this may not apply under pathological conditions of the lungs, airways, chest wall and/or respiratory musculature (Sinderby et al., 2001; Steier et al., 2009; Qin et al., 2010; Reilly et al., 2011).

### 4.2. Critique of methods

Criticisms of using a multipair esophageal electrode catheter positioned at the crux of the diaphragm to assess neural respiratory drive in humans have been described in detail elsewhere (Luo et al., 2001, 2008; ATS/ERS, 2002; Qin et al., 2010). Briefly, the use of EMGdi as a representative measure of neural respiratory drive is based on the fact that (i) the phrenic nerve is the only motor nerve of the diaphragm and (ii) there is a strong positive correlation between simultaneously measured changes in phrenic nerve EMG and diaphragm EMG during both normal and obstructed breathing (Lourenco et al., 1966; Aubier et al., 1981; Hussain et al., 1985). In addition, both animal (D’Angelo et al., 2010) and human (Amirjani et al., 2011) studies have indicated uniform changes in the level of crural and costal diaphragm EMG activity during various respiratory maneuvers.

It could be argued that DSL-induced changes in the behavior of dynamic operating lung volumes (e.g., EELV), the velocity of shortening of the diaphragm and/or the spatial recruitment of ‘other’ respiratory muscles (e.g., intercostals, accessory muscles) during exercise may have influenced our measurement of EMGdi and subsequent interpretation of results. However, in the present study, no significant difference in the behavior of dynamic IC (or EELV) was observed during exercise under DSL vs. CTRL conditions (Table 2). Furthermore, Luo et al. (2000) previously found that experimentally induced increases in EELV of up to 21 above normal resting levels had little effect on multipair esophageal electrode catheter derived measures of the amplitude of the diaphragm compound muscle action potential. Moreover, the results of an earlier study by Beck et al. (1998) provided no evidence for an influence of increased inspiratory flow rates of up to 1.4 l/s on multipair esophageal electrode catheter derived measures of EMGdi in healthy, young volunteers. In light of the above, it is unlikely that DSL-induced alterations in dynamic operating lung volumes and/or the velocity of diaphragm shortening influenced our measurements and interpretation of results. Nevertheless, we cannot rule out the possibility that differences in the spatial recruitment of ‘other’ respiratory muscles during DSL vs. CTRL exercise may have helped to ‘unload’ the diaphragm and, in this manner, preserve the inter-relationships between EMGdi%max, Pes,tidal%Pmax, $VE$ and dyspnea intensity ratings, particularly near the limits of tolerance.

Unlike the commonly observed response of a reduction in PET$_{CO_2}$ from mild-to-peak exercise (Wasserman et al., 2005), there was no drop in PET$_{CO_2}$ during the latter stages of exercise under both CTRL and DSL conditions (Fig. 1, Table 2). The reason for
inventory: the relatively large $V_{Dapp}$ (545 ml and 1045 ml under CTRL and DSL conditions, respectively), which, in the setting of progressive exercise-induced increases in VT, $V_{CO_2}$, and mixed-venous $P_{CO_2}$, may have served to increase the $P_{CO_2}$ of the gas that remained in the breathing apparatus at end-expiration during exercise.

The incremental cycle exercise test employed in the current study provided only a short period of time (i.e., 2-min) in which the subjects were exposed to the conditions that may have predisposed them to dynamic respiratory mechanical constraints. In this regard, a series of high-intensity, constant work rate cycle exercise tests (e.g., 60%, 80%, 100% of the maximal incremental work rate) may have provided a better opportunity to determine whether DSL affects the inter-relationships between $EMGdi%\text{max}$, $P_{es, tidal}\% P_{imax}$ and $VE$ in healthy adults.

Finally, we must acknowledge that the generalizability of our results may be limited to the characteristics of the subjects studied here (i.e., healthy, non-smoking, normal weight, Chinese adults – the majority of whom were women).

5. Conclusions

In conclusion: (1) DSL decreased exercise tolerance, accelerated the rise in exertional dyspnea intensity ratings, and had little/no demonstrable effect on neuro-muscular and neuro-ventilatory coupling of the respiratory system during exercise in healthy adults; and (2) DSL-induced increases in exertional dyspnea intensity ratings rose linearly in association with concomitant increases in neural respiratory drive, contractile respiratory muscle effort and ventilatory output.

Authors contributions

DJ contributed to conception and design of the experiment; collection, analysis and interpretation of data; and drafting of the article. RL contributed to the collection and analysis of data. DEO contributed to the interpretation of data and drafting of the article. YML contributed to conception and design of the experiment; the interpretation of data; and drafting of the article.

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References
