Expiratory threshold loading impairs cardiovascular function in health and chronic heart failure during submaximal exercise

Jordan D. Miller, Sarah J. Hemauer, Curtis A. Smith, Michael K. Stickland, and Jerome A. Dempsey

University of Wisconsin-Madison, John Rankin Laboratory of Pulmonary Medicine, Madison, Wisconsin

Submitted 17 July 2005; accepted in final form 10 March 2006

Miller, Jordan D., Sarah J. Hemauer, Curtis A. Smith, Michael K. Stickland, and Jerome A. Dempsey. Expiratory threshold loading impairs cardiovascular function in health and chronic heart failure during submaximal exercise. J Appl Physiol 101: 213–227, 2006. First published March 30, 2006; doi:10.1152/japplphysiol.00862.2005.—We determined the effects of augmented expiratory intrathoracic pressure (PITP) production on cardiac output (QTOT) and blood flow distribution in healthy dogs and dogs with chronic heart failure (CHF). From a control expiratory PITP excursion of 7 ± 2 cmH2O, the application of 5, 10, or 15 cmH2O expiratory threshold loads increased the expiratory PITP excursion by 47 ± 23, 67 ± 32, and 118 ± 18% (P < 0.05 for all). Stroke volume (SV) rapidly decreased (onset < 10 s) with increases in the expiratory PITP excursion (−2.1 ± 0.5%, −2.4 ± 0.9%, and −3.6 ± 0.7%, P < 0.05), with slightly smaller reductions in QTOT (0.8 ± 0.6, 1.0 ± 1.1, and 1.8 ± 0.8%, P < 0.05) owing to small increases in heart rate. Both QTOT and SV were restored to control levels when the inspiratory PITP excursion was augmented by the addition of an inspiratory resistive load during 15 cmH2O expiratory threshold loading. The highest level of expiratory loading significantly reduced hindlimb blood flow by −5 ± 2% owing to significant reductions in vascular conductance (−7 ± 2%). After the induction of CHF by 6 wk of rapid cardiac pacing at 210 beats/min, the expiratory PITP excursions during nonloaded breathing were not significantly changed (8 ± 2 cmH2O), and the application of 5, 10, and 15 cmH2O expiratory threshold loads increased the expiratory PITP excursion by 15 ± 7, 23 ± 7, and 31 ± 7%, respectively (P < 0.05 for all). Both 10 and 15 cmH2O expiratory threshold loads significantly reduced SV (−3.5 ± 0.7 and −4.2 ± 0.7%, respectively) and QTOT (−1.7 ± 0.4 and −2.5 ± 0.4%, P < 0.05) after the induction of CHF, with the reductions in SV predominantly occurring during inspiration. However, the augmentation of the inspiratory PITP excursion now elicited further decreases in SV and QTOT. Only the highest level of expiratory loading significantly reduced hindlimb blood flow (−4 ± 2%) as a result of significant reductions in vascular conductance (−5 ± 2%). We conclude that increases in expiratory PITP production-similar to those observed during severe expiratory flow limitation-reduce cardiac output and hindlimb blood flow during submaximal exercise in health and CHF.

cardiac output; blood flow distribution; exercise; expiratory flow limitation; heart failure

EXPIRATORY FLOW LIMITATION (EFL) is a phenomenon that occurs when expiratory airflow can no longer be increased by further elevations in intrathoracic pressure (PITP) (30). Although EFL is most prevalent in patients with chronic obstructive pulmonary disease during exercise, where EFL develops primarily as a result of a loss of lung recoil, highly trained athletes during near-maximal exercise (13) and patients with chronic heart failure (CHF) during submaximal exercise (11) also frequently experience EFL. Although the highly trained athlete develops EFL as a result of extremely high expiratory airflows that approach the maximal capacities of the respiratory system (13), the patient with CHF may suffer from EFL as a result of increases in airway resistance due to bronchial cuffing or airway hyperreactivity (6) and may also have a loss of alveolar recoil as a result of a smoking history (11, 28).

Regardless of etiology, EFL ultimately limits further increases in alveolar ventilation and results in increases in both expiratory muscle pressure production and work (25). However, our understanding of the cardiovascular consequences of increases in PITP during exercise remains meager. Early investigations used high levels (15–30 cmH2O) of continuous positive airway pressure to increase PITP during submaximal exercise in healthy humans, which resulted in significant reductions in stroke volume and cardiac output ranging from 15 to 25% (4). However, the application of continuous positive airway pressure does not mimic the breathing mechanics present during physiological EFL, and more recent investigations using mild levels of expiratory threshold loading (10 cmH2O) have suggested a smaller effect of expiratory loading alone on stroke volume and cardiac output in healthy humans (34).

Whether augmented respiratory muscle pressure production contributes to the blunted cardiac output and locomotor limb blood flow responses to exercise (18, 35, 36) in CHF is unclear. Direct measurements of respiratory muscle blood flow in animal models of CHF have shown markedly elevated levels of respiratory muscle blood flow (24). That both the inspiratory and expiratory muscles can “steal” blood flow from the locomotor limb is supported by the observation that the activation of the respiratory muscle metaboreflex via the injection of lactic acid into these vascular beds elicits a reflex vasoconstriction in the exercising locomotor limb in healthy dogs (32). However, whether a more physiological stimulus such as increases in expiratory muscle work can elicit further reductions in cardiac output and/or locomotor limb blood flow in CHF is unknown.

We used varying levels of expiratory threshold loading to mimic EFL in chronically instrumented dogs during submaximal exercise to the test the following hypotheses: 1) Augmenting the expiratory PITP excursion is detrimental to the cardiac response to exercise and will result in rapid (onset < 10 s) reductions in cardiac output and stroke...
Table 1. Summary of cardiovascular consequences of expiratory threshold loading during treadmill exercise at 2.5 mph/5% grade in all dogs while healthy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (Absolute value)</th>
<th>ETL − 5 cmH₂O (Δ from control)</th>
<th>ETL − 10 cmH₂O (Δ from control)</th>
<th>ETL − 15 cmH₂O (Δ from control)</th>
<th>IL + ETL − 15 cmH₂O (Δ from control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTOT, l/min</td>
<td>5.97 ± 0.17</td>
<td>−0.05 ± 0.04*</td>
<td>−0.06 ± 0.07*</td>
<td>−0.11 ± 0.05*</td>
<td>−0.01 ± 0.06</td>
</tr>
<tr>
<td>SV, ml/beat</td>
<td>42.1 ± 0.9</td>
<td>−0.9 ± 0.2*</td>
<td>−1.0 ± 0.4*</td>
<td>−1.5 ± 0.3*</td>
<td>0.0 ± 0.3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>142 ± 2</td>
<td>2 ± 1</td>
<td>2 ± 2</td>
<td>3 ± 2*</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>90 ± 1</td>
<td>−1.7 ± 1</td>
<td>0 ± 1</td>
<td>2 ± 1</td>
<td>3 ± 2*</td>
</tr>
<tr>
<td>Gsys, l/min/mmHg⁻¹</td>
<td>66.3 ± 1.5</td>
<td>0.6 ± 1</td>
<td>−0.5 ± 0.5</td>
<td>−2.6 ± 0.3*</td>
<td>−2.5 ± 1.0*</td>
</tr>
<tr>
<td><strong>Peripheral effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QHL, l/min</td>
<td>1.20 ± 0.03</td>
<td>0.00 ± 0.02</td>
<td>0.01 ± 0.03</td>
<td>−0.06 ± 0.02*</td>
<td>−0.10 ± 0.02*</td>
</tr>
<tr>
<td>Ghl, l/min/mmHg⁻¹</td>
<td>13.3 ± 0.5</td>
<td>0.2 ± 0.5</td>
<td>0.1 ± 0.4</td>
<td>−0.9 ± 0.3*</td>
<td>−1.5 ± 0.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. QTOT, cardiac output; SV, stroke volume; HR, heart rate; MAP, mean arterial pressure; Gsys, systemic vascular conductance; Qhl, hindlimb blood flow; Ghl, hindlimb vascular conductance. Control values represent the grand mean from all trials combined. None of the control measurements for any intervention were significantly different from one another. For each intervention, the absolute change (Δ) from its immediately preceding the control condition is presented. *P < 0.05 for each intervention vs. its own respective control.

Fig. 1. Raw data traces showing the cardiovascular consequences of 15 cmH₂O expiratory threshold loading in 1 representative healthy dog. Note that stroke volume decreases rapidly after the application of the 15 cmH₂O expiratory threshold load and remains depressed for the duration of the intervention. Hindlimb blood flow is markedly reduced ~15 s after the application of the expiratory load and remains depressed despite increases in mean arterial pressure.
volume during exercise in both healthy dogs and dogs with pacing-induced CHF. 2) Augmenting the expiratory P ITP excursion is detrimental to the locomotor limb hyperemic response to exercise and will result in time-dependent reductions in both absolute locomotor limb blood flow and the fraction of cardiac output delivered to the locomotor limb during exercise in healthy dogs and dogs with pacing-induced CHF.

Fig. 2. Effects of 5 and 15 cmH2O expiratory threshold loading on cardiac function over time in all 5 dogs while healthy [change in mean intrathoracic pressure (P ITP) = 1.3 ± 0.3 cmH2O and 4.8 ± 0.5 cmH2O, respectively; average of 3 ± 1 trials per dog]. Note that cardiac output is rapidly reduced owing to reductions in stroke volume (onset < 15 s) with even small increases in expiratory pressure production. EPAP, expiratory positive airway pressure. Significant main effects and absolute values during control conditions are reported in Table 1. *P < 0.05 vs. control conditions.
METHODS

Chronic Instrumentation

All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Madison Medical School and conducted in accordance with the American Physiological Society’s “Guiding Principles in the Care and Use of Animals.” Five female mixed-breed hound dogs weighing between 19 and 23 kg were trained to run on a motorized treadmill. After training, two surgical procedures separated by at least 3 wk were required to instrument the dogs for study. General anesthesia and strict sterile techniques were used during all surgical procedures, and appropriate antibiotics and analgesics were used postoperatively. A chronic tracheostomy was created in all of the dogs via a midline incision caudal to the larynx and the subsequent removal of the ventral aspect of four or five cartilaginous rings. Ultrasonic, transit-time flow probes (Transonic, Ithaca, NY) were placed around the ascending aorta (n = 5 dogs) and terminal aorta (n = 4 dogs) for the measurement of cardiac output and hindlimb blood flow, respectively. A catheter was placed in the abdominal aorta via the cannulation of a small side branch of the femoral artery for the measurement of arterial blood pressure. A 7.5-mm-diameter flat-headed pressure transducer (Konigsberg Instruments, Pasadena, CA) was implanted in the intrathoracic space between the 9th and 10th ribs for the direct measurement of PITP. A bipolar pacing lead was sutured to the epicardium of the right ventricle and connected to a pacemaker (Medtronic, Minneapolis, MN) implanted in a subcutaneous tissue pocket for the induction of tachycardia-induced CHF. All cables, catheters, and electrode wires were exteriorized 3–5 cm lateral to the caudal thoracic spine.

All signals were digitized and stored on the hard drive of a personal computer for subsequent analysis and on a polygraph (AstroMed K2G, West Warwick, RI). All ventilatory, blood flow, and blood pressure data were analyzed on a beat-by-beat basis, or by signal-averaging each variable over the course of a breath by use of custom analysis software developed in our laboratory.

Protocols

Timeline of data collection. The animals underwent both surgical procedures to complete their chronic instrumentation and were allowed to recover for ~2 wk after the second surgery. Experimental testing sessions were separated by at least 24 h with no more than eight trials performed per session. Each animal performed the protocol described below over the course of 2–3 wk while healthy. CHF was then induced by rapid ventricular pacing at 210 beats/min for 3–6 wk. CHF was defined as an ejection fraction < 45% with a considerably blunted cardiac output and stroke volume response to a fixed exercise workload (2.5 mph/5% grade). The protocols were then repeated while the animal was in heart failure over the course of 1–2 wk. The baseline hemodynamic consequences of the pacing-induced heart failure are reported in Table 1.

Animal preparation for study. The animal was guided onto a motorized treadmill and stood quietly while all implanted instrumentation was connected. The tracheostomy was cannulated with a 4.0- to 6.0-mm ID cuffed endotracheal tube. Airflow was measured by a heated pneumotachograph that was connected to the endotracheal tube. The treadmill was then started, and the animal exercised at 2.5 mph/5% grade for a minimum of 4 min, or until cardiac output, hindlimb blood flow, blood pressure, and minute ventilation reached a steady state. At this point, one of the following two protocols was initiated. If the animal exhibited any signs of distress or discomfort (excessive head movement, unwillingness to continue exercise despite encouragement, etc.), the intervention and/or exercise bout was immediately stopped.

EXPIRATORY THRESHOLD LOAD IN THE TREATMENT OF CHF. HOW DO AUGMENTED EXPIRATORY PRESSURES AFFECT CARDIOVASCULAR FUNCTION AND ITS DISTRIBUTION? The tubing connected to the nonrebreathing valve was attached to posts on a cart placed immediately next to the treadmill. Once steady-state conditions were reached, expiratory threshold loads of 5, 10, or 15 cmH2O were placed on the expiratory arm of the breathing circuit for a minimum of 30 s (see Fig. 1).

COMBINED INSPIRATORY AND EXPIRATORY LOADING: IS CARDIOVASCULAR FUNCTION DICTATED BY MEAN PITP? A fixed inspiratory resistance (~40 cmH2O·1·s−1) was placed on the inspiratory arm of the breathing circuit in addition to a 15 cmH2O expiratory threshold valve placed on the expiratory side of the breathing apparatus (see Fig. 2). This expiratory load was sufficient enough to cause a positive shift in mean PITP of at least 50% of that elicited by inspiratory loading alone, while leaving the magnitude of the inspiratory pressure excursion relatively unaffected (see Fig. 1).

Data Analysis

The transient cardiovascular responses to alterations in PITP were analyzed with custom-made computer software on a beat-by-beat basis for cardiac output, heart rate, stroke volume, mean arterial pressure, terminal aortic blood flow, and regional and systemic vascular conductances. Transpulmonary pressure was calculated as mouth pressure minus PTP. For each individual variable, 5-s averages were obtained during the control period and for 1–2 min after the onset of each intervention. The change from baseline for each 5-s block during expiratory loading or combined inspiratory and expiratory loading was compared with the 5-s blocks from the preceding control condition by a two-way ANOVA with repeated measures and Dunnett’s post hoc test. Statistical significance was considered to be present when P < 0.05. Data are presented as means ± SE in all figures, tables, and text.

RESULTS

Healthy Dogs

Changes in cardiovascular function over time in response to expiratory loading. During control conditions, the inspiratory and expiratory PTP excursions averaged −14 ± 3 and 7 ± 2 cmH2O, respectively. The addition of a 5, 10, or 15 cmH2O expiratory threshold load resulted in increases in the expiratory PTP excursion of 47 ± 23% (P < 0.05), 67 ± 32% (P < 0.05), and 118 ± 18% (P < 0.05), respectively. The magnitude of the inspiratory PTP excursion was not significantly affected by the addition of an expiratory load.

The raw data traces from one representative trial in a healthy animal are shown in Fig. 1, with the mean cardiac responses to increases in the expiratory PTP excursion over time in five dogs shown in Fig. 2. Steady-state cardiac output was significantly reduced by all three levels of expiratory loading owing to significant reductions in stroke volume (−2 ± 1, −2 ± 1, and −4 ± 1%, respectively, P < 0.05 for all) (see Figs. 1–2 and Table 1). A compensatory tachycardia was only evident

Fig. 3. Effects of 5 and 15 cmH2O expiratory threshold loading on systemic and hindlimb vascular conductances over time in 4 dogs with terminal aortic flow probes while healthy (average of 3 ± 1 trials per dog). Note that hindlimb blood flow is significantly decreased with 15 cmH2O expiratory threshold loading (−5 ± 2%) owing to significant reductions in hindlimb vascular conductance (−7 ± 2%). Significant main effects and absolute values during control conditions are reported in Table 1. *P < 0.05 vs. control conditions.
EXPIRATORY LOADING IMPAIRS CARDIOVASCULAR FUNCTION IN HEALTH AND CHF

Mean Arterial Pressure
(Δ from mean, mm Hg)

Hindlimb Vascular Conductance
(Δ from mean, L·min⁻¹·mm Hg⁻¹)

Systemic Vascular Conductance
(Δ from mean, L·min⁻¹·mm Hg⁻¹)

Hindlimb Blood Flow
(Δ from mean, L·min⁻¹)

Cardiac Output
(Δ from mean, L·min⁻¹)

5 cm H₂O EPAP

15 cm H₂O EPAP
significant decreases from end-expiratory levels during the
In contrast, stroke volume and mean arterial pressure were
in systemic vascular conductance (\(\text{SV} \times \text{MAP} \div \text{CO} \))

blood gas parameters in response to 5, 10, and 15 cmH2O
(15 cmH2O expiratory load resulted in significant reductions in stroke volume and mean arterial pressure over the course of the breath, whereas cardiac output was significantly increased during expiration. \(Q_{\text{TOT}}\), cardiac output; \(\text{SV}\), stroke volume; \(\text{MAP}\), mean arterial blood pressure; \(\text{EELV-C}\) and \(\text{EELV-EL}\), end-expiratory lung volume during control conditions and expiratory loading, respectively. \(\*P < 0.05\) for peak or nadir values vs. end-expiratory levels; \(\dagger P < 0.05\) for peak or nadir values vs. control conditions.

## Table 2. Ventilatory and blood gas responses to expiratory threshold loading during exercise at 2.5 mph/5% grade in all dogs while healthy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (Absolute value)</th>
<th>ETL = 5 cmH2O ((\Delta) from control)</th>
<th>ETL = 10 cmH2O ((\Delta) from control)</th>
<th>ETL = 15 cmH2O ((\Delta) from control)</th>
<th>IL + ETL = 15 cmH2O ((\Delta) from control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(V_e), l/min</td>
<td>15.2 ± 0.4</td>
<td>-0.2 ± 0.8</td>
<td>-3.0 ± 0.5*</td>
<td>-2.5 ± 0.3*</td>
<td>14.8 ± 1.7</td>
</tr>
<tr>
<td>(V_t), ml</td>
<td>337 ± 12</td>
<td>73 ± 18*</td>
<td>20 ± 13</td>
<td>55 ± 16</td>
<td>298 ± 38</td>
</tr>
<tr>
<td>(f_s), breaths/min</td>
<td>45 ± 3</td>
<td>7 ± 3*</td>
<td>-11 ± 2*</td>
<td>-15 ± 3*</td>
<td>49 ± 6</td>
</tr>
<tr>
<td>(\text{Ti}/\text{Ttot})</td>
<td>0.59 ± 0.03</td>
<td>0.05 ± 0.02</td>
<td>0.07 ± 0.02*</td>
<td>0.07 ± 0.02*</td>
<td>-0.04 ± 0.01</td>
</tr>
<tr>
<td>(\text{pH}) units</td>
<td>7.410 ± 0.013</td>
<td>-0.006 ± 0.003</td>
<td>-0.009 ± 0.005*</td>
<td>0.018 ± 0.009*</td>
<td>7.370 ± 0.009*</td>
</tr>
<tr>
<td>(\text{PCO}_2), Torr</td>
<td>31.1 ± 1.6</td>
<td>1.0 ± 0.2</td>
<td>1.9 ± 0.4</td>
<td>2.9 ± 0.4*</td>
<td>7.7 ± 0.9*</td>
</tr>
<tr>
<td>(\text{PO}_2), Torr</td>
<td>90.6 ± 4.0</td>
<td>1.3 ± 3.9</td>
<td>-3.6 ± 3.6</td>
<td>-6.5 ± 1.5</td>
<td>-23.8 ± 2.5*</td>
</tr>
<tr>
<td>([\text{HCO}_3^-])</td>
<td>19.7 ± 0.7</td>
<td>0.1 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>0.2 ± 0.2</td>
<td>1.2 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. \(V_e\), minute ventilation; \(V_t\), tidal volume; \(f_s\), breathing frequency; \(\text{Ti}/\text{Ttot}\), expiratory time/total breath time; \(\text{pH}\), \(\text{PCO}_2\), \(\text{PO}_2\), and \([\text{HCO}_3^-]\), bicarbonate concentration in arterial blood. Control values represent the grand mean from all trials combined. None of the control measurements for any intervention were significantly different from one another. For each intervention, the absolute change from the control for those trials is presented. \(\*P < 0.05\) for each intervention vs. its own respective control.

during 15 cmH2O expiratory threshold loading (2 ± 1%, \(P < 0.05\); see Fig. 2).

As reported in Table 1 and Fig. 2, mean arterial pressure was significantly elevated only during 15 cmH2O expiratory threshold loading (2 ± 1%, \(P < 0.05\)) owing to significant reductions in systemic vascular conductance (−4 ± 1%, \(P < 0.05\), Fig. 3). Hindlimb blood flow and vascular conductance were also significantly reduced by −5 ± 2 and −7 ± 2%, respectively (\(P < 0.05\) for both, see Fig. 3 and Table 1).

Changes in minute ventilation, breathing pattern, and arterial blood gas parameters in response to 5, 10, and 15 cmH2O expiratory threshold loading are reported in Table 2. Briefly, minute ventilation was significantly reduced during both 10 and 15 cmH2O expiratory threshold loading owing exclusively to reductions in breathing frequency, whereas tidal volume increased slightly (but not significantly) during both levels of expiratory loading. The expiratory duty cycle (expiratory time/total breath time) increased significantly with all three levels of expiratory loading (see Table 2). Transpulmonary pressure at zero flow of 1 cmH2O and a small positive shift in transpulmonary pressure at zero flow of 1 ± 2 cmH2O (\(P = \text{NS}\)). Combined inspiratory and expiratory loading did not significantly affect left ventricular stroke volume, heart rate, or cardiac output (see Table 1).

### CHF Dogs

Changes in cardiovascular function over time. During control conditions, the inspiratory and expiratory \(P_{\text{ETP}}\) excursions averaged −13 ± 2 and 8 ± 2 cmH2O, respectively. The addition of 5, 10, or 15 cmH2O expiratory threshold loads resulted in increases in the peak expiratory \(P_{\text{ETP}}\) excursion of 15 ± 7% (\(P < 0.05\)), 23 ± 7% (\(P < 0.05\)), and 31 ± 7% (\(P < 0.05\)), respectively, and resulted in increases in mean \(P_{\text{ETP}}\) over the course of the entire breath of 1.2 ± 0.3 (\(P < 0.05\)), 2.1 ± 1.6 (\(P < 0.05\)), and 2.6 ± 0.2 cmH2O (\(P < 0.05\)). The magnitude of the inspiratory \(P_{\text{ETP}}\) excursion was not significantly affected across any of the expiratory loaded conditions relative to nonloaded breathing conditions.

The raw data traces from one representative trial in an animal after the induction of CHF are shown in Fig. 5, with the mean cardiac responses to increases in the expiratory \(P_{\text{ETP}}\) excursion over time in five dogs shown in Fig. 6. Steady-state cardiac output was significantly reduced by both 10 and 15
219

EXPIRATORY LOADING IMPAIRS CARDIOVASCULAR FUNCTION IN HEALTH AND CHF

J Appl Physiol • VOL 101 • JULY 2006 • www.jap.org

Percentage of breath

Cardiac Output
(Δ from value at EELV, L min⁻¹)

Stroke Volume
(Δ from value at EELV, mL beat⁻¹)

Mean Arterial Pressure
(Δ from value at EELV, mm Hg)

Intrathoracic Pressure
(cm H₂O)

Mouth Pressure
(cm H₂O)

* Control Conditions
† Expiratory Loading

Qₜot_EELV-C = 5.518 + 0.739 L min⁻¹
Qₜot_EELV-EL = 5.200 + 0.766 L min⁻¹
SVₑELV-C = 40.2 + 0.5 mL beat⁻¹
SVₑELV-EL = 38.6 + 0.5 mL beat⁻¹
MAPₑELV-C = 86 + 4 mm Hg
MAPₑELV-EL = 88 + 4 mm Hg
cmH₂O expiratory threshold loads owing to significant reductions in stroke volume of 3 ± 1 and 5 ± 1%, respectively (see Figs. 5 and 6 and Table 3, P < 0.05 for all). A compensatory tachycardia was only evident during 15 cmH₂O expiratory threshold loading (see Fig. 6, P < 0.05).

The application of a 15 cmH₂O expiratory threshold load resulted in significant reductions in systemic and hindlimb vascular conductance of −4 ± 1 and 4 ± 2%, respectively (P < 0.05; see Fig. 7), with the latter resulting in significant reductions in hindlimb blood flow (5 ± 2%, P < 0.05 see Fig. 5).

Changes in minute ventilation, breathing pattern, and arterial blood gas parameters in response to 5, 10, and 15 cmH₂O expiratory threshold loading are reported in Table 4. Briefly, minute ventilation was significantly reduced during 5 and 15 cmH₂O expiratory threshold loading owing exclusively to reductions in breathing frequency. Tidal volume was significantly increased during 10 and 15 cmH₂O expiratory loading. The expiratory duty cycle (expiratory time/total breath time) increased significantly with 5, 10, and 15 cmH₂O by 7 ± 2, 9 ± 3, and 12 ± 2%, respectively. Transpulmonary pressure at zero flow increased by 1.7 ± 0.7 cmH₂O (P = NS), 2.8 ± 1.1 cmH₂O (P = NS), and 3.7 ± 0.8 cmH₂O (P < 0.05) with 5, 10, and 15 cmH₂O expiratory loading, respectively. Arterial PCO₂, PO₂, and HCO₃⁻ concentration were not significantly affected by any level of expiratory threshold loading.

**Within-breath changes in cardiac function.** During control conditions, cardiac output, heart rate, and mean arterial pressure did not vary significantly over the course of a breath, although stroke volume was significantly decreased during the inspiratory phase of the breath (see Fig. 8). In contrast to control conditions, increasing the expiratory PEEP excursion by the addition of a 15 cmH₂O expiratory threshold load resulted in significant decreases in cardiac output during the inspiratory phase. Note that cardiac output, stroke volume, and hindlimb blood flow were all markedly reduced after the application of a 15 cmH₂O expiratory threshold load.

Fig. 5. Raw data traces showing the cardiovascular consequences of 15 cmH₂O expiratory threshold loading in 1 representative dog with chronic heart failure (CHF). Note that cardiac output, stroke volume, and hindlimb blood flow are all markedly reduced after the application of a 15 cmH₂O expiratory threshold load.
phase of the breath \((P < 0.05\) vs. end-expiratory levels, see Fig. 6). Increasing the expiratory \(P_{EPAP}\) excursion also significantly increased the magnitude of the inspiratory reductions in stroke volume (see Fig. 8) but had no effect on changes heart rate over the course of a breath. Reductions in mean arterial pressure lagged slightly behind changes in cardiac output, with the maximal reductions in mean arterial pressure occurring during early expiration \((P < 0.05\) vs. end-expiratory levels).

Fig. 6. Effects of 5 and 15 cm\(\text{H}_2\text{O}\) expiratory threshold loading on cardiac function over time in all 5 dogs after the induction of chronic heart failure (change in mean \(P_{EPAP} = 0.8 \pm 0.5\) cm\(\text{H}_2\text{O}\) and 2.3 \(\pm 1.1\) cm\(\text{H}_2\text{O}\), respectively; average of 3 \(\pm 1\) trials per dog). Note that 5 cm\(\text{H}_2\text{O}\) expiratory threshold loading has no effect on stroke volume or cardiac output. The reductions in stroke volume with 15 cm\(\text{H}_2\text{O}\) expiratory threshold loading are more delayed (–25–30 s delay) after the induction of CHF. *\(P < 0.05\) for peak or nadir values vs. end-expiratory levels.
Changes in cardiac function over time in response to inspiratory and combined inspiratory and expiratory loading. The mean cardiovascular and ventilatory responses to inspiratory loading and combined inspiratory and expiratory loading from four CHF dogs with terminal aortic flow probes are reported in Table 3 and in Table 4, respectively. Compared with control conditions, combined loading increased the inspiratory and expiratory P_{ITP} excursions to 191 ± 6 and 202 ± 42% of control conditions, respectively (P < 0.05 for both). This resulted in a net shift in mean P_{ITP} of −2 ± 3 cmH_{2}O (P = NS vs. control) and a small shift in transpulmonary pressure at zero flow of 2 ± 2 cmH_{2}O (P = NS). Stroke volume was significantly reduced by combined inspiratory and expiratory loading (see Table 3). Cardiac output was also significantly decreased despite the presence of significant increases in heart rate (P < 0.05 for both conditions; see Table 2).

Effects of expiratory loading on cardiovascular function at rest. Only a 5 cmH_{2}O expiratory threshold load was tolerated by all of the animals at rest, which elicited an increase in the expiratory P_{ITP} excursion of 1.6 ± 0.8 cmH_{2}O while the animals were healthy and 4.0 ± 1.5 cmH_{2}O after the induction of CHF (P < 0.05 for both). None of the steady-state cardiovascular parameters measured were significantly affected by the application of a 5 cmH_{2}O expiratory threshold load while the animals were healthy or after the induction of CHF.

DISCUSSION

The main findings of the present investigation can be summarized as follows: 1) In the submaximally exercising healthy dog, 5, 10, and 15 cmH_{2}O expiratory threshold loading elicited rapid (onset < 10 s) reductions in cardiac output (1–2%) and stroke volume (2–4%), although only 15 cmH_{2}O reduced hindlimb blood flow (~5%) and vascular conductance (~5%). 2) Augmenting the inspiratory P_{ITP} excursion during 15 cmH_{2}O expiratory threshold loading restored cardiac output and stroke volume to control levels, although hindlimb blood flow and vascular conductance remained depressed. 3) In the submaximally exercising dog with heart failure, the application of 10 and 15 cmH_{2}O expiratory threshold loading significantly reduced cardiac output (2–3%) and stroke volume (3–4%), although only 15 cmH_{2}O significantly reduced hindlimb blood flow (~4%) and vascular conductance (~5%). 4) In contrast to the healthy dog, augmenting the inspiratory P_{ITP} excursion during 15 cmH_{2}O expiratory threshold loading in the CHF dog resulted in further reductions in cardiac output, stroke volume, hindlimb blood flow, and vascular conductance. Collectively, these data strongly suggest that augmented expiratory pressure has deleterious effects on cardiovascular function during exercise in both health and CHF.

Expiratory threshold loading impairs cardiac function in healthy dogs during exercise by reducing cardiac preload. In the present investigation, relatively small increases in expiratory P_{ITP} production (~3 cmH_{2}O) significantly reduced cardiac output and stroke volume in healthy dogs during submaximal exercise, with greater increases in expiratory P_{ITP} resulting in reductions in stroke volume as large as ~10% (see Fig. 9). Our observations that these reductions in stroke volume occur rapidly (onset < 10 s) and are directionally opposite to changes in systemic oxygen demand suggest that increases in the magnitude of the expiratory P_{ITP} excursion may mechanically constrain cardiac filling by reducing the transmural pressure gradient across the ventricles during diastole.

Our reductions in stroke volume (5–10%) with severe expiratory loading are comparable to those observed by Stark-Leyva et al. (34) (approximately ~7%) during cycling exercise in the healthy human, but considerably smaller than those observed in anesthetized animals in response to increases in P_{ITP} resulting from either continuous or intermittent positive pressure ventilation [which typically report 20% (23) to 40% (16, 20) reductions]. This discordance can likely be explained by three main factors: 1) intact, nonobtundned reflexes in unanesthetized humans and animals (1, 2) the presence of the peripheral skeletal muscle pump forcing blood centrally and counteracting the increases in right atrial pressure resulting from expiratory loading during exercise (7), and 3) an unaffected inspiratory P_{ITP} excursion, which likely serves to facilitate venous return during the inspiratory phase of the breath (21).

During control, nonloaded breathing conditions in the healthy dog, we did not observe any significant within-breath changes in cardiac output or stroke volume in response to the normally produced inspiratory and expiratory P_{ITP} excursions. However, increasing the expiratory P_{ITP} excursion resulted in
Fig. 7. Effects of 5 and 15 cmH₂O expiratory threshold loading on systemic and hindlimb vascular conductances over time in 4 dogs with terminal aortic flow probes after the induction of CHF (average of 3 ± 1 trials per dog). Note that hindlimb blood flow is significantly decreased only with 15 cmH₂O expiratory threshold loading owing to significant reductions in hindlimb vascular conductance. Significant main effects and absolute values during control conditions are reported in Table 1.
significant reductions in stroke volume during inspiration, whereas cardiac output was significantly increased during expiration owing solely to increases in heart rate. That these inspiratory reductions in stroke volume are not the primary cause for the reductions in steady-state stroke volume and cardiac output is supported by the observation that combined inspiratory and expiratory loading conditions do not have an effect on stroke volume or cardiac output. Instead, our data support the postulate that the increases in cardiac output during the expiratory phase of the breath result in a loss of central blood volume (5, 10) that is not regained during the ensuing inspiratory phase of the breath because of the relative prolongation of the expiratory phase of the breath. This notion is supported by the recent work of Stark-Leyva et al. (34) in healthy, exercising humans, which demonstrated that progressive hyperinflation during expired loading conditions, which increases the negativity of the inspiratory PitP excursion, reduces the detrimental effect of increases in the expiratory PitP excursion on steady-state stroke volume and cardiac output.

**Table 4. Ventilatory and blood gas responses to expiratory threshold loading during exercise at 2.5 mph/5% grade after the induction of chronic heart failure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control ( Absolute value)</th>
<th>ETL = 5 cm H2O (Δ from control)</th>
<th>ETL = 10 cm H2O (Δ from control)</th>
<th>ETL = 15 cm H2O (Δ from control)</th>
<th>IL + ETL = 15 cm H2O (Δ from control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇E, l/min</td>
<td>16.4±0.6</td>
<td>−2.4±0.6*</td>
<td>−0.8±1.4</td>
<td>−2.8±1.0*</td>
<td>14.8±1.7</td>
</tr>
<tr>
<td>Vt, ml</td>
<td>260±3</td>
<td>14±7</td>
<td>58±15*</td>
<td>64±20*</td>
<td>298±38</td>
</tr>
<tr>
<td>s, breaths/min</td>
<td>63±2</td>
<td>−12±4*</td>
<td>−13.8*</td>
<td>−22±9*</td>
<td>49±6</td>
</tr>
<tr>
<td>Ts/Ttot</td>
<td>0.58±0.02</td>
<td>0.04±0.01</td>
<td>0.05±0.02*</td>
<td>0.07±0.01*</td>
<td>−0.02±0.02</td>
</tr>
<tr>
<td>pH, units</td>
<td>7.428±0.003</td>
<td>−0.018±0.006</td>
<td>−0.019±0.007</td>
<td>−0.029±0.006*</td>
<td>−0.058±0.009*</td>
</tr>
<tr>
<td>Pco2, Torr</td>
<td>28.5±0.3</td>
<td>1.2±0.6</td>
<td>0.5±1.6</td>
<td>2.3±1.0</td>
<td>4.2±2.5</td>
</tr>
<tr>
<td>Po2, Torr</td>
<td>94.1±3.8</td>
<td>−0.7±3.1</td>
<td>−0.4±4.8</td>
<td>−1.4±2.9</td>
<td>−15.4±3.6*</td>
</tr>
<tr>
<td>[HCO3−]</td>
<td>18.6±0.3</td>
<td>−0.1±0.4</td>
<td>−0.6±0.8</td>
<td>0.1±0.4</td>
<td>0.2±0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. Control values represent the grand mean from all trials combined. None of the control measurements for any intervention were significantly different from one another. For each intervention, the absolute change from the control for those trials is presented. *P < 0.05 for each intervention vs. its own respective control.

Expiratory threshold loading reduces locomotor limb blood flow in both healthy dogs and dogs with CHF. The addition of the highest expiratory load (15 cmH2O) significantly reduced hindlimb blood flow due to significant reductions in vascular conductance in these animals both while healthy and after the induction of CHF. The reductions in hindlimb vascular conductance appear to be due in part to a systemic sympathoexcitatory response to increases in expiratory PitP and expiratory muscle work in our animals both while healthy and after the induction of CHF. Furthermore, the percent changes in hindlimb vascular conductance were approximately double those observed in systemic vascular conductance (~3% reduction in systemic conductance vs. a ~6% reduction in hindlimb vascular conductance).

It is possible that the reductions in hindlimb vascular conductance with increases in expiratory PitP production are the result of reflex-mediated increases in sympathetic outflow originating from the activation of type III and IV thin-fiber afferents in the expiratory muscles (22), as the injection of lactic acid into the expiratory muscle vascular bed results in sympathetically-mediated reductions in locomotor limb blood flow in the resting and exercising healthy dog (32). However, we cannot exclude the possibility that increases in expiratory PitP activated the cardiopulmonary and aortic baroreflexes (2), both of which would send the sympathoexcitatory signal of an apparent hypotension to the cardiovascular control centers in the brain stem.

**Table 4. Ventilatory and blood gas responses to expiratory threshold loading during exercise at 2.5 mph/5% grade after the induction of chronic heart failure**

---

**Fig. 8.** Within-breath changes in cardiac function over time during control breathing (●) and during application of 15 cmH2O expiratory threshold loading (○) in all 5 dogs after the induction of CHF. Significant within-breath variation of cardiac output and stroke volume exists during control nonloaded breathing conditions and is significantly augmented by the addition of a 15 cmH2O expiratory threshold load. *P < 0.05 for peak or nadir values vs. end-expiratory levels; †P < 0.05 for peak or nadir values vs. control conditions.

J Appl Physiol • VOL 101 • JULY 2006 • www.jap.org
EXPIRATORY LOADING IMPAIRS CARDIOVASCULAR FUNCTION IN HEALTH AND CHF

Cardiac Output
($\Delta$ from value at EELV, L * min$^{-1}$)

Stroke Volume
($\Delta$ from value at EELV, mL * beat$^{-1}$)

Mean Arterial Pressure
($\Delta$ from value at EELV, mm Hg)

Intrathoracic Pressure
(cm H$_2$O)

Mouth Pressure
(cm H$_2$O)

Percentage of breath

$\bar{Q}_{TOT,EELV-C} = 4.710 + 0.278 \text{ L } \cdot \text{min}^{-1}$

$\bar{Q}_{TOT,EELV-EL} = 4.627 + 0.287 \text{ L } \cdot \text{min}^{-1}$

$SV_{EELV-C} = 29.4 + 0.2 \text{ mL } \cdot \text{beat}^{-1}$

$SV_{EELV-EL} = 28.7 + 0.2 \text{ mL } \cdot \text{beat}^{-1}$

$MAP_{EELV-C} = 74 + 6 \text{ mmHg}$

$MAP_{EELV-EL} = 76 + 6 \text{ mmHg}$
expiratory flow rate (12, 25), and a progressive alveolar hypoventilation with increasing severities of airflow limitation (27). These changes occurred despite the fact that our expiratory threshold loading device did not constrain expiratory airflow. Thus humans or animals may choose to defend their end-expiratory lung volume and alveolar ventilation if an expiratory threshold load is added under conditions in which background ventilatory drive is considerably higher (e.g., exercise at higher intensities). However, under the present conditions we feel that our expiratory threshold loading intervention effectively replicates the pulmonary mechanics observed in patients with severe expiratory flow limitation.

**Limitations**

In the present investigation, the application of an expiratory load resulted in progressive dynamic hyperinflation, as evidenced by increases in the transpulmonary pressure at end expiration (i.e., zero airflow conditions) (14). Thus we cannot rule out the possibility that these increases in lung volume impaired cardiac filling because of reductions in the size and compliance of the cardiac fossa (17). However, two observations would speak against this phenomenon being a primary determinant of the cardiovascular responses to expiratory loading. First, the shear modulus of the lung is relatively low over most operating lung volumes, thus making it more likely to be deformed rather than compressing or deforming another object (15). Second, the investigation of Stark-Levya et al. (34) demonstrated that the reductions in cardiac output and stroke volume in response to expiratory threshold loading were actually smaller when the subjects were allowed to hyperinflate, which strongly suggests that the central cardiovascular responses to expiratory loading are mediated primarily by increases in P_{ITP}.

**Implications for Humans During Exercise**

When extrapolating findings from quadrupeds to upright humans, it is important to consider the fact that the directionality of the hydrostatic column is reversed; that is, during exercise ~70% of the circulating blood volume is below the heart in humans, whereas 70% of the circulating blood volume is above the heart in the exercising dog (33). However, it is likely that this change in the directionality of the hydrostatic pressure would favor even larger decreases in stroke volume and cardiac output with expiratory loading in healthy humans, because a given increase in expiratory P_{ITP} would only have to overcome the increases in intravascular pressure due to the peripheral skeletal muscle pump.

Patients with CHF exhibit augmented inspiratory and expiratory P_{ITP} excursions during submaximal exercise. Thus it may be possible that the normally produced respiratory muscle pressures compromise cardiac function during exercise in CHF and may further compromise cardiac function during an episode of acute decompensation or if the patient also suffers from COPD. Support for such a postulate comes from the observation that both inspiratory muscle (28) and combined inspiratory and expiratory muscle unloading (19) improve exercise performance in patients with CHF. Furthermore, our data support a role for inspiratory pressure production as a major contributor to increases in ventricular afterload with expiratory loading (which makes the confounding influence of the differences in the directionality of the hydrostatic column negligible); we believe that cardiovascular consequences of expiratory flow limitation in humans with CHF would be very similar to those observed in the present investigation.

Finally, we do acknowledge that the magnitude of the changes in blood flow we observed in the present investigation is rather small and may have a relatively modest impact on locomotor limb fatigue at the workloads examined. However, we expect that the cardiovascular effects of expiratory loading would persist during higher intensities of exercise. During maximal exercise, whole body maximal oxygen uptake is reduced directly in proportion to reductions in maximal oxygen delivery (9, 31), and reductions in blood flow, per se, can
significantly increase locomotor limb fatigue (3). Consequently, it is plausible to suggest that both maximal oxygen uptake and exercise performance would be significantly reduced in the presence of lowered locomotor limb blood flow and oxygen delivery due to expiratory loading (or expiratory flow limitation) during high-intensity exercise.

ACKNOWLEDGMENTS

We recognize the assistance of Kathleen S. Henderson, Hans C. Haverkamp, and Andrew T. Lovering during these studies, the considerable effort put forth by Anthony J. Jacques in the design and continual modification of our data acquisition and processing software, and the technical assistance and surgical expertise provided by Larry F. Whitesell throughout these studies.

GRANTS

This work was supported by a Grant-in-Aid from the American Heart Association, as well as a grant from the National Heart, Lung, and Blood Institute (ROI-HL-015469). J. D. Miller was supported as a predoctoral fellow by T32-HL-007654 from the National Heart, Lung, and Blood Institute.

REFERENCES


J Appl Physiol • VOL 101 • JULY 2006 • www.jap.org