Ventilation Increases with Lower Extremity Venous Occlusion in Young Adults

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ABSTRACT

KELLER-ROSS, M. L., A. L. SARKINEN, T. CROSS, B. D. JOHNSON, and T. P. OLSON. Ventilation Increases with Lower Extremity Venous Occlusion in Young Adults. *Med. Sci. Sports Exerc.*, Vol. 48, No. 3, pp. 377–383, 2016. **Introduction**: Venous distention via subsystolic occlusion of the lower limbs may augment ventilation via stimulation of group III/IV afferent neurons. **Purpose**: The purpose of this study was to examine the ventilatory response to graded lower extremity venous occlusion during exercise in healthy adults. **Methods**: Nineteen adults (9 men, 25 ± 5 yr) completed two visits. Visit 1 included a maximal cycle ergometry exercise test. Visit 2 included a 30% peak workload cycle exercise with randomized inflations of bilateral thigh pressure tourniquets to 20, 40, 60, 80, and 100 mm Hg for 2 min each, separated by 2 min of deflation. Three minutes of cycling occurred before cuffing (control [CTL]). Expired minute ventilation ($\dot{V}_E$), whole body gas exchange, rating of perceived exertion, and dyspnea were measured during each session. **Results**: $\dot{V}_E$ increased significantly from the control condition (exercise only, CTL) to each occlusion pressure ($P < 0.05$) with the greatest increase at 100 mm Hg (CTL to 100 mm Hg: 31.5 ± 6.6 to 40.1 ± 10.7 L·min^{-1}). Respiratory rate (R_R) increased as well (CTL to 100 mm Hg: 24.8 ± 6.0 to 30.9 ± 11.5 breaths per minute, $P < 0.05$, condition effect) with no change in tidal volume ($P > 0.05$). Tidal volume to inspiratory time (V_T/T_I) increased significantly from the CTL condition to each occlusion pressure (CTL to 100 mm Hg: 1.5 ± 0.3 to 1.8 ± 0.4 L·min^{-1}, $P < 0.05$, all pressures). Dyspnea and RPE increased with all occlusion pressures from CTL exercise ($P < 0.05$, all pressures). **Conclusions**: Our findings suggest that mild-to-moderate venous occlusion of the lower extremity evokes a tachypneic breathing pattern which, in turn, augments $\dot{V}_E$ and perceived breathing effort during exercise. **Key Words:** VENOUS DISTENTION, GROUP III AND IV MUSCLE AFFERENTS, LIMB CONGESTION, LOWER EXTREMITY EXERCISE

BASIC SCIENCES

Several lines of evidence suggest that skeletal muscle afferents (groups III and IV) contribute to ventilatory control during exercise (2,34). Locomotor muscle afferents appear to play two major roles in the healthy human: 1) to stimulate optimal cardioventilatory responses in the effort to preserve oxygen (O_2) transport to working muscles, and 2) to provide feedback of the metabolic state of the locomotor muscles to influence central command (19). A number of techniques have been used to activate skeletal muscle afferents to determine their role in ventilatory control at rest, during exercise, and postexercise. The most common of these techniques is vascular occlusion via pressure tourniquets proximal to or at the site of the exercising limb using suprasystolic pressure to effectively arrest circulation immediately after exercise (1). The theory supporting this methodology is that the metabolic byproducts produced during exercise by the active skeletal muscle will remain "trapped" within the muscle postexercise, subsequently maintaining the activation of primarily group IV muscle afferents. In turn, these afferents will feed back to the medullary respiratory centers (i.e., rostral ventral medulla, caudal ventrolateral medulla, nucleus tractus solitaries [NTS], lateral tegmental field, nucleus ambiguous, and the ventromedial region of the rostral periaqueductal gray) via the dorsal horn of the spinal cord (6,21,22,25,26) to increase efferent respiratory motor output, thereby increasing ventilation ($\dot{V}_E$).

This ventilatory response, however, may be more appropriately elicited during exercise and lower cuff pressure, which may reduce the potential activation of nociceptors, as extreme cuff pressures and pain tend to do (17). For example, in contrast to complete circulatory occlusion, subsystolic occlusion has been used to promote limb venous congestion triggering a similar rise in afferent feedback (30). It has also been demonstrated that local distension of the femoral-saphenous vein by a large range of venous pressures evokes reflex activation of respiratory centers from group III afferents in cats (9,33). In addition, evidence suggests that the increase in intravascular pressure with subsystolic occlusion may cause greater activation of mechanosensitive afferents (30).

The link between changes in skeletal muscle intravascular pressure and ventilatory control has been suggested in previous work (18). In particular, venous distension can be sensed

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by mechanosensitive afferents, facilitating increases in ventilation at rest and during exercise (17). Importantly, limb congestion, caused by lower extremity edema, is often noted in patients such as those with heart failure (HF) (35,36). Patients with HF demonstrate exercise intolerance at low levels of activity, and group III/IV muscle afferents have shown to play a major role in exercise intolerance in HF (3,37,38). Therefore, using venous occlusion to cause venous distention might be an intriguing technique to simulate limb congestion in patients with HF, which may ultimately elicit an exaggerated response of the skeletal muscle afferents during physical activity in these patients.

Both mechanoreceptor and metaboreceptors seem to be stimulated by distension of venules rather than large veins alone, which provides a mechanism of cardiovascular and ventilatory control based on the degree of blood flow and vascular conductance in the periphery (17). However, the specific effects of this feedback on ventilatory control during exercise are not completely understood. The present study uses subsystolic venous occlusion of the bilateral proximal quadriceps muscles to induce limb congestion during low-intensity dynamic exercise which, in turn, activates skeletal muscle afferents. We quantified the influence of venous distention on ventilation ($\dot{V}_E$) and breathing pattern and expect that limb congestion during exercise will increase $\dot{V}_E$ in young healthy men and women.

METHODS

Subjects. Nineteen healthy subjects (9 men) participated in the study. Inclusion criteria were a minimum of 18 yr of age with no previous history of cardiovascular, pulmonary, metabolic, neurologic, orthopedic, or other diseases affecting the neuromuscular system. Female participants were excluded if pregnant or breast feeding. Menstrual cycle was not controlled for but was documented. One woman reported regular use of oral contraceptives, two women reported use of an intrauterine device (IUD), and one did not report menstrual history. The six remaining women were split between luteal (n = 3) and follicular phase (n = 3). There were no systematic differences between hormonal phases in any variable for these women, and therefore, the data has been combined for the women.

All participants gave written informed consent to participate after being provided a description of study requirements. This study was approved by Mayo Clinic institutional review board and conducted in accordance with the Declaration of Helsinki.

Experimental protocol. Participants attended the laboratory for two experimental visits. During visit 1, participants completed a health screening form, and female participants completed a urine pregnancy test. Participants then completed an incremental exercise test to peak $\dot{V}O_2$ on a semirecumbent bike. Visit 2 included semirecumbent cycling exercise at 30% peak workload with randomized cuff inflation/deflation, 2 min on/2 min off. Before exercise, bilateral pressure tourniquets (Delfi Medical Innovations, Vancouver, British Colombia) of a 6-inch width were applied to the proximal thighs and were connected to a rapid cuff-inflator system (Hokanson Inc, Bellevue, WA). Three minutes of resting baseline data were collected, followed by 3 min of exercise at 30% of peak workload at 65 to 70 rpm. After 3 min of exercise, cuffs were inflated intermittently to subsystolic pressures (20, 40, 60, 80, and 100 mm Hg) in a randomized order. Inflations lasted for a 2-min period, followed by a 2-min deflation between occlusions (Fig. 1).

Physiologic monitoring and data collection. Ventilation and whole body gas exchange were continually collected throughout rest and exercise using noninvasive instrumentation. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) were measured with a metabolic measurement system through a mouth piece and pneumotachograph while wearing a nose clip for the entire measurement period (MedGraphics CPX/C, St. Paul, MN). Additional measures included respiratory exchange ratio (RER), respiratory rate (RR), tidal volume (V_T), inspiratory time (T_I), total respiratory time (T_{TOT}), index of neural drive (T_I/T_{TOT}), mean inspiratory flow (V_T/T_I), and ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$). Manual volume calibration was performed with a 3–L syringe, and gas calibration was performed with manufacturer-recommended gases of known concentration immediately before each testing protocol. Rating of perceived exertion (RPE; scale 6–20) and dyspnea (scale 0–10) were measured during exercise and at the end of each 2-min inflation/deflation (5). Blood pressure was measured with a manual sphygmomanometer at the start and end of exercise to ensure that systolic blood pressure was above 100 mm Hg for each individual.

Statistical analysis. Data throughout the final 30 s of each 2-min inflation or deflation period were averaged. Data reported are means ± standard deviations. A repeated measures ANOVA with a main effect of condition (graded cuff occlusion pressures) and sex as well as a condition–sex interaction was performed. A Bonferroni adjustment was conducted for multiple comparisons of CTL to each cuff pressure (20, 40,

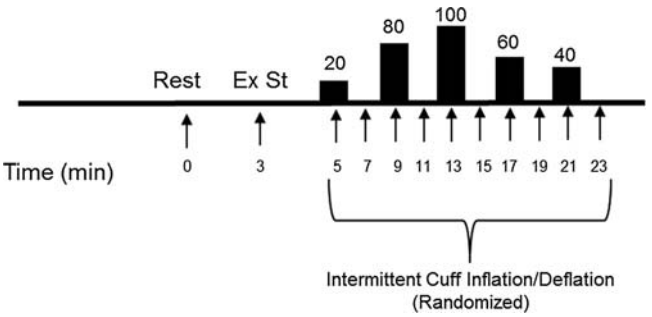

FIGURE 1—Experimental protocol. During visit 2, participants cycled at 30% of their peak work for 23 min. Randomized bilateral cuff occlusions of the proximal thighs began after 3 min of exercise and were intermittently inflated to various cuff pressures (20, 40, 60, 80, and 100 mm Hg). Ex St indicates start of the cycling exercise at 30% of peak work.

TABLE 1. Participant characteristics.

	Men	Women	Combined
N	9	10	19
Age (yr)	25.2 ± 3.8	25.0 ± 5.4	25.2 ± 4.6
Height (cm)	180 ± 4	170 ± 6*	175 ± 7
Weight (kg)	80.9 ± 14.5	61.3 ± 7.9*	70.6 ± 15.0
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	39.3 ± 6.8	38.1 ± 4.2	38.6 ± 5.4
Peak workload (W)	236 ± 58	176 ± 34*	204 ± 55
Submaximal workload (W)	71 ± 17	53 ± 10*	61 ± 16
Start exercise SBP (mm Hg)	150 ± 20	120 ± 10*	133 ± 22
End exercise SBP (mm Hg)	150 ± 20	120 ± 14*	133 ± 22

$\dot{V}O_2$ indicates volume of oxygen consumption; SBP, systolic blood pressure.
*Sex differences, $P < 0.05$.

60, 80, and 100 mm Hg) and for each cuff pressure to be compared with one another (20–40, 40–60 mm Hg, etc). For ordinal data (RPE and dyspnea), nonparametric statistics were used including the Friedman test for ANOVA, Mann Whitney *U* for independent samples, and Wilcoxon signed rank test for paired *t* testing. Statistical analyses were performed using SPSS 20.0 (SPSS, Inc., Chicago, IL), and were considered significant if $P < 0.05$.

RESULTS

Subject characteristics. Participant characteristics are presented in Table 1. Men and women were similar in age ($P = 0.88$). On average, the men were taller and weighed more than the women ($P < 0.05$, for both). Men had a higher maximal workload and, therefore, a higher submaximal workload ($P < 0.05$), but men and women had a similar peak $\dot{V}O_2$ ($P = 0.65$). Blood pressure was similar at the start and end of exercise ($P > 0.05$) and was greater for men compared with women ($P < 0.05$).

Ventilation and whole body gas exchange. Ventilation ($\dot{V}_E$) increased overall with cuff occlusion (condition effect, $P < 0.05$; Fig. 2A). In addition, a pairwise comparison with Bonferroni correction indicated that $\dot{V}_E$ increased significantly at each cuff occlusion pressure from CTL exercise ($P < 0.05$, for all). In addition, $\dot{V}_E$ was greater at 80 and 100 mm Hg when compared with 20 mm Hg ($P < 0.05$). $\dot{V}_E$ was greater for men compared with women during exercise and cuff occlusions (sex effect, $P = 0.007$) with no interaction (condition × sex, $P = 0.71$). Respiratory rate (R_R) increased overall with cuff occlusion (condition effect, $P < 0.01$; Fig. 2B), but was not significant for each cuff occlusion pressure when compared with CTL exercise ($P > 0.05$). R_R increased similarly for men and women during exercise and cuff occlusions (sex effect, $P = 0.80$) with no interaction (condition × sex, $P = 0.59$). However, there was no effect of the cuff occlusion pressure on tidal volume (V_T) when compared with CTL exercise (condition effect, $P = 0.61$; Fig. 2C). V_T was greater for men compared with women (sex effect, $P = 0.02$) with no interaction (condition × sex, $P = 0.34$).

Carbon dioxide production ($\dot{V}CO_2$) was greater overall with cuff occlusion (condition effect, $P < 0.05$; Fig. 3A) with significance at all cuff pressures ($P < 0.05$, for all). Men had greater levels of $\dot{V}CO_2$ during exercise and cuff occlusion (sex effect, $P < 0.05$) with no interaction (condition × sex, $P = 0.65$). The ventilatory equivalent for carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) increased with cuff occlusion pressures compared with CTL exercise (condition effect, $P < 0.05$; Fig. 3B). A pairwise comparison with Bonferroni correction indicated that $\dot{V}_E/\dot{V}CO_2$ increased significantly only at 100 mm Hg ($P = 0.047$). There was no difference in $\dot{V}_E/\dot{V}CO_2$ between men and women (sex effect, $P = 0.20$) and no interaction (condition × sex, $P = 0.56$). Partial pressure of end tidal CO_2 ($P_{ET}CO_2$) decreased with cuff occlusion pressures compared with CTL exercise (condition effect, $P < 0.05$;

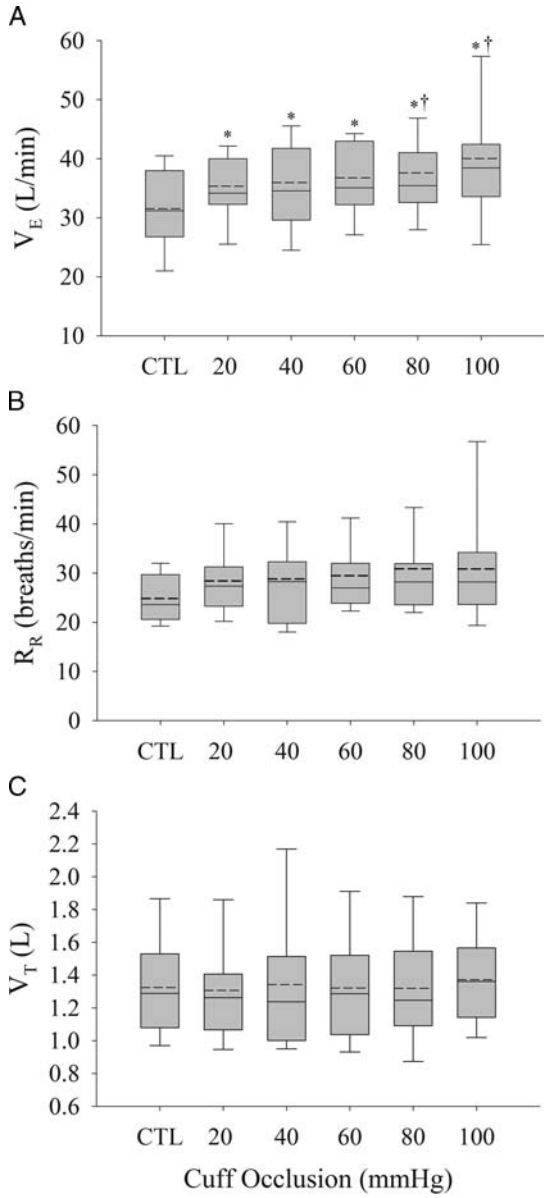

FIGURE 2—Ventilation ($\dot{V}_E$) (A), respiratory rate (R_R) (B), and tidal volume (V_T) (C). $\dot{V}_E$ increased with cuff occlusions (condition effect, $P < 0.05$) with a pairwise comparison Bonferroni correction indicating that $\dot{V}_E$ increased significantly at each pressure from CTL exercise ($P < 0.05$ for all). R_R was elevated with cuff occlusions (condition effect, $P < 0.05$). There was no effect of cuff occlusion on V_T (condition effect, $P = 0.32$). *Mean versus CTL; †Mean versus 20 mm Hg. Dashes represent mean, and vertical lines represent 10th and 90th percentiles.

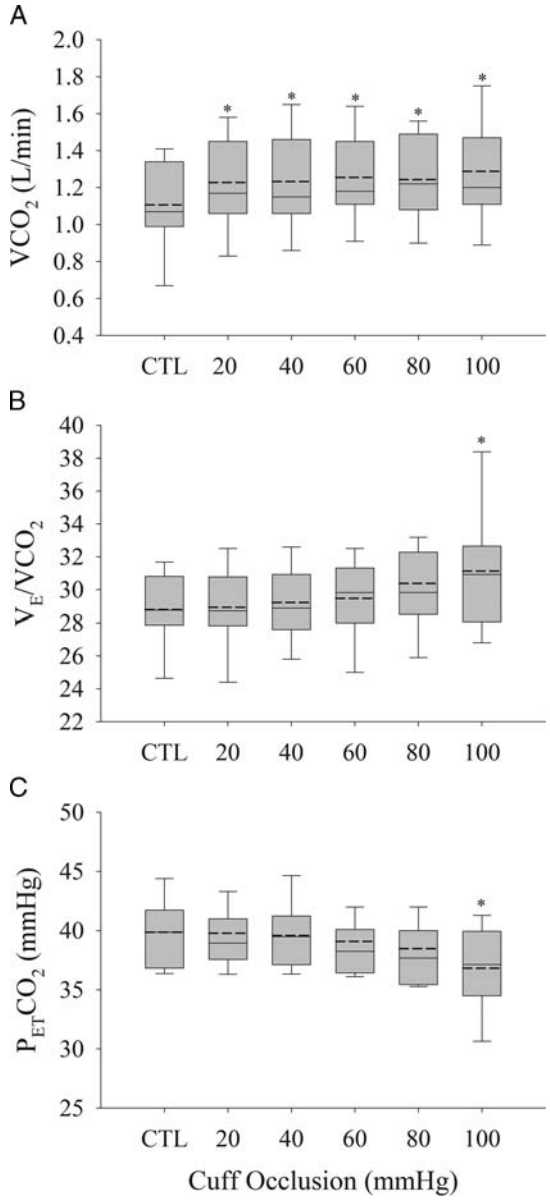

FIGURE 3—Carbon dioxide production ($\dot{V}CO_2$) (A), ventilatory equivalent to $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$) (B), and end tidal CO_2 ($P_{ET}CO_2$) (C). $\dot{V}CO_2$ was greater during cuff occlusion (condition effect, $P < 0.05$) with a pairwise comparison Bonferroni correction indicating significance at all cuff pressures ($P < 0.05$, for all). $\dot{V}_E/\dot{V}CO_2$ was increased with cuff occlusion (condition effect, $P < 0.05$). $P_{ET}CO_2$ decreased with cuff occlusion (condition effect, $P < 0.05$). A pairwise comparison with Bonferroni correction indicated that $P_{ET}CO_2$ decreased significantly only at 100 mm Hg ($P < 0.05$). *Mean versus CTL. Dashes represent mean, and vertical lines represent 10th and 90th percentiles.

Fig. 3C). A pairwise comparison with Bonferroni correction indicated that $P_{ET}CO_2$ decreased significantly only at 100 mm Hg ($P < 0.01$). $P_{ET}CO_2$ was overall elevated in men compared with women (sex effect, $P = 0.02$). RER increased overall from CTL exercise with cuff occlusion pressure (CTL: 0.84 ± 0.10 to 100 mm Hg: 0.96 ± 0.07, condition effect, $P < 0.01$) with significance at all cuff pressures ($P < 0.01$). RER was similar in men and women (0.87 ± 0.10 vs 0.81 ± 0.10 at CTL and 0.98 ± 0.07 vs 0.94 ± 0.07 at 100 mm Hg, sex effect, $P = 0.13$) with no interaction (condition × sex, $P = 0.76$).

Tidal volume to inspiratory time (V_T/T_T) increased overall during cuff occlusion pressure from CTL exercise (condition effect, $P < 0.01$; Fig. 4A), with significance at all cuff pressures ($P < 0.05$). V_T/T_T was overall elevated in men compared with women (sex effect, $P = 0.03$). Total inspiratory time to total respiratory cycle time (T_I/T_{TOT}) was not different from CTL exercise to cuff occlusion pressures (condition effect, $P = 0.08$; Fig. 4B). Men had a greater T_I/T_{TOT} than women (sex effect, $P = 0.05$) with no interaction (condition × sex, $P = 0.97$).

Perceived exertion and breathing. Rating of perceived exertion (RPE) progressively increased from CTL exercise with cuff occlusion pressures ($X^2_2 = 60.1$, $P < 0.05$) with significance between different pressure cuffs (Fig. 5A). RPE was not different for men and women ($P > 0.05$). Dyspnea progressively increased during cuff occlusion pressures from CTL exercise ($X^2_2 = 49.7$, $P < 0.05$) with significance between different cuff pressures (Fig. 5B). Dyspnea was not different for men and women ($P > 0.05$).

DISCUSSION

This study used graded subsystolic venous occlusion of the lower extremity during exercise to cause venous distension

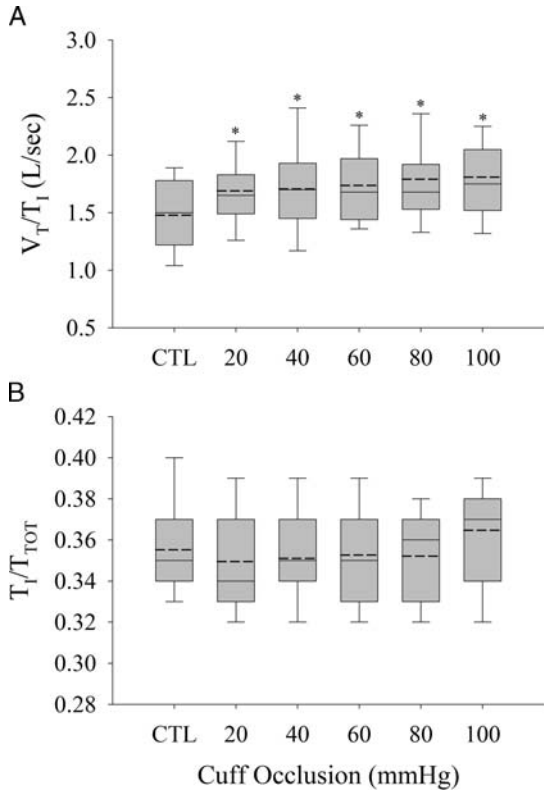

FIGURE 4—Tidal volume to inspiratory time (V_T/T_T) (A) and total inspiratory time to total respiratory cycle time (T_I/T_{TOT}) (B). V_T/T_T increased during cuff occlusion (condition effect, $P < 0.05$) with a pairwise comparison Bonferroni correction demonstrating significance at all pressure cuffs ($P = 0.08$). T_I/T_{TOT} was not different for cuff occlusions (condition effect, $P = 0.03$). *Mean versus CTL. Dashes represent mean, and vertical lines represent 10th and 90th percentiles.

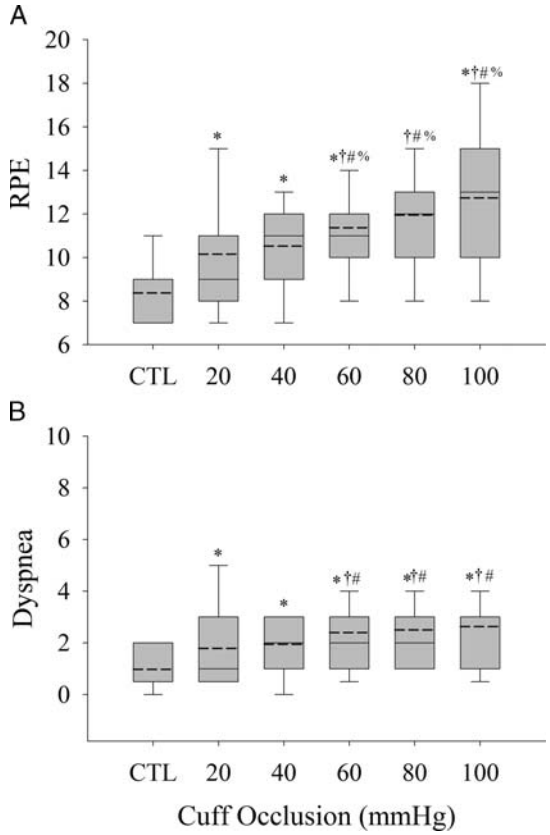

FIGURE 5—Rating of perceived exertion (RPE) (A) and dyspnea (B). RPE progressively increased from CTL exercise with cuff occlusion pressures ($P < 0.05$). Dyspnea progressively increased during cuff occlusions (condition effect, $P < 0.05$). *Mean versus CTL; †Mean versus 20; #Mean versus 40; %Mean versus 60. Dashes represent mean, and vertical lines represent 10th and 90th percentiles.

(30). The novel findings from this study were as follows: 1) graded venous occlusion increased $\dot{V}_E$ with increasing cuff occlusion pressure; 2) the rise in $\dot{V}_E$ was primarily mediated by an increasing R_R with no change in V_T, 3) V_T/T_I increased with venous occlusion with no increase in T_I/T_{TOT}, and 3) both perceived exertion and dyspnea were directly related to the increases in venous occlusion during exercise.

Venous distension increases ventilation. The results from this study indicate that venous distention during low levels of exercise activate skeletal muscle afferents and subsequently increase V_E. This is consistent with current theories for the contribution of group III muscle afferent activity on sympathetic activity and V_E in both humans and animals (17,18,30), and there are numerous lines of evidence suggesting that metabolically sensitive afferents contribute to increased sympathetic activity and increased $\dot{V}_E$ (2,3,23,24,38,39). Furthermore, the increase in $\dot{V}_E$ was due to an increase in R_R and not V_T. V_T/T_I increased progressively without a change in T_I/T_{TOT}, suggesting that muscle afferent stimulation via venous distention may increase respiratory drive (27,28). Importantly, group III/IV skeletal muscle afferents have been implicated in increased R_R in diseased populations. For example, Olson et al. (2014) blocked locomotor muscle afferents via injections of a μ-opioid agonist (fentanyl) in HF patients, which reduced $\dot{V}_E$ by a reduction in R_R (37). Additionally, during afferent inhibition at rest before exercise, HF patients displayed a significant reduction in PaO_2 and an increase in $PaCO_2$, which was not found in the healthy controls (37). The present data indicate that venous distention and potential greater activation of skeletal muscle afferents may contribute to the development of tachypnea. Therefore, it would appear that venous distension contributes to increases in ventilation during low-to-moderate levels of exercise in healthy adults and may play a key role in ventilatory abnormalities in HF.

In the current study, $\dot{V}CO_2$ significantly increased with cuff occlusion at 100 mm Hg, and $P_{ET}CO_2$ decreased significant at 100 mm Hg during exercise. The ventilatory equivalent for carbon dioxide production ($\dot{V}_E/\dot{V}CO_2$) increased across cuff pressures, despite the increase in $\dot{V}CO_2$ indicating ventilation increased to a greater degree with venous distention. Therefore, by activating mechanosensitive skeletal muscle afferents via venous distention during low levels of activity in healthy individuals, we observed elevations in $\dot{V}_E/\dot{V}CO_2$ despite the increases in $\dot{V}CO_2$. This observation is important because exaggerated skeletal muscle afferent feedback (primarily group IV) has been linked to poor ventilatory efficiency which is closely related to disease severity and mortality in patients with chronic disease (4,37).

Importantly, our data demonstrate that skeletal muscle afferents contribute to perceived effort and the development of dyspnea during exercise. Participants in the current study indicated that they perceived the exercise to be harder and their breathing was more labored with the graded cuff occlusion (greater RPE and dyspnea levels, respectively) even at low levels of occlusion (20 and 40 mm Hg). Importantly, perceived exertion progressively increased with most pressure cuff occlusions with the exceptions of 20 to 40 mm Hg and 80 to 100 mm Hg. Our findings are consistent with a previous study that used venous occlusion pressures of 90 mm Hg to cause venous distention during static handgrip exercise (30). Despite the fact that perceived levels of exertion have been linked to central command (10), our data as well as others (30) indicate that information regarding perception of effort can also be influenced by the periphery and, in particular, the skeletal muscle afferents. Because $\dot{V}_E$ increased with an increase in the cuffing pressures compared with the CTL, the increases in dyspnea may also be a direct result of the increases in $\dot{V}_E$.

Dyspnea and fatigue upon exertion are the two most common complaints of HF patients (7,35). Increased afferent feedback from the skeletal muscle (primarily group IV muscle afferents) has been demonstrated to contribute to increases in $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$ and dyspnea in healthy individuals and those with HF (2,3,13,37). Our results are consistent with previous work and indicate that skeletal muscle afferents when activated by venous distention contribute to perceptions of breathlessness during exercise (13). Our analysis of dyspnea indicates that each cuff pressure significantly increased when compared with the control

(exercise only), and the higher cuff pressures were greater than those at 20 and 40 mm Hg. It is important to note that the data reflect responses from healthy volunteers during a low-intensity exercise with dyspnea overall rated low with small but significant increases with cuff occlusion. Although this should be interpreted with caution, clinically, this may suggest that patients sensing an increased breathlessness with low levels of activities, such as walking or stair climbing, might have greater sensory input from skeletal muscle afferents.

Sex differences in ventilation. Several of the whole body gas exchange variables including, $\dot{V}_E$, V_T, $\dot{V}CO_2$ production, and RER were greater for men compared with women during the relative cycling exercise. Several reasons for these differences may exist. It is well established that, even after correction for differences in body height, women have smaller lungs, narrower airways, and weaker respiratory musculature than age-matched men (8,12,14,29,32,42). During maximal cycling exercise, therefore, women have relatively reduced maximal ventilatory capacity; they are at higher risk of developing expiratory flow limitation and dynamic lung hyperinflation, adopt a more rapid and shallow breathing pattern, and have a higher mechanical work of breathing, with evidence of relatively and greater dynamic mechanical constraints on V_T expansion (15,16,31,40,41). In addition, because men had a greater peak work rate, their submaximal work rate was greater (70 W vs 52 W). This, along with physiological and anatomical differences between men and women, would warrant greater $\dot{V}_E$, V_T, and so on in men compared with women during a relative, submaximal exercise.

Notably, there were no sex differences in the ventilatory response to venous distention, and therefore, that data have been pooled for the representation of figures. Activation of the mechanoreflex by passive stretch (20) and activation of the metaboreflex (11) have demonstrated a blunted sympathetic response in women compared with men. This blunted sympathetic response however did not translate to differential activation in muscle afferents contributing to sex differences in the ventilatory response to venous occlusion in this study. The reason for this is not clear, but perhaps there is no sex difference in the population of receptors being activated by venous occlusion in contrast to passive stretch or complete circulatory occlusion. Alternatively, the sex difference in ventilation with venous occlusion may have been masked by the greater ventilatory response to the exercise in men. Overall, this lack of sex difference with venous distention to activate skeletal muscle afferents needs to be further explored.

Limitations. A limitation of this study is that the contribution of group III versus group IV muscle afferents to the $\dot{V}_E$ response during exercise is speculative as afferent neural traffic (group III vs. group IV) is not possible to directly measure in humans. Because of this, the activation of specific populations of afferents activated can only be inferred from animal studies. Although we feel this exercise paradigm along with the venous cuff occlusion caused venous distention and may have predominately activated mechanosensitive skeletal muscle afferents, metabolites were not tested in this study, and it is possible that the metaboreflex may be activated in our paradigm, particularly with the higher cuff pressures when blood perfusion may have been disrupted. Muscle ischemia could have also affected a rise in ventilatory drive if it were present in the lower limbs during subsystolic vascular occlusion. To this point, the role of nociceptor activation associated with cuffing in mediating the observed responses was not measured, and therefore, the contribution of nociceptors to the increases in ventilation and perceived effort cannot be excluded. Furthermore, the current study did not measure intravascular, interstitial, or intramuscular pressure, and therefore, it is unclear how cuff pressure influenced the pressure in each of these compartments.

CONCLUSIONS

In conclusion, skeletal muscle afferents may sense changes in venular structures with changes in either blood volume or pressure in the lower limb and transmit information to the central nervous system regarding changes in vascular conductance or of the extent of vascular bed perfusion and thus of blood flow. In this context, this may be a key site of mediation between the regulation of circulation, V_E, and whole body gas exchange in a healthy adult. Lastly, similar studies in clinical populations with leg edema (35,36), such as HF, may significantly contribute to the importance of group III skeletal muscle afferents to V_E and respiratory drive during exercise and need further exploration.

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