Effect of induced leg muscle fatigue on exertional dyspnea in healthy subjects

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J Appl Physiol 118: 48-54, 2015. First published November 6, 2014; doi:10.1152/japplphysiol.00393.2014.—The genesis of dyspnea is complex. It appears to be related to central respiratory drive although prevailing leg fatigue could independently potentiate dyspnea. We hypothesized that experimentally induced leg fatigue generates more intense exertional dyspnea for a given level of ventilatory drive. Following familiarization, 19 healthy subjects (32.2 ± 7.6 yr; 11 men) performed a 5-min treadmill test (speed: ~4 km/h; grade: ~25%) on two separate days randomized between control (C) and experimentally induced leg fatigue (E) achieved by repeated knee extension against 40% body weight until task failure. Oxygen uptake (VO₂, l/min), carbon dioxide output (VCO₂, l/min), ventilation (VE, l/min), and respiratory rate (fR) were measured breath by breath. Heart rate (HR) and perceived dyspnea intensity (0–10 numerical scale) were recorded continuously. Data were averaged over 30-s intervals. Exertional dyspnea during E was statistically significantly higher (E vs. C: 4.2 ± 0.2 vs. 3.4 ± 0.2, P < 0.001) and accompanied by a significant increase in VE (E vs. C: 61.7 ± 3.7 vs. 55.3 ± 2.8, P = 0.005) and fR (E vs. C: 26.7 ± 1.0 vs. 24.2 ± 1.3, P = 0.036). Dyspnea following E remained significantly higher after allowing for the VE confound (ANCOVA, P = 0.003). VO₂, VCO₂, and HR were not significantly different between two conditions. However, the slopes for dyspnea vs. VO₂ and dyspnea vs. VE were similar between E and C, which suggested that gain in dyspnea per unit change in VO₂ or VE was not altered by leg fatigue. These findings support the hypothesis that the intensity of exertional dyspnea is exacerbated by peripheral afferent information from fatigued leg muscles.

Dyspnea; leg fatigue; oxygen uptake; ventilation

Dyspnea and leg fatigue are the two most common exercise-related symptoms in both healthy populations (36, 41) and patients with chronic cardiorespiratory disease like COPD, chronic heart failure, and pulmonary arterial hypertension (13, 18, 21).

In the past, it has been assumed that dyspnea becomes the major symptom limiting exercise in patients with chronic obstructive pulmonary disease (COPD) (16). However, a number of studies have shown that exercise in patients with COPD can be limited primarily by leg fatigue, dyspnea, or a combination of these (28, 36).

Dyspnea is a fearful experience in patients with chronic heart and lung disease and is known to be a major factor promoting exercise avoidance in this population (18, 19, 29). Avoiding daily activities due to fear of dyspnea results in deconditioning and a vicious cycle of deteriorating functional status as well as isolating COPD patients and imposing a growing burden on their carers (8, 35). Considering the increasing burden of COPD worldwide (20, 25), the prevalence of this debilitating symptom and its psychosocial consequences are likely to increase in the years ahead. A better understanding of the physiological basis of exertional dyspnea could lead to management strategies that would enable sufferers to maintain higher levels of physical activity and improve life quality despite their lung disease.

There is now a consensus of opinion that despite its complex and multifactorial nature, exertional dyspnea is a function of the relationship between the increased ventilatory drive accompanying exercise and feedback from the achieved ventilation (6, 27, 34). In a recent study, Grippo et al. (12) reported that experimentally induced leg fatigue in healthy subjects was associated with a heightened perception of respiratory effort accompanying the addition of inspiratory resistive loads.

The purpose of the present study was to examine the impact of experimental leg fatigue in healthy subjects on the level of perceived dyspnea intensity during a standard exercise bout. In particular, we wished to test the hypothesis that preinduced leg fatigue would increase the intensity of dyspnea during a standard exercise bout independent of the level of exercise ventilation. Such an outcome would be consistent with the idea that altered afferent information from fatigued peripheral muscles could directly contribute to dyspnea perception. More generally, our study aimed to provide insight into how the cardinal exercise symptoms of leg fatigue and dyspnea interact. For instance, a heightened level of one symptom might potentiate the other, resulting in lower exercise tolerance.

To examine this hypothesis, we performed two identical dyspnea-inducing exercise tests on separate days in a group of healthy subjects recruited from the general population. Tests were immediately preceded by either an experimental leg-fatiguing protocol or a period of rest. The preliminary findings of this study have been presented at an American Thoracic Society International Conference and have been published in abstract form (37).

Materials and Methods

Subjects

We recruited 20 healthy volunteers (Table 1) from the Griffith University staff/student population following approval by Griffith University Human Research Ethics Committee. Subjects were screened using the AHA/ACSM Health/fitness preparticipation screening questionnaire (1) to meet the criteria for undertaking a standard exercise test without medical supervision. Resting blood pressure and forced spirometry (Medikro Spirostar 2000, Medikro Oy, Kuopio, Finland) were measured according to standard protocols (22) (Table 1) as part of the screening process. The number of subjects recruited to the study was based on data obtained in a similar study by our group (24) giving a power of 90% to detect a 1.0 difference in dyspnea (0–10 visual analog scale) with P < 0.05 of a Type I error. This calculation indicated a sample size of 17. Participants were asked to attend our Research...
Table 1. General characteristics of participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>21–42</td>
<td>(30.7 ± 8.3)</td>
</tr>
<tr>
<td>No. of participants</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122 ± 10</td>
<td>121 ± 9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>71 ± 16</td>
<td>75 ± 8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177.0</td>
<td>171.8 ± 4.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3 ± 2.0</td>
<td>22.4 ± 3.5</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>96 ± 12</td>
<td>106 ± 13</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>104 ± 17</td>
<td>108 ± 12</td>
</tr>
</tbody>
</table>

Values are means SD; n = 19 participants [1 of 20 recruited subjects was not studied due to exercise-induced cardiac arrhythmia (see text)]. BMI, body mass index, FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

Laboratory on three different occasions with at least one visit per week and with no studies undertaken on consecutive days.

Aerobic Exercise Protocol

A 5-min dyspnea challenge treadmill exercise at a relatively comfortable walking speed and steep slope (speed ~ 4 km/h, and grade ~ 25%) was used as a stimulus to induce exertional dyspnea (24). This arrangement allowed us to continuously record breathing and gas exchange variables using a commercial metabolic system (Quark, Cosmed Srl) along with monitoring of heart rate, ECG, and arterial oxygen saturation.

Cardiorespiratory Measurements During Exercise

Ventilation (Ve), oxygen uptake (Vo₂), carbon dioxide output (VCO₂), tidal volume (Vₜ), and respiratory frequency (fr) were measured by breath by breath via a facemask. Heart rate (HR) was recorded using a Polar heart rate monitor linked directly to the metabolic system. ECG and arterial O₂ saturation (SpO₂) were monitored continuously using an ECG/pulse oximeter monitor (Prizm 5 patient monitor, Charmcare, Seoul, Korea). The CMS ECG configuration was used to optimize the detection of any exercise-related rhythm disturbances.

Rating of Dyspnea and Leg Fatigue

Subjects continuously rated their intensity of perceived dyspnea using a previously validated 0–10 numeric scale (24). The rating was made using a PC-based system with a computer monitor mounted in front of the treadmill. The number displayed on the monitor was controlled by a clicker attached to the handrail of the treadmill. The displayed number changed by 0.5 unit with each click, and subjects had the option of increasing or decreasing the value according to level of breathing exertion they experienced during the exercise. We also obtained a single measure of the level of leg fatigue, using a similar 0–10 number scale, during the last 10 s of exercise (reported verbally within 30 s of the test ending).

Leg Muscle-Fatiguing Protocol

To induce fatigue in the lower limbs, we used a knee extensor ergometer loaded with weights equal to 40% of the subject’s body weight. Subjects performed repeated knee extension exercise at 0.5-Hz frequency (metronome assisted) until task failure. Task failure was assessed subjectively by the investigator as an inability to consistently maintain adequate extensions at the required pace. Following a 20-s rest period, a second bout of extensions was performed again until task failure. Four further bouts of exercise were undertaken with rest periods increasing by 10 s after each bout. In total, the average number of contractions achieved was 321 ± 154 for men and 196 ± 45 for women. This fatiguing protocol was modified from analogous fatiguing methodologies reported by Padua el al. (33) and Gandevia (10).

Assessment of Leg Fatigue

The degree of induced leg fatigue was quantified by measuring the maximal voluntary contraction (MVC) force of the preferred limb. MVC force measurement was carried out using a force transducer mounted to a fixed structure at ankle level and custom-built software (Labview, National Instruments). Subjects were seated comfortably with the pelvic region restrained with a seat belt. They were strongly encouraged to maximally extend their leg isometrically for a period of 5 s while maintaining a relaxed upper body. The procedure was repeated at least three times with 2-min intervals between trials. In each test, MVC was measured as the maximum force which was sustained for 2 s. Stability was ascertained by ensuring less than a 10% difference between the best two measures with the higher value recorded as the MVC.

Experimental Protocol

Visit 1 (familiarization visit). The first visit involved familiarizing the participant with the laboratory environment. During this visit, informed written consent was obtained and height, weight, resting blood pressure, and forced spirometry were measured enabling risk stratification screening (1). Subjects then practiced walking on the treadmill while wearing a facemask connected to the metabolic system. They were also trained to attend to symptoms of dyspnea and leg fatigue and to report the intensity of these symptoms during exercise using the 0–10 scale. During this visit we established an individualized speed and grade combination (speed ~ 4 km/h, grade ~ 25%), referenced to the subject’s height and fitness level, to produce a peak of 80–85% maximum age-predicted heart rate. This form of exercise, similar to stair climbing, has been shown to rapidly induce substantial dyspnea in healthy subjects (24). During this visit, subjects also practiced the MVC maneuvers described above.

Visits 2 and 3. During each of the second and third visits, a single 5-min treadmill exercise test was performed. These two tests were randomly assigned to be preceded by 1) a period of rest (control; C), or 2) the leg-fatiguing protocol (experimental; E). During both the exercise tests, continuous measurements of cardiorespiratory variables and dyspnea were made. MVC was determined 1) before the control exercise bout as an estimate of the nonfatigued state and 2) immediately after the experimental exercise bout as an estimate of fatigue present during the exercise. Following the fatigueng protocol each subject was refitted with the facemask and the subject returned to the treadmill at the individualized speed and grade. This took ~3 min to complete and was similar for each subject.

Data Analysis

All cardiorespiratory variables and dyspnea ratings were averaged over 30-s intervals and analyzed using two-way repeated-measures analysis of variance (ANOVA). Data for leg fatigue and maximum voluntary contraction force (MVC) were analyzed using one-way ANOVA. All statistical analysis was carried out using a standard package (IBM SPSS statistics 21.0). To explore possible mechanistic links between measured variables, we used regression analysis of individual responses to exercise in the E and C conditions and calculation of Pearson correlation coefficients to highlight any statistically significant associations. For all statistical analyses, a P value of <0.05 was used to establish significance.

RESULTS

Of 20 subjects recruited, one subject was excluded due to development of exercise-induced premature ventricular contractions (PVCs) during the familiarization visit. All subjects studied were nonsmokers, normotensive, and had normal lung function; no subject showed arterial desaturation, cardiac arrhythmias, or reported untoward symptoms during exercise.
Table 2. Measures of cardiorespiratory variables, dyspnea, and leg fatigue during exercise following prefatiguing (E) and control (C) conditions

<table>
<thead>
<tr>
<th>Measured Variables</th>
<th>Control (C)</th>
<th>Experimental (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC force, N</td>
<td>441 ± 96</td>
<td>362 ± 74*</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) l/min</td>
<td>2.13 ± 0.10</td>
<td>2.16 ± 0.10</td>
</tr>
<tr>
<td>( \dot{V}CO_2 ) l/min</td>
<td>2.00 ± 0.10</td>
<td>2.16 ± 0.10</td>
</tr>
<tr>
<td>( \dot{V}E ), liters</td>
<td>2.15 ± 0.12</td>
<td>2.28 ± 0.11</td>
</tr>
<tr>
<td>( f_R ), breaths/min</td>
<td>24.2 ± 1.3</td>
<td>26.7 ± 1.0*</td>
</tr>
<tr>
<td>( V_t ), liters</td>
<td>55.3 ± 2.8</td>
<td>61.7 ± 3.7*</td>
</tr>
<tr>
<td>( \dot{V}E/\dot{V}CO_2 )</td>
<td>27.2 ± 0.9</td>
<td>28.1 ± 1.2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>140 ± 2</td>
<td>146 ± 3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.4 ± 0.2</td>
<td>4.2 ± 0.2*</td>
</tr>
<tr>
<td>Leg fatigue</td>
<td>5.2 ± 0.3</td>
<td>6.7 ± 0.3*</td>
</tr>
</tbody>
</table>

Values are expressed as 5 min mean ± SE, except for MVC, which is the maximal voluntary contraction of the preferred leg. \( \dot{V}O_2 \), oxygen uptake; \( \dot{V}CO_2 \), carbon dioxide output; \( V_t \), tidal volume; \( \dot{V}E \), ventilation; \( f_R \), respiratory frequency; HR, heart rate. *Statistically significant difference between experimental and control groups, \( P < 0.05 \).

All subjects indicated that they were confident in using the numerical scale to rate their perceived intensity of dyspnea (and leg fatigue) associated with exercise.

Leg Fatigue

The leg-fatiguing protocol decreased the MVC force by an average of 22% and this was associated with a 29% increase in perceived leg fatigue (Table 2). Both these changes were statistically significant (\( P = 0.009 \) and 0.003, respectively). Further analysis showed there to be no significant correlation between individual differences in MVC force and perceived leg fatigue measured during the fatiguing and nonfatiguing sessions (\( r = 0.19, P = 0.437 \)).

Physiological Data

We did not observe any statistically significant differences in the levels of \( \dot{V}O_2 \), \( \dot{V}CO_2 \), \( V_t \), or HR with exercise following experimental fatigue (E) compared with the control condition (C). However, overall \( \dot{V}E \) was 12% higher and \( f_R \) was 10% higher in the E compared with the C condition (\( P = 0.005 \)) (Table 2; Fig. 1). Post hoc analysis of the data collected during the final minute of exercise revealed no statistically significant difference (\( P = 0.157 \)) in \( \dot{V}E/\dot{V}CO_2 \) between the E (27.7 ± 1.2) and C (26.1 ± 1.0) conditions. There was no significant difference in the change in \( \dot{V}E \) over time during the exercise challenge between the E and C conditions (\( P = 0.996 \)). The relationship between \( \dot{V}E \) and \( \dot{V}O_2 \) is shown in Fig. 2C. Following the fatiguing protocol, subjects had a significantly higher \( \dot{V}E \) throughout the exercise period. However, the \( \dot{V}E/\dot{V}O_2 \) slope (over the final 3 min of exercise) was not significantly different between the E and C conditions (\( P = 0.23 \)).

Exertional Dyspnea

Throughout the 5-min period of exercise, the level of exertional dyspnea was 24% higher in the E compared with the C condition (\( P < 0.001 \), Table 2; Fig. 1). There was no difference in the pattern by which dyspnea developed during exercise between the E and C conditions (\( P = 0.094 \)). Further analysis revealed that there was no significant correlation between individual differences in dyspnea between the E and C conditions and corresponding differences in ventilation (both averaged over the final 2 min of exercise) (\( r = 0.002, P = 0.995 \)). Moreover, there was no significant relationship between individual differences in dyspnea (final 30 s of exercise) and perceived leg fatigue (single end-exercise assessment) between the two exercise bouts (\( r = 0.28, P = 0.248 \)).
In view of the statistically significantly higher levels of both exertional dyspnea and ventilation following experimental fatigue, we questioned whether the changes in dyspnea could be accounted for by the increased ventilatory drive. We thus reanalyzed exertional dyspnea between the two conditions (experimental fatigued group vs. control group) using repeated-measures analysis of covariance (ANCOVA) with ventilation as a covariate. This analysis showed that the level of exertional dyspnea remained statistically significantly higher in the experimental group compared with control ($P < 0.003$).

In addition, we examined the relationship between the change in dyspnea per unit change in $\dot{V}O_2$ and $VE$ between the E and C conditions (Fig. 2, A, B, and D). Figure 2, A and B, shows the relationship between dyspnea and $\dot{V}O_2$. From Figure 1 it can be seen that while dyspnea continues to rise markedly in the final 3 min of exercise, $\dot{V}O_2$ essentially plateaus with only a small rise (~0.25 l/min) during the same period due to the constant-load nature of the exercise. To account for this small rise in $\dot{V}O_2$, but large rise in dyspnea, we have replotted Fig. 2A on a narrower range of $\dot{V}O_2$ in Fig. 2B to highlight the changes in dyspnea over this time. From Fig. 2B the dyspnea vs. $\dot{V}O_2$ slope was calculated (E: 3.95 ± 0.74; C: 3.57 ± 0.75) and found to be nonsignificantly different ($P = 0.72$) between conditions. Similarly, we found there to be no significant difference ($P = 0.98$) in the dyspnea vs. $VE$ slope for either condition (Fig. 2C; E: 0.22 ± 0.01; C: 0.2 ± 0.01).

DISCUSSION

The key finding of this study is that, in healthy subjects, experimentally induced limb muscle fatigue is associated with an increased intensity of dyspnea during subsequent aerobic exercise compared with the same exercise without prefatigue. We induced peripheral fatigue in quadriceps muscle by using knee extensor exercise until task failure. Our approach was modified from isometric fatiguing protocols reported by other groups (4, 26) to enable leg flexion/extension. We assessed fatigue by measuring the decrease in the maximal voluntary contraction (MVC) force (10) following the fatiguing protocol compared with that achieved in the resting state. Although the MVC force was measured on each of the two lab visits, it was performed before treadmill exercise on the control visit and immediately after exercise on the experimental visit. The significant decline in mean MVC force (22%), associated with an increase in perceived fatigue of 29%, was similar to the level found by other groups (4, 33, 42). Of particular relevance is the study by Yates and coworkers (42) who described the dynamics of force production recovery following exhaustive arm flexion exercise. These workers reported an average decline in MVC force of 25–20% with 7–10 min of recovery (analogous to the time of our exercise bout plus time to reliably estimate postexercise MVC force). Further inspection of their data shows that after between 1 and 6 min of recovery (equivalent to our period of treadmill exercise) fatigue ranged between 55 and 30%. This would suggest that over the period of our dyspnea measurements, the actual level of fatigue in the exercising muscles was somewhat greater than the level we measured following exercise. In our subjects, the levels of MVC force reduction...
induced by the fatiguing protocol ranged between 0 and 40%. However, the lack of correlation between this measure and increases in either exertional dyspnea or perceived leg fatigue provides no evidence of a relationship across individuals between objectively measured fatigue and the intensity of exercise-related symptoms.

Our finding of a significant increase in exertional dyspnea following induction of peripheral muscle fatigue is consistent with the findings by Grippo et al. (12). Although there are a number of methodological differences between our study and that of Grippo’s group, the principal difference is that their subjects rated the magnitude of respiratory effort during resistive loading at rest while ours rated the intensity of a commonly experienced respiratory sensation (i.e., shortness of breath) while exercising. Although both experiences are uncomfortable, most would agree that they are qualitatively quite different. Indeed, Grippo and coworkers acknowledged that their subjects denied that “air hunger” was a component of their respiratory discomfort whereas this perception is typically reported as a feature of exertional dyspnea (38). Despite these differences, the two studies are consistent in demonstrating increased respiratory discomfort (dyspnea) in response to a fixed respiratory stimulus following induced leg fatigue. Whereas Grippo’s group speculates that increased sense of effort might reflect a modulation of cortical control of breathing, the present findings of greater exertional shortness of breath may implicate an impact of peripheral muscle fatigue on the central neural processes that give rise to the perception of exertional dyspnea, including brain stem and suprapontine networks.

A potential confound in interpreting findings from the present study is that despite controlling for workload (and oxygen uptake) across the two exercise tests, ventilation was significantly greater following fatigue compared with control. Since there is a well-established relationship between the magnitude of ventilatory stimulation during exercise and the associated intensity of dyspnea (2, 17) it is possible that the increased dyspnea that we observed could simply reflect the increased ventilation seen following fatigue. However, closer inspection of the data revealed that all subjects reported greater dyspnea following fatigue (0.5–2.0 units) whereas 9 of 19 showed either a lower or a slightly higher (<5 l/min over the final minutes of exercise) ventilation following fatigue. Moreover, in three subjects, experimental fatigue increased ventilation by greater than 17.5 l/min placing the increase in ventilation outside 2 SDs of the mean of the rest of the cohort; these changes could therefore be considered as statistical outliers. We have elected not to exclude these data from our analysis since there is no technical reason to do so. However, had we done so, the difference in mean ventilation between the two exercise conditions (over the final 2 min) falls from 7.0 to 3.3 l/min with no corresponding change in mean dyspnea scores. To gain further insight into the effect of the ventilation following fatigue, on exertional dyspnea, we repeated our statistical analysis of the dyspnea data using a repeated-measures analysis of covariance, with ventilation now included as a confounding variable. This analysis also revealed a statistically significantly higher level of exertional dyspnea following experimental fatigue compared with control.

We also analyzed the change in dyspnea per unit change in \( \dot{V}O_2 \) and \( \dot{V}E \) between E and C conditions (Fig. 2). Previous studies have examined this relationship using an incremental exercise test, for example; Ofir et al. (30) used an incremental cycle protocol to examine dyspnea responses in COPD patients compared with healthy controls. This study demonstrated that dyspnea/work rate and dyspnea/ventilation slopes were steeper in the COPD patients compared with the control. The present study did not use an incremental exercise; rather it was a steady-state exercise. However, we were able to examine change in dyspnea per unit change in \( \dot{V}O_2 \) and \( \dot{V}E \) (Fig. 2) over the final 2–3 min of exercise. Examining the data this way demonstrated that while dyspnea was higher in the fatigued state, the slopes for dyspnea vs. \( \dot{V}O_2 \) and dyspnea vs. \( \dot{V}E \) were similar over the final 3 min of exercise (Fig. 2, B and D). This suggests that gain in dyspnea per unit change in \( \dot{V}O_2 \) or \( \dot{V}E \) was not altered in the fatigued state, and that the higher dyspnea in the E condition may be related to the increased baseline level of \( \dot{V}O_2 \) and \( \dot{V}E \), which implied that the perturbations of leg muscle fatigue on central dyspnogenic effect remained constant during the exercise. We acknowledge that our results only apply to a narrow range of \( \dot{V}O_2 \) and \( \dot{V}E \) (Fig. 2), and further work comparing this response across a wider range of \( \dot{V}E \) and \( \dot{V}O_2 \), using an incremental exercise test experimental design, is warranted.

With respect to our hypothesis, we would argue that our findings are consistent with the view that fatigued peripheral muscles give rise to increased exertional dyspnea over and above their stimulation of ventilation. As discussed above, the impact on ventilation is variable but remains significant whether or not the statistical outliers are included. From our data, we are not able to ascertain the mechanism of the enhanced exercise hyperpnea, but possible explanations include increased anaerobiosis and/or increased activation of peripheral muscle afferent fibers.

With respect to our measurements of exercise symptomatology, there is clear evidence of an effect of induced muscle fatigue both on perceived leg fatigue and more interestingly on exertional dyspnea. In terms of the latter, our findings support those of Grippo and co-workers even though the methodologies used and the qualitative aspects of respiratory discomfort assessed were very different. Beyond measuring MVC force at a single time point, we did not quantify the degree or nature of fatigue, but we did use a fatiguing protocol analogous to ones used by others (33, 42). Muscle fatigue can be associated with modulation of contraction-related neural activity in all types of muscle afferents (39) raising the possibility of fatigue-related effects on respiratory perceptions arising from any single or combination of nerve fiber types.

In discussing this possibility, Grippo and colleagues hypothesize that type III and/or type IV are the most likely source of fatigue-related effects on respiratory perception. These fiber types carry information from so called ergoreceptors (14, 15) and type IV fibers, innervated by metaboreceptors known to be chronically stimulated by fatigue-producing metabolites (15). In a recent article, Dempsey et al. (9) have reviewed the evidence implicating type III–IV muscle afferents in exercise hyperpnea. It light of this, it is reasonable to assign a putative role for these afferents in the genesis of exertional dyspnea. Our findings would suggest that if fatigue-related modulation of such afferent activity is giving rise to dyspnea then it is doing so over and above its impact on ventilation. Such afferent information might act directly on neural networks.
responsible for respiratory perceptions or via other sensations (e.g., fatigue) that could modify respiratory perceptions. Another possibility is that the heightened exertional dyspnea that our subjects reported in the presence of peripheral muscle fatigue could be related to a generalized sense of discomfort arising from multiple sensory and/or cognitive processes.

Our findings are potentially relevant to an understanding of the nature of exertional dyspnea in patients with chronic cardiorespiratory disease. Peripheral muscle dysfunction secondary to deconditioning and/or systemic inflammation is now well established in patients with COPD (3, 5, 7, 23) and in those with heart failure (32). Limb muscle dysfunction encompasses structural and functional alteration, including a decreased proportion of fatigue-resistant fibers, decreased capillarization, and reduced activity of metabolic enzymes (11, 31, 40). These factors, in promoting earlier fatigue during exertion, could contribute to increased dyspnea, poorer exercise tolerance, and impaired quality of life.

In conclusion, this study provides evidence that experimentally induced muscle fatigue in healthy subjects increases the intensity of exertional dyspnea compared with that reported for the same exercise following rest. The increase in dyspnea was not fully accounted for by the small and inconsistent increase in minute ventilation. Future studies could examine the impact of exercise dyspnea by inducing fatigue on nonambulatory muscles. Contrasting the results of such study with those of the present study would potentially provide insight into whether any exacerbation of exertional dyspnea by prevailing fatigue was specific to the exercising muscle or related to a more general comorbid experience perhaps reflecting a central neural processing phenomenon. We note that the present study was not without limitation. For example, we did not measure leg discomfort at the same time as we measured dyspnea. This would have enabled an examination of the relationship between changes in leg discomfort and dyspnea. However, for the purpose of this study, we chose not to measure leg fatigue as so as not to contaminate the perception of breathlessness with the perception of leg fatigue, and it would have required an additional visit to achieve this outcome.

ACKNOWLEDGMENTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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