Physiological mechanisms of dyspnea during exercise with external thoracic restriction: Role of increased neural respiratory drive

Cassandra T. Mendonca, Michele R. Schaeffer, Patrick Riley, and Dennis Jensen

Clinical Exercise and Respiratory Physiology Laboratory, Department of Kinesiology and Physical Education, McGill University, Montréal, Québec, Canada

Submitted 19 August 2013; accepted in final form 17 December 2013

Mendonca CT, Schaeffer MR, Riley P, Jensen D. Physiological mechanisms of dyspnea during exercise with external thoracic restriction: Role of increased neural respiratory drive. J Appl Physiol 116: 570–581, 2014. First published December 19, 2013; doi:10.1152/japplphysiol.00950.2013.—We tested the hypothesis that neuromechanical uncoupling of the respiratory system forms the mechanistic basis of dyspnea during exercise in the setting of “abnormal” restrictive constraints on ventilation ($V_E$). To this end, we examined the effect of chest wall strapping (CWS) sufficient to mimic a “mild” restrictive lung deficit on the interrelationships between $V_E$, breathing pattern, dynamic operating lung volumes, esophageal electrode-balloon catheter-derived measures of the diaphragm electromyogram (EMGdi) and the transdiaphragmatic pressure time product (PTPdi), and sensory intensity and unpleasantness ratings of dyspnea during exercise. Twenty healthy men aged 25.7 ± 1.1 years (means ± SE) completed symptom-limited incremental cycle exercise tests under two randomized conditions: unrestricted control and CWS to reduce vital capacity (VC) by 21.6 ± 0.5%. Compared with control, exercise with CWS was associated with 1) an exaggerated EMGdi and PTPdi response; 2) no change in the relationship between EMGdi and each of tidal volume (expressed as a percentage of VC), inspiratory reserve volume, and PTPdi; thus indicating relative preservation of neuromechanical uncoupling; 3) increased sensory intensity and unpleasantness of dyspnea; and 4) no change in the relationship between increasing EMGdi and each of the intensity and unpleasantness of dyspnea. In conclusion, the increased intensity and unpleasantness of dyspnea during exercise with CWS could not be readily explained by increased neuromechanical uncoupling but likely reflected the awareness of increased neural respiratory drive (EMGdi) needed to achieve any given $V_E$ during exercise in the setting of “abnormal” restrictive constraints on tidal volume expansion.

dyspnea; exercise; diaphragm EMG; respiratory mechanics; neural respiratory drive; thoracic restriction; chest wall strapping

SPIROMETRICALLY DEFINED RESTRICTIVE lung impairment is common in the general population of adults aged ≥40 years, with a prevalence ranging from 12.5% to 14.5% (28, 56). Although spirometry (56). Indeed, exertional dyspnea and a prevalence ranging from 12.5% to 14.5% (28, 56). Although spirometry (56). Indeed, exertional dyspnea and a prevalence ranging from 12.5% to 14.5% (28, 56). Although spirometry (56). Indeed, exertional dyspnea and a prevalence ranging from 12.5% to 14.5% (28, 56). Although spirometry (56). Indeed, exertional dyspnea and a prevalence ranging from 12.5% to 14.5% (28, 56). Although spirometry (56), the awareness of increased neural respiratory drive (EMGdi) needed to achieve any given $V_E$ during exercise in the setting of “abnormal” restrictive constraints on tidal volume ($V_T$) expansion remain poorly understood and largely understudied.

On the basis of a comprehensive review of the literature, O’Donnell et al. (42) hypothesized that neuromechanical uncoupling of the respiratory system may form the mechanistic basis of increased activity-related dyspnea in individuals with restrictive pulmonary disorders. According to this hypothesis, dyspnea reflects the awareness of the widening disparity (as exercise progresses) between the magnitude of increased central neural respiratory motor drive and the simultaneous mechanical/muscular response of the respiratory system, particularly as it relates to $V_T$ expansion (42). This concept of dyspneogenesis is supported by the following observations: 1) the ratio of contractile respiratory muscle effort to thoracic volume displacement (tidal esophageal pressure swing expressed as a percentage of maximum inspiratory pressure: $V_T$ expressed as a percentage of the predicted vital capacity; Pes,tidal%PImax,$V_T$%predVC), a crude index of neuromechanical uncoupling, is significantly higher than normal at any given ventilation ($V_E$) during cycle ergometer exercise in ILD and correlated positively with dyspnea intensity ratings (40); and 2) external thoracic restriction by chest wall strapping (CWS) sufficient to decrease VC by 40% at rest caused a large increase [compared to the unrestricted control (CTRL) condition] in dyspnea intensity ratings and in the Pes,tidal%PImax,$V_T$%predVC ratio during cycle ergometer exercise in healthy young men (41). These observations notwithstanding, accumulating evidence indicates that Pes-derived measurements of contractile respiratory muscle effort may not accurately reflect neural respiratory motor drive, particularly during exercise in the setting of “abnormal” restrictive constraints on $V_T$ expansion (19). Furthermore, previous studies that have expressed $V_T$ as a percentage of the predicted VC (rather than as a percentage the measured VC) under both CTRL and CWS conditions (41) may have overestimated the extent of neuromechanical uncoupling and its role in dyspnea causation by not accounting for CWS-induced reductions in the true operating limits for $V_T$ expansion during exercise. Finally, in patients with chronic restrictive lung disease (e.g., ILD), it is very difficult (beyond correlation) to isolate the role of pathophysiological derangements in neural respiratory drive, dynamic respiratory mechanical/muscular function, and their complex interaction in exertional dyspnea causation due to the presence of multiple “other” potential dyspneogenic stimuli (e.g., psychological, cardiovascular, metabolic, and/or peripheral locomotor muscle disorder/dysfunction).

Therefore the purpose of our study was to test the hypothesis that neuromechanical uncoupling of the respiratory system forms the mechanistic basis of increased dyspnea during exercise in the setting of “abnormal” restrictive constraints on $V_T$.
METHODS

Subjects. Subjects included 20 healthy, nonsmoking, normal-weight men aged 20–40 years with normal spirometry (48). Exclusion criteria included history of cardiovascular, respiratory, metabolic, musculoskeletal, endocrine, and/or neuromuscular disease/dysfunction; unable to perform exercise and/or pulmonary function tests; taking doctor-prescribed medications; and/or allergy to latex. Participants were recruited from Montréal and surrounding areas by word of mouth and online postings in the McGill and Concordia University classifieds.

Experimental study design. This was a single-center, controlled, randomized, crossover study wherein participants visited the laboratory on three separate occasions over a period of ~2 wks. Visit 1 included pulmonary function testing and a symptom-limited incremental cardiopulmonary cycle exercise test (CPET) for familiarization purposes. Visits 2 and 3 included pulmonary function tests and a CPET with added measurements of EMGdi and respiratory pressures under one of the following two conditions, in randomized order: 1) unrestricted CTRL and 2) external thoracic restriction by CWS to reduce slow vital capacity (SVC) by 20% of its baseline value at rest. All visits were separated ≥48 h and were conducted at the same time of day (±1 h) for each subject. Subjects were instructed to avoid alcohol, caffeine, and strenuous exercise on each test day. The study protocol and consent form were approved by the Institutional Review Board of the Faculty of Medicine at McGill University in accordance with the Declaration of Helsinki.

Pulmonary function tests. Spirometry and SVC maneuvers were performed with the subjects seated upright using automated testing equipment (SensorMedics Vs229d, Yorba Linda, CA) (35). Measured parameters were standardized as percentage of predicted normal values (12).

External thoracic restriction. An inelastic strap (Nike Structured Strength Training Belt, Beaverton, OR) was fitted just beneath the axillae and around the chest to envelope the rib cage. The desired degree of volume restriction was achieved by tightening a Velcro strap at the back of the belt while subjects expired to residual volume. The extent of lung volume reduction during CWS was measured through a series of SVC maneuvers performed after ≥10 min of acclimatization to the CWS. Spirometry and SVC maneuvers were performed ≥10 min after optimal fitting and adjustment of the CWS.

Pilot testing revealed that CWS sufficient to decrease SVC by an amount (40%) directly comparable to that of previous external thoracic restriction studies (14, 19, 34, 41) caused our participants considerable chest pain/discomfort at rest and particularly during exercise, which negatively affected their ability to distinguish between any painful sensation of chest tightness and progressive exercise-induced increases in dyspnea, our primary outcome variable. However, this was not the case with a 20% decrease in SVC by CWS.

Cardiopulmonary exercise testing. Exercise tests were performed on an electronically braked cycle ergometer (ViaSport 150P; Ergoline, Bitz, Germany) using a SensorMedics Vs229d CPET system (Yorba Linda, CA) and consisted of a steady-state resting period of ≥6 min, followed by 25 watt increases in work rate (starting at 25 watts) every 2 min to the point of symptom limitation. Standard respiratory and gas exchange parameters were collected on a breath-by-breath basis at rest and during exercise while subjects breathed through a mouthpiece and low-resistance flow transducer with nasal passages occluded by a noseclip. Cardiovascular hemodynamic parameters, including heart rate, cardiac output, and stroke volume, were measured continuously at rest and during exercise using an impedance cardiograph (PhysioFlow®, NeuMedX, Bristol, PA).

Operating lung volumes. Changes in dynamic end-expiratory lung volume were estimated from inspiratory capacity (IC) maneuvers performed at rest, at the end of every 2 min stage during exercise, and at end-exercise. Assuming that total lung capacity does not change during exercise (57), changes in IC and IRV (calculated as the difference between IC and V̇E) reflect changes in dynamic end-expiratory lung volume and dynamic end-inspiratory lung volume, respectively. Satisfactory technique and reproducibility of IC maneuvers performed at rest and during exercise were confirmed for each subject by evaluating the consistency of peak inspiratory esophageal pressure measurements. Tidal volume, IC, and IRV were expressed in absolute values (in liters) and as a percentage of the SVC measured under CTRL and CWS conditions, respectively.

Symptom assessment. Using Borg’s 0–10 category-ratio scale (3), subjects provided ratings to the following questions at rest, within the last 30 s of every 2 min stage during exercise, and at end-exercise: How intense is your sensation of breathing overall? How unpleasant or distressed does your breathing make you feel? How intense is your sensation of leg discomfort?

Breathing overall (hereafter referred to as dyspnea) was defined as “the global awareness of your breathing,” which is consistent with the American Thoracic Society’s most recent recommendation that “...the definition of dyspnea should be neutral with respect to any particular quality” of breathing (46). Leg discomfort was defined as “the difficulty associated with pedaling.” Prior to each CPET, subjects were familiarized with the Borg scale and its endpoints were anchored such that “0” represented “no intensity (unpleasantness) at all” and “10” represented “the most severe intensity (unpleasantness) you have ever experienced or could ever imagine experiencing” and a script derived from Price et al. (47) was read to each participant to help them distinguish between the intensity and unpleasantness of dyspnea.

Symptom ratings preceded IC maneuvers by several breaths to avoid interference with pre-IC breathing patterns and the possible influence that performance of an IC maneuver might have on intensity and unpleasantness ratings of dyspnea. At end-exercise, subjects were asked to verbalize their main reason(s) for stopping (i.e., dyspnea, leg discomfort, combination of dyspnea and leg discomfort, or other), to quantify the relative (%) contribution of dyspnea and leg discomfort to exercise cessation, and to select the most appropriate qualitative descriptors of dyspnea from a list of 15 phrases (41).

Diaphragm EMG and respiratory pressures: Measurement and analysis. The electromyogram of the crural diaphragm (EMGdi) and respiratory pressures were recorded from a multipair esophageal electrode-balloon catheter (Guangzhou Yinghui Medical Equipment, Guangzhou, China). The configuration of the catheter has been described in detail by Luo et al. (24). Briefly, the catheter consists of ten 1-cm silver coils that form five consecutive EMGdi recording pairs and an esophageal and gastric balloon for measurement of respiratory pressures.

After “numbing” of the nasal and pharyngeal passages with a 2% endotracheal lidocaine spray (Lidodan®; Odan Laboratories, Montréal, QC, Canada), the catheter was passed through the nose and positioned based on the strength of EMGdi recorded simultaneously from different pairs of electrodes during spontaneous breathing (21, 51). Raw EMGdi signals were sampled at a rate of 2,000 Hz using a PowerLab 16/30 analog-to-digital converter (model ML880) running LabChart Pro Version 5.4 software (ADInstruments, Castle Hill, Australia) and amplified and band-pass filtered between 20 and 1,000 Hz (bioamplifier model RA-8, Guangzhou Yinghui Medical Equipment Ltd, Guangzhou, China).
Raw EMGdi signals were converted to root-mean-square (RMS) using a time constant of 100 msec and a moving window (LabChart Pro Version 5.4 software, ADInstruments, Castle Hill, Australia). The maximum RMS value during 100 msec subdivisions of each inspired breath was determined by manually selecting EMGdi signals falling between QRS complexes so as to avoid the influence of ECG artefact on EMGdi. The RMS selected was from the electrode pair with the largest EMGdi amplitude for each breath. Maximum voluntary EMGdi (EMGdi,max) was identified as the largest of all the RMS values obtained from IC maneuvers performed either at rest or during exercise.

The esophageal and gastric balloons were filled with 1.0 ml and 1.2 ml of air, respectively. Esophageal (Pes), gastric (Pga), and transdiaphragmatic (Pdi = Pga - Pes) pressures were sampled continuously at a rate of 200 Hz using the abovementioned PowerLab data acquisition system, a differential pressure transducer (model DP15-34, Validyne Engineering, Northridge, CA), and a signal conditioner (model CD280-4, Validyne Engineering, Northridge, CA). The continuous flow signal from the V<sub>s</sub>229d CPET system was simultaneously input into the PowerLab data-acquisition system and sampled at a rate of 200 Hz.

Esophageal (PTPes) and transdiaphragmatic (PTPdi) pressure-time products were calculated by integrating Pes and Pdi over the period of inspiratory flow. The baseline for PTPes and PTPdi was determined for each breath as the Pes and Pdi observed at end-expiration. PTPes and PTPdi were multiplied by breathing frequency (f<sub>B</sub>) expressed as (cmH<sub>2</sub>O·s)/min and used as indices of the cumulative force output of all the inspiratory muscles and of the diaphragm, respectively. Peak expiratory Pga (Pga,peak) was taken as index of expiratory muscle activity.

**Analysis of exercise end points.** Physiological parameters measured on a breath-by-breath basis were averaged in 30 s intervals at rest and during exercise. These parameters, collected over the first 30 s period of every 2 min stage during exercise, were linked with symptom IC maneuvers. Four main time points were used for the evaluation of the steady-state period after at least 2 min of breathing on the cycle ergometer before the commencement of exercise: VT, IC, and IRV were significantly lower at any given work rate throughout much of exercise with vs. without CWS (Table 2, Fig. 2). As illustrated in Fig. 1, CWS had no demonstrable effect on the cardiometabolic response to progressive exercise. Apart from a significant decrease in peak V<sub>E</sub> (by 12.9 ± 4.7 L/min, P = 0.01), CWS had no effect on the V<sub>E</sub>-work rate relationship during progressive exercise (Table 2, Fig. 2A). CWS-induced reductions in SVC and FVC were associated with increased dynamic mechanical constraints on VT expansion and tachypnea during exercise: V<sub>T</sub>%VC and f<sub>T</sub> were significantly higher, while VT, IC, and IRV were significantly lower at any given work rate throughout much of exercise with vs. without CWS (Table 2, Fig. 2). As illustrated in Fig. 2E, CWS had no significant effect on the behavior of dynamic IC during exercise: IC increased by 0.37 ± 0.07 L vs. 0.34 ± 0.10 L (P = 0.840) from rest to end-exercise with vs. without CWS, respectively (Table 2). It follows that CWS-induced reductions in V<sub>T</sub> expansion during exercise could be largely accounted for by simultaneous reductions in dynamic IRV (Fig. 2F).

Mean values of EMGdi max were not significantly different with vs. without CWS: 222.8 ± 16.0 μV vs. 199.7 ± 11.9 μV, respectively (P = 0.070). Similarly, mean values of EMGdi of and of peak inspiratory Pes obtained during serial IC maneuvers performed at rest, within the last 30 s of every 2-min stage

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CTRL</th>
<th>CWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC, liters</td>
<td>5.4 ± 0.2</td>
<td>4.2 ± 0.2*</td>
</tr>
<tr>
<td>ΔSVC, % of daily control value</td>
<td>21.6 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>FVC, liters</td>
<td>5.4 ± 0.2</td>
<td>4.3 ± 0.2*</td>
</tr>
<tr>
<td>ΔFVC, % predicted</td>
<td>96.3 ± 3.4</td>
<td>76.7 ± 2.3</td>
</tr>
<tr>
<td>ΔFVC, % of daily control value</td>
<td>20.3 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, liters</td>
<td>4.3 ± 0.2</td>
<td>3.4 ± 0.1*</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, % predicted</td>
<td>97.8 ± 2.8</td>
<td>78.2 ± 2.5*</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC, %</td>
<td>76.5 ± 3.9</td>
<td>80.4 ± 1.7</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC, % predicted</td>
<td>97.4 ± 5.0</td>
<td>102.3 ± 2.2</td>
</tr>
<tr>
<td>PEFR, l/s</td>
<td>9.9 ± 0.4</td>
<td>8.4 ± 0.5*</td>
</tr>
<tr>
<td>PEFR, % predicted</td>
<td>100.5 ± 3.4</td>
<td>85.4 ± 4.6*</td>
</tr>
<tr>
<td>PEFR&lt;sub&gt;5&lt;/sub&gt;–75&lt;sub&gt;r&lt;/sub&gt;, l/s</td>
<td>4.6 ± 0.2</td>
<td>3.3 ± 0.2*</td>
</tr>
<tr>
<td>PEFR&lt;sub&gt;5&lt;/sub&gt;–75&lt;sub&lt;r&lt;/sub&gt;, % predicted</td>
<td>88.8 ± 4.5</td>
<td>72.0 ± 4.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. CTRL, unencumbered control; CWS, chest wall strapping; SVC, slow vital capacity; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; PEFR<sub>5</sub>–75<sub<r</sub>, forced expiratory flow between 25% and 75% of the FVC maneuver; *P < 0.05 vs. CTRL. Δ, change.
were not significantly different during exercise with vs. with

exercise with CWS (e.g., by 28.6 ± 3.6% and 24.8 ± 5.7% at

isowork and iso-VE, respectively) (Table 2); however, these

to VT%VC (Fig. 3

and during exercise in healthy, young men

Cardiovascular, metabolic and pulmonary gas exchange

parameters

\[ \text{VO}_2 \text{, ml kg}^{-1} \text{ min}^{-1} \]

\[ \text{VO}_2 \text{ % predicted} \]

\[ \text{RER} \]

\[ \text{VE/VCO}_2 \]

\[ \text{VT} \text{, %IC} \]

\[ \text{CO}, \text{l/min} \]

\[ \text{SV}, \text{l/s} \]

\[ \text{HR}, \text{beats/min} \]

\[ \text{Dyspnea intensity, Borg 0–10} \]

\[ \text{EMGdi, \%} \]

\[ \text{IRV, liters} \]

\[ \text{IRV, \%VC} \]

\[ \text{Tl, s} \]

\[ \text{Tl, s} \]

\[ \text{TV, %} \]

\[ \text{TV, %} \]

\[ \text{VfTl, l/s} \]

\[ \text{VfTv, l/s} \]

\[ \text{Pga peak, cmH}_2\text{O} \]

\[ \text{Perceptual Responses} \]

\[ \text{Dyspnea intensity, Borg 0–10} \]

\[ \text{Dyspnea unpleasantness, Borg 0–10} \]

\[ \text{Leg discomfort, Borg 0–10} \]

\[ \text{Values are means \pm SE (n = 20).} \]

\[ \text{VO}_2 \text{, metabolic rate of oxygen consumption; RER, respiratory exchange ratio; } \]

\[ \text{VE/VCO}_2 \text{, ventilatory equivalent for carbon} \]

\[ \text{dioxide; PETCO}_2 \text{, partial pressure of end-tidal CO}_2 \text{; CV, cardiac output; SV, stroke volume; HR, heart rate; } \]

\[ \text{VE}, \text{ ventilation; Vt, tidal volume; IC, inspiratory capacity; VC, vital capacity; } \]

\[ \text{fB, breathing frequency; } \]

\[ \text{VT, %IC} \text{ and during exercise in healthy, young men} \]

\[ \text{R, breaths/min} \]

\[ \text{Borg 0 – 10 scale units} \]

\[ \text{Sensitivity and unpleasantness ratings of dyspnea were significantly} \]

\[ \text{higher at any given work rate and } \text{VE} \text{ during exercise with CWS (e.g., by 28.6 ± 6.3% and 24.8 ± 5.7% at} \]

\[ \text{isowork and iso-VE, respectively) (Table 2); however, these} \]

\[ \text{disparities disappeared when EMGdi was examined in relation to} \]

\[ \text{VT} \text{ % VC (Fig. 3C) and IRV (Fig. 3D). Mean values of PTPes} \]

\[ \text{were not significantly different during exercise with vs. without} \]

\[ \text{CWS (Fig. 4A). By contrast, CWS significantly increased} \]

\[ \text{both Pga,peak (Fig. 4B) and PTPdi (Fig. 4C) at rest and during} \]

\[ \text{exercise. The PEGdi:PTPdi ratio related relatively} \]

\[ \text{preserved during exercise with CWS (Fig. 4D).} \]

\[ \text{Perceptual responses to exercise.} \]

\[ \text{Borg 0–10 scale intensity} \]

\[ \text{ratings of leg discomfort were significantly different only at} \]

\[ \text{end-exercise with vs. without CWS (Table 2).} \]
CWS (Table 2, Figs. 5, A–D); however, these differences disappeared when dyspnea intensity and unpleasantness ratings were examined in relation to simultaneous CWS-induced changes in each of EMGdi, VT%VC, and IRV (Fig. 5, E–J).

The relative contribution of dyspnea and leg discomfort to exercise cessation under CWS vs. CTRL conditions significantly increased (from 22.5 ± 4.0% to 48.5 ± 6.9%, P = 0.001) and decreased (from 77.5 ± 4.0% to 50.5 ± 7.0%, P = 0.001), respectively. The distribution of reasons for stopping exercise was as follows: dyspnea, 2 with vs. 0 without CWS; leg discomfort, 6 with vs. 12 without CWS; and combination of dyspnea and leg discomfort, 12 with vs. 8 without CWS. Finally, CWS was associated with an increase in the selection frequency of the following qualitative descriptor phrases of dyspnea at end-exercise: “My chest feels tight” (from 15% to 70%); “My breath does not go all the way in” (from 40% to 70%); “I cannot take a deep breath in” (from 45% to 75%); and “My breathing feels shallow” (from 35% to 60%).

**DISCUSSION**

The key findings of this study include 1) neuromechanical coupling of the respiratory system remained relatively preserved throughout exercise with external thoracic restriction and 2) CWS-induced increases in the intensity and unpleasantness of activity-related dyspnea likely reflected the awareness of increased neural respiratory drive needed to overcome the “abnormal” restrictive constraints on VT expansion and maintain an appropriate VE response to exercise.

Chest wall strapping as a model of “abnormal” restrictive constraints on VT expansion during exercise in restrictive pulmonary disorders. Consistent with the results of earlier studies (14, 19, 41, 59), CWS sufficient to decrease VC by ∼20% was associated with increased dynamic mechanical constraints on VT expansion and tachypnea during exercise (Fig. 2). In keeping with the results of O’Donnell et al. (41), CWS had no effect on the behaviour of dynamic IC during exercise (Table 2, Fig. 2E), thus indicating that CWS-induced reductions in VT expansion during exercise reflected simultaneous reductions in resting and dynamic IRV (Fig. 2F). The relative preservation of the behavior of dynamic IC during exercise with CWS helped to prevent even further encroachment of dynamic IRV on total lung capacity and likely reflected the influence of increased expiratory muscle activation (Fig. 4B) on the regulation of dynamic end-expiratory lung volume during exercise (1, 16, 52).

CWS had no effect on PTPes at rest or during exercise (Fig. 4A). By contrast, PTPdi was significantly increased at rest and during exercise with CWS (Fig. 4C). These findings agree closely with those of other investigators (19, 34, 59) and indicate that by decreasing chest wall compliance and interfer-
ing with thoracic volume displacement, CWS effectively eliminated the inspiratory action(s) of the rib cage muscles, thus forcing the diaphragm to generate the negative intrathoracic pressures throughout inspiration needed to maintain an appropriate VE response to exercise (Fig. 2A). At the same time, increased abdominal muscle pressure development during expiration (Fig. 4B) presumably increased the storage of elastic energy in the abdominal compartment at end-expiration during exercise with CWS, which likely assisted the diaphragm during inspiration by compensating, in whole or in part, for the limited inspiratory action(s) of the rib cage muscles (1, 32).

In persons with restrictive pulmonary disorders, VT expansion is mechanically constrained from above by the reduced total lung capacity and IRV (30, 31, 40). During exercise in these individuals, VT is forced to expand on the upper alinear (noncompliant) portion of the respiratory systems sigmoid

Fig. 2. Effects of chest wall strapping (CWS) on ventilation (A), breathing pattern (B–D), and dynamic operating lung volumes (E–F) during symptom-limited incremental cycle exercise. Data points are means ± SE at rest, standardized submaximal work rates including isowork (equivalent to 205 ± 12 watts), and at peak exercise. CWS, chest wall strapping; VE, minute ventilation; fR, breathing frequency; VT, tidal volume; VC, vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; TLC, total lung capacity. *P < 0.05 vs. control.
pressure-volume relation where there is increased elastic loading and functional weakening of the inspiratory muscles. Under these circumstances, relatively greater neural respiratory motor drive would be needed to achieve any given VE during exercise. Indeed, mouth occlusion pressure-derived indices of neural inspiratory drive are higher than normal during exercise-and hypercapnia-induced hyperpnea in ILD (11, 60). Consistent with these observations as well as the results of Hussain et al. (19), we found that EMGdi was significantly higher at any given work rate and VE during exercise with CWS (Fig. 3, A and B). However, we are the first to show that CWS sufficient to mimic a “mild” restrictive lung deficit, which is common in the general population of adults aged ≥40 years (28, 56), had no appreciable effect on the relationship between exercise-induced changes in EMGdi and each of VT%VC (Fig. 3C), IRV (Fig. 3D), and PTPdi (Fig. 4D). On the basis of these observations we concluded that 1) neuromechanical coupling of the respiratory system remained relatively preserved throughout exercise with CWS and 2) the exaggerated EMGdi response to exercise with CWS likely reflected the increased neural respiratory drive needed to overcome the “abnormal” restrictive constraints on VT expansion and maintain an appropriate VE response to exercise (Fig. 2A).

Several investigators have reported that pulmonary stretch receptor (PSR) stimulation caused by both lung inflation and VT expansion inhibits phrenic motor nerve activity in nonhuman mammals and that this reflex inhibition is diminished or abolished by vagotomy, vagal cooling, and PSR blockade (2, 4, 6, 8, 44, 45, 50). Perusal of Fig. 3, C and D, indicates a precipitous rise in EMGdi once VT%VC and IRV reached their respective maximal and minimal value of 50–55% and 0.5–1.0 L during exercise with and without CWS. Thus it is possible that the exaggerated EMGdi response to exercise with CWS reflected, at least in part, loss of PSR feedback inhibition of central respiratory motor output command due to reduced VT expansion, particularly near the limits of tolerance.

In our study, decreasing VC by ~20% of its baseline value at rest was associated with 1) a change in the locus of symptom limitation; 2) a twofold increase in the percentage contribution of dyspnea to exercise cessation; 3) a 65–75% increase in the selection frequency of “My breath does not go all the way in,” “I cannot take a deep breath in,” and “My breathing feels shallow” to describe the quality of dyspnea at end-exercise; and 4) statistically significantly and clinically meaningful (49) increases in the intensity and unpleasantness of exertional dyspnea (Fig. 5, A–D). These findings confirm and extend the

Fig. 3. Effects of chest wall strapping (CWS) on the relationship between diaphragm EMG and each of work rate (A), ventilation (B), tidal volume expansion (C), and dynamic inspiratory reserve volume (D) during symptom-limited incremental cycle exercise. Data points are means ± SE at rest, standardized submaximal work rates including isowork (equivalent to 205 ± 12 watts; Panel A) and isoventilation (equivalent to 91.2 ± 6.2 L/min; Panels B–D), and at peak exercise. EMGdi, root mean square of the diaphragm electromyogram. *P < 0.05 vs. control.
results of earlier CWS studies that reduced VC by 30–45% (14, 18, 41, 59) and are consistent with observations made in ILD vs. health (40).

**Physiological mechanisms of dyspnea during exercise with chest wall strapping.** O’Donnell et al. (40) have provided cross-sectional and correlative evidence that neuromechanical uncoupling of the respiratory system, as reflected by a higher than normal Pes,tidal%PImax:VT%predVC ratio, may be fundamental to the increased perception of activity-related dyspnea in patients with ILD. A subsequent study by the same investigators (41) reported that CWS sufficient to decrease VC by 40% of its baseline value at rest caused a large increase (compared with CTRL) in dyspnea intensity ratings and in the Pes,tidal%PImax:VT%predVC ratio during exercise in 12 healthy young men. In light of these observations, our a priori hypothesis was that neuromechanical uncoupling of the respiratory system would be largely responsible for the increased intensity and unpleasantness of dyspnea during exercise with CWS. However, our findings do not support this interpretation: sensory intensity (Figs. 5, A and C) and unpleasantness (Figs. 5, B and D) ratings of dyspnea were significantly higher at any given work rate and V̇E during exercise with CWS, whereas the relationship between exercise-induced changes in EMGdi and each of V̇T%VC (Fig. 3C), IRV (Fig. 3D), and PTPdi (Fig. 4D) remained relatively preserved throughout exercise with external thoracic restriction. As illustrated in Fig. 5, E–J, the influence of CWS on dyspnea intensity and unpleasantness ratings disappeared when these parameters were examined in relation to simultaneous changes in each of EMGdi, V̇T%VC, and IRV. On the basis of these observations and our current understanding of the neurophysiology of dyspnea (22, 39, 42), we concluded that the increased intensity and unpleasantness of dyspnea during exercise with CWS likely reflected the awareness of increased central respiratory motor output command (as sensed by increased “central corollary discharge” to sensory areas of the brain) needed to achieve any given V̇E during exercise in the presence of “abnormal” (albeit “mild”) restrictive constraints on V̇T expansion.

The discrepancy in the results between our study and those of O’Donnell et al. (41) may reflect several important methodological differences. First, the 20% reduction in VC imposed in our study [vs. 40% by O’Donnell et al. (41)] may not have been large enough to cause neuromechanical uncoupling. As previously discussed, however, pilot testing revealed that decreasing VC by 40% caused our participants considerable chest pain/discomfort, which adversely affected their ability to distinguish between any painful sensation(s) of chest tightness and dyspnea during exercise. Second, O’Donnell et al. (41)
Fig. 5. Effects of chest wall strapping (CWS) on sensory intensity and unpleasantness ratings of dyspnea during symptom-limited incremental cycle exercise. Data points are means ± SE at rest, standardized submaximal work rates including isowork (equivalent to 205 ± 12 watts; Panels A–B) and isoventilation (equivalent to 91.2 ± 6.2 L/min; Panels C–J), and at peak exercise. *P < 0.05 vs. control.
used $P_{ES,tidal}/P_{max}$ (vs. EMGdi in our study) as an index of neural respiratory drive, which may not be appropriate inasmuch as CWS-induced reductions in VC by 20% in our study and by 40% in the studies of Hussain et al. (19) and Tomczak et al. (59) had no significant effect on the PTPes response to cycle exercise, despite significant increases in EMGdi. Third, O’Donnell et al. (41) expressed $V_T$ as a percentage of the predicted VC (vs. the measured VC in our study) under both CTRL and CWS conditions, which may have overestimated the extent of neuromechanical uncoupling by not accounting for reductions in the true operating limits for $V_T$ expansion during exercise with CWS.

An inverse relationship exists between $V_T$ expansion and dyspnea intensity at fixed (elevated) levels of end-tidal PCO$_2$ ($P_{ET,CO_2}$) in mechanically ventilated quadriplegics (27) and healthy adults (61). Lung transplant recipients, in whom PSR innervation is presumably absent, report less dyspnea relief than healthy controls in response to $V_T$ expansion (9, 15). Furthermore, inhalation of nebulized furosemide, a loop diuretic known to sensitize slowly adapting PSRs (58), relieves dyspnea provoked by a variety of respiratory stimuli in healthy (36, 37) and in patients with chronic obstructive pulmonary disease (20, 43). Thus we must also consider that CWS-induced increases in exertional dyspnea may reflect, at least in part, loss of PSR feedback inhibition of central respiratory drive due to reduced $V_T$ expansion, particularly near the limits of tolerance. Indeed, examination of Fig. 3, C and D, and Fig. 5, G–J, indicate an abrupt increase in EMGdi and in the intensity and unpleasantness of dyspnea once $V_T$%VC and IRV reached their respective maximal and minimal values during exercise with and without CWS.

Stimulation of respiratory muscle mechanoreceptors (i.e., muscle spindles and Golgi tendon organs) by chest wall vibration in phase with inspiration has previously been shown to relieve the intensity of perceived dyspnea provoked by hypercapnia, inspiratory resistive loading, and/or exercise in normal subjects and in patients with chronic obstructive pulmonary disease (5, 7, 10, 26, 53). The corollary of these findings is that CWS-induced reductions in the rib cage contribution to $V_E$ during exercise (19) in our study may have had a direct influence on the intensity and/or unpleasantness of dyspnea by reducing sensory feedback information from chest wall mechanoreceptors, including those in the intercostal muscles.

**Methodological considerations.** Criticisms of using a multipair esophageal electrode catheter positioned at the crus of the diaphragm to assess neural respiratory drive in humans have been reviewed in detail elsewhere (21, 23, 25, 51).

In this crossover study, EMGdi was reported in absolute terms (i.e., $\mu$V), which is advocated for within-subject comparisons of diaphragm activation (55), rather than as percentage of EMGdi,max obtained during a maximal inspiratory effort, which is advocated for between-subject comparisons (54, 55). EMGdi,max is a valid means of normalizing diaphragm activation only if the diaphragm and accessory inspiratory muscles are similarly recruited during a maximal inspiratory effort performed on separate occasions in the same subject (33). As illustrated in Fig. 4, A and C, it is highly unlikely that these criterion were met during IC maneuvers performed at rest and during exercise with vs. without CWS. For these reasons, EMGdi expressed in absolute terms likely provided the most representative estimate of neural respiratory drive (i.e., diaphragm motor unit recruitment and firing rate) under both experimental conditions.

It could be argued that the exaggerated EMGdi response to exercise with CWS (Fig. 3, A and B) may be due, at least in part, to increased velocity of diaphragm shortening, relatively greater arterial blood gas/acid-base disturbances, and/or diaphragm fatigue (18, 59). In our study, neither $P_{ET,CO_2}$ nor mean tidal inspiratory flow rates were significantly increased throughout exercise with vs. without CWS (Table 2). Furthermore, the collective results of earlier studies suggest that CWS sufficient to decrease VC by ~40% of its baseline value at rest (i.e., twofold more than in our study) has little/no effect on arterial blood O$_2$ saturation during exercise in healthy adults (14, 38, 41, 59). Thus it is unlikely that relatively greater velocity of diaphragm shortening and/or arterial blood gas/acid-base disturbances can account for the increased EMGdi response to exercise with CWS observed here. However, we cannot rule out the possibility that diaphragm fatigue (18, 59) may have contributed to the exaggerated EMGdi (and dyspnea) response to exercise with CWS since objective measures of this phenomenon were not made.

**Conclusion and implications.** The results of this study suggest that the increased perception of dyspnea during exercise with CWS sufficient to mimic a “mild” restrictive lung deficit in healthy men cannot be readily explained by increased neuromechanical uncoupling of the respiratory system but that it likely reflects the awareness of increased neural respiratory drive needed to achieve any given $V_E$ during exercise in the setting of “abnormal” restrictive constraints on $V_T$ expansion. From a clinical perspective, these findings provide new insight into the physiological mechanisms underlying the increased perception of activity-related dyspnea in the 12.5–14.5% of adults in the general population with (“mild”) restricted spirometry (28, 56) and in patients with chronic restrictive pulmonary disorders (e.g., ILD, kyphoscoliosis, sarcoidosis, heart failure, obesity).

**ACKNOWLEDGMENTS**

The authors would like to thank all of the study participants for their time and cooperation, Marc C. LeVangie for his contribution to data analysis, and Michael K. Stickland (University of Alberta) and Jordan A. Guenette (University of British Columbia) for helpful feedback and thoughtful discussions on the manuscript.

**GRANTS**

Financial support was provided by the Natural Sciences and Engineering Research Council of Canada (RGPIN 402598-2011). C.T.M. was supported by a Canadian Institutes of Health Research-Quebec Respiratory Health Training Program Award. P.R. was supported by a Respiratory Epidemiology and Clinical Research Unit Summer Research Studentship Award (Montreal Chest Institute, McGill University Health Center). D.J. was supported by a Chercheurs-Boursiers Junior 1 salary award from the Fonds de Recherche du Québec-Santé and by a William Dawson Research Scholars Award (McGill University).

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: C.T.M., M.R.S., and P.R. performed experiments; C.T.M. and M.R.S. analyzed data; C.T.M. and D.J. interpreted results of experiments; C.T.M. prepared figures; C.T.M. and D.J. drafted manuscript; C.T.M. and D.J. edited and revised manuscript; C.T.M., M.R.S., P.R., and D.J. approved final version of manuscript; D.J. conception and design of research.
REFERENCES


