The effects of inspiratory intrathoracic pressure production on the cardiovascular response to submaximal exercise in health and chronic heart failure

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Miller JD, Smith CA, Hemauer SJ, Dempsey JA. The effects of inspiratory intrathoracic pressure production on the cardiovascular response to submaximal exercise in health and chronic heart failure. Am J Physiol Heart Circ Physiol 292: H580–H592, 2007. First published September 22, 2006; doi:10.1152/ajpheart.00211.2006.—We sought to determine whether the normal inspiratory intrathoracic pressures (P_{ITP}) produced during exercise contribute to the blunted cardiac response to submaximal exercise in health and chronic heart failure (CHF). Five chronically instrumented dogs exercised on a treadmill at 2.5 mile/h at 5% grade while healthy or after the induction of tachycardia-induced CHF. We observed several key differences in the cardiovascular responses to changes in the inspiratory P_{ITP} excursion between health and CHF; namely, 1) removing 70% of the normally produced inspiratory P_{ITP} excursion during exercise (with 15 cmH_2O inspiratory positive pressure ventilation) significantly reduced stroke volume (SV) in healthy animals by 5 ± 2% (P < 0.05) but significantly increased SV and cardiac output (Q_{TOT}) in animals with CHF by 5 ± 1% (P < 0.05); 2) doubling the magnitude of the inspiratory P_{ITP} excursion had no effect on SV or Q_{TOT} in healthy animals but significantly reduced steady-state Q_{TOT} and SV in animals with CHF by −4 ± 3% and −10 ± 3%, respectively; 3) removing the majority of the normally produced inspiratory P_{ITP} excursion had no effect on blood flow distribution in healthy animals but increased hindlimb blood flow (9 ± 3%, P < 0.05) out of proportion to the increases in Q_{TOT}; and 4) the only similarity between healthy and CHF animals was that increasing the inspiratory P_{ITP} excursion significantly reduced steady-state locomotor limb blood flow by 5 ± 2% and 6 ± 3%, respectively (P < 0.05 for both). We conclude that 1) the normally produced inspiratory P_{ITP} excursions are required for a maximal SV response to submaximal exercise in healthy animals but detrimental to the SV and Q_{TOT} responses to submaximal exercise in CHF, 2) the respiratory muscle ergoreflex tonically restrains locomotor limb blood flow during submaximal exercise in CHF, and 3) excessive inspiratory muscle work further compromises cardiac function and blood flow distribution in both health and CHF.

Muscle metaboreflex; respiratory muscle pump; cardiopulmonary interactions

MUCH OF OUR UNDERSTANDING of the interactions between the cardiovascular and pulmonary systems has been derived from observations in anesthetized, mechanically ventilated animals. A near universal finding is that relatively small increases in mean intrathoracic pressure (P_{ITP}, <5 cmH_2O) cause marked reductions in cardiac output, stroke volume, and systemic oxygen delivery in anesthetized preparations (10, 21, 26, 43, 44). However, the depressant effects of anesthesia on autonomic reflexes make the extrapolation of these data to an awake animal difficult at best (1, 10).

Few observations on the interactions between the cardiovascular and respiratory systems have been made in the exercising animal or human. The earliest observations were made by Gunteroth and colleagues (28, 42), who reported that changes in venous return and stroke volume were frequently phasic with spontaneous respiration in the healthy, exercising dog. However, Harms et al. (14) conducted the first experiments to experimentally reduce the inspiratory P_{ITP} excursion and found significant reductions in both cardiac output and stroke volume, which suggested the normally produced inspiratory P_{ITP} excursion was required for preload recruitment and a normal stroke volume response to maximal exercise. Conversely, blood flow to the locomotor limb was increased with inspiratory muscle unloading, suggesting that the blood flow demands of the respiratory muscles during maximal exercise could result in a sympathetically mediated “stealing” of blood flow from the locomotor limb (13).

A growing body of literature suggests that patients with chronic heart failure (CHF) may have a cardiac response to positive pressure ventilation that is opposite to that observed in normal, healthy subjects. More specifically, several groups have reported that patients and animals with severe chronic heart failure exhibited increases in cardiac output and stroke volume in response to acutely applied continuous positive airway pressure at rest (7, 9, 10) that may be a result of reductions in left ventricular transmural pressure at end systole (10). If this is in fact true, one would expect that the more negative inspiratory P_{ITP} excursions associated with whole-body exercise would contribute to the blunted cardiac output and stroke volume responses to exercise in these patients. This may be especially true in patients with more severe CHF, where more negative inspiratory P_{ITP} excursions due to reductions in lung compliance (2) and an augmented hyperventilatory response to exercise (36) result in disproportionate increases in transmural pressure at a given metabolic rate.

However, evaluation of the direct mechanical effects of P_{ITP} on the heart are complicated by reductions in cardiac norepinephrine spillover (17), reductions in peripheral muscle sympa-thetic nerve activity (15), and systemic vascular resistance in response to continuous positive airway pressure (CPAP) in patients with CHF. Although it would appear that spontaneous respiratory muscle work contributes to sympathetic outflow...
only during high-intensity exercise in healthy humans (46), the
blunted cardiac output response and exaggerated ventilatory
response to exercise in both patients and animals with CHF
may cause a competition for blood flow between the respira-
tory muscle and locomotor limb muscles at much lower work-
loads.

Thus, in the present study, we used chronically implanted
ultrasonic flow probes to measure beat-by-beat changes in
cardiac output and its distribution in a canine model of tachy-
cardia-induced CHF, which allowed us to measure relatively
rapid (e.g., onset of <10 s) changes in stroke volume following
alterations in the inspiratory PITP excursion, which would
exclude the possibility of cardiac output or stroke volume
merely changing in parallel with oxygen consumption (14). We
tested the following hypotheses: 1) normally produced inspira-
tory PITP excursions are required for a normal stroke volume
response to submaximal exercise in the healthy dog, 2) nor-

mally produced PITP excursions do not compromise locomotor
limb blood flow during submaximal exercise due to the pres-
ence of a considerable cardiac output reserve, 3) the normally
produced inspiratory PITP excursion is detrimental to the stroke
volume response to submaximal exercise in the dog with
pacing-induced CHF, and 4) reducing the magnitude of the inspiratory
PITP excursion will preferentially redistribute blood
flow toward the locomotor limbs during submaximal exercise
in the dog with pacing-induced CHF.

METHODS

Chronic Instrumentation

All surgical and experimental procedures were approved by
the Institutional Animal Care and Use Committee at the University of
Wisconsin-Madison 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 lie quietly on a bed and to run on a
motorized treadmill. After the training, two surgical procedures sep-
parated by at least 2 wk were required to instrument the dogs for study.
The animals were induced using pentothal sodium (20 mg/kg), and a
surgical plane of anesthesia was maintained using halothane gas (1%).
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 (Transonics, Ithaca, NY) were placed around the ascending
aorta (n = 5 dogs) and terminal aorta (n = 4 dogs) for the measure-
ment 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
(Königsberg Instruments, Pasadena, CA) was implanted in the in-
trathoracic space between the 9th and 10th ribs for the direct mea-
surement of PTP. 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 using custom
analysis software developed in our laboratory.

Protocols

Time line 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. Each animal
performed the protocols described below over the course of 2 to 3 wk
while healthy. Chronic heart failure was then induced by rapid
ventricular pacing at 210 beats/min for 3–6 wk. The animals were
routinely exercised and underwent each experimental protocol 2 to 3
times/wk during this pacing period to maintain a constant level of
training and familiarity with the protocol. The pacemaker was turned
off for 15–20 min, 2 to 3 times/wk to track changes in cardiac function
using echocardiography. Briefly, animals were placed in the right
lateral decubitus position on an examination table, and images were
acquired in the short axis using standard echocardiographic landmarks
(6). The area of the left ventricular cavity was measured using a
computerized planimeter, and end-diastolic area (maximal area), end-
systolic area (minimal area), and area ejection fraction [(end-diastolic
volume – end-systolic volume)/end-diastolic volume] were calcu-
lated. CHF was defined as an ejection fraction <45% with a consider-
ably blunted cardiac output and stroke volume response to a fixed
exercise workload (2.5 mile/h at 5% grade). The protocols were then
repeated while the animal was in heart failure over the course of 1 to
2 wk. The baseline hemodynamic consequences of the pacing-induced
heart failure are reported in Table 1.

Animal preparation for exercise studies. The animal was guided
onto a motorized treadmill and stood quietly while all hardwired
instrumentation was connected. The tracheostomy was cannulated
with auffed endotracheal tube (4.0–6.0 mm ID). 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 mile/h at 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 during the intervention or exercise bout (exces-
sive head movement, unwillingness to continue exercise despite
encouragement, etc.), the intervention and/or exercise bout was im-
mediately stopped.

INSPIRATORY UNLOADING: HOW DO THE NORMALLY PRODUCED
INSPIRATORY PITP EXCursions AFFECT CARDIOVASCULAR Func-
TION DURING EXERCISE IN HEALTH AND CHF? A customized non-
rebreathing valve was then connected to the pneumotachograph that
allowed for the connection of a two-arm, piston-operated, prototype
ventilator. Inspiratory positive pressure ventilation was then applied in

Table 1. Echocardiographic measurements before and after tachycardia-induced CHF

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic area, cm²</td>
<td>9.60±0.70</td>
<td>17.69±0.78*</td>
</tr>
<tr>
<td>End-systolic area, cm²</td>
<td>3.86±0.65</td>
<td>13.12±1.87*</td>
</tr>
<tr>
<td>Area ejection fraction</td>
<td>0.60±0.04</td>
<td>0.22±0.04*</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>3.401±0.120</td>
<td>2.686±0.407*</td>
</tr>
<tr>
<td>SV, ml/beat</td>
<td>38±1</td>
<td>28±2*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>90±3</td>
<td>96±12</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>86±5</td>
<td>78±2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. End-diastolic area, end-systolic area, and area
ejection fraction are measured from echocardiographic images in the resting
animal placed in the right lateral decubitus position. Cardiac output, stroke
volume, and heart rate are measured in the resting animal from ascending
aortic flow probe. CHF, chronic heart failure; SV, stroke volume; HR, heart
rate; MAP, mean arterial pressure (in the resting animal). *P < 0.05, signif-
icant difference from healthy conditions.
random order at levels of 5, 10, and 15 cmH2O for a minimum of 1 min (see representative raw data trace in Fig. 1).

INSPIRATORY LOADING: HOW DO AUGMENTED INSPIRATORY \( P_{\text{ITP}} \) EXCURSIONS AFFECT CARDIOVASCULAR FUNCTION DURING EXERCISE IN HEALTH AND CHF? A fixed resistance \((\sim 40 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1})\) was placed on the inspiratory arm of the breathing circuit for a minimum of 30 s (see representative raw data trace in Fig. 4).

Animal preparation for resting studies. At the beginning of each study, the dog was placed on a padded bed in a sound-attenuated room, at which point all hardwired instrumentation was connected. The tracheostomy was cannulated with a cuffed endotracheal tube (4.0–6.0 mm ID). Airflow was measured by a heated pneumotachograph connected to the endotracheal tube.

Once the animal entered non-rapid eye movement (REM) sleep, one of the following two interventions was performed: 1) the magnitude of the inspiratory \( P_{\text{ITP}} \) excursion was reduced by the application of 5 cmH2O inspiratory positive pressure ventilation (IPPV) using a mechanical ventilator (Veolar, Hamilton), or 2) the magnitude of the inspiratory \( P_{\text{ITP}} \) excursion was increased by applying a fixed inspiratory resistance \((\sim 40 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1})\).

Data Analysis

The transient cardiovascular responses to alterations in \( P_{\text{ITP}} \), were analyzed with custom-made computer software on a beat-by-beat basis for cardiac output, heart rate, mean arterial pressure, and hindlimb blood flow. Data averaged in 5-s intervals were used to derive systemic and hindlimb vascular conductances, which were calculated as the ratio cardiac output or hindlimb blood flow to mean arterial pressure, respectively.

For each individual variable, 5-s averages were obtained during the control period and for 1 min after the onset of each intervention. Each 5-s block during inspiratory unloading or inspiratory loading was compared with its preceding control condition using a two-way ANOVA with repeated measures and Dunnett’s post hoc testing. Statistical significance was considered to be present when \( P < 0.05 \).

RESULTS

Effects of Reducing the Magnitude of the Inspiratory \( P_{\text{ITP}} \) Excursion on Cardiovascular Function

Healthy conditions. The inspiratory \( P_{\text{ITP}} \) excursion averaged \(-13 \pm 2 \text{ cmH}_2\text{O}\) in healthy dogs under control conditions. The cardiovascular responses to 15 cmH2O IPPV in health are shown in raw data traces in Fig. 1, left, with the mean cardiac responses of all five dogs shown in Fig. 2. The application of 15 cmH2O IPPV reduced the magnitude of the negative inspiratory \( P_{\text{ITP}} \) excursion by \( 69 \pm 9\% \) \((P < 0.05, \text{ see Fig. 2})\) and significantly reduced stroke volume within 10 s of the onset of IPPV \((P < 0.05, \text{ see Figs. 1, left, and 2})\). Cardiac output was not significantly affected due to the presence of a compensatory tachycardia (see Table 2). Systemic vascular conductance,
hindlimb conductance, hindlimb blood flow, and mean arterial pressure were not significantly changed with 15 cmH₂O IPPV (see Fig. 3).

**CHF conditions.** Following 3–6 wk of rapid cardiac pacing, the animals exhibited significant increases in end-diastolic and end-systolic cardiac left ventricular areas at rest, as well as significant reductions in left ventricular area ejection fraction at rest ($P < 0.05$ for all, see Table 1). Cardiac output, stroke volume, and mean arterial pressure were all reduced at a constant, submaximal exercise workload, and heart rate was significantly increased ($P < 0.05$ for all, see Table 2).

After the induction of CHF, the inspiratory PTIP excursion averaged $-12 \pm 1$ cmH₂O ($P = $ not significant vs. healthy), and the application of 5, 10, or 15 cmH₂O IPPV elicited similar, significant reductions in the magnitude of the negative inspiratory PTIP excursion of 22 ± 3%, 52 ± 13%, or 72 ± 16% ($P < 0.05$ for all vs. control), respectively, compared with control conditions.

In contrast to the effects of IPPV under healthy conditions, all three levels of IPPV significantly increased left ventricular stroke volume within the first 15 s of IPPV (see Fig. 2), with this effect being sustained for the duration of the application of IPPV (see steady-state responses reported in Table 2). Furthermore, 15 cmH₂O IPPV significantly increased cardiac output ($P < 0.05$) following the induction of CHF (see Fig. 2).

Systemic vascular conductance was increased by 1.5 ± 1.0 ($P < 0.05$), 1.6 ± 1.5 ($P < 0.05$), and 3.4 ± 1.1 ml·min⁻¹·mmHg⁻¹ ($P < 0.05$) during the first minute of 5, 10, and 15 cmH₂O IPPV (see Fig. 3 and Table 2) in animals
Effects of a More Negative Inspiratory \( P_{ITP} \) Excursion on Cardiovascular Function

Healthy conditions. Raw data traces showing the cardiovascular responses to 1 min of inspiratory loading in one dog are shown in Fig. 4, with the mean cardiac responses of the four dogs with terminal aortic flow probes shown in Fig. 5. The addition of a fixed inspiratory resistance increased the magnitude of the inspiratory \( P_{ITP} \) excursion to 192 \( \pm \) 39\% of control conditions (\( P < 0.05 \)). Unlike 15 cmH\(_2\)O IPPV, inspiratory loading had no significant effect on left ventricular stroke volume, cardiac output, systemic vascular conductance, and heart rate (see Figs. 2, 4, and 5). However, mean arterial pressure was significantly elevated during the first minute of inspiratory loaded conditions as a result of a combined effect of slight increases in cardiac output and slight decreases in systemic vascular conductance (see Fig. 6).

Hindlimb vascular conductance and blood flow progressively declined during the application of the inspiratory load and were significantly lower than control conditions during the second minute of inspiratory loading (see Fig. 6). Subsequently, the fraction of the total cardiac output going to the hindlimb was slightly but significantly reduced during inspiratory loaded conditions (20 \( \pm \) 1\% during control and 19 \( \pm \) 1\% during inspiratory loading, \( P < 0.05 \); range from 82\% to 98\% of control).

\( \text{CHF} \) conditions. Raw data traces showing the cardiovascular responses to 1 min of inspiratory loading in one dog are shown in Fig. 4, with the mean cardiac responses of the four dogs with terminal aortic/hindlimb blood flow probes shown in Fig. 5. The addition of a fixed inspiratory resistance increased the magnitude of the inspiratory \( P_{ITP} \) excursion by 112 \( \pm \) 34.4 on March 30, 2017 http://ajpheart.physiology.org/ Downloaded from
3\%, respectively (see Fig. 6). The fraction of the total cardiac output going to the hindlimb was not significantly altered by inspiratory loading (21 ± 2\% during control and 20 ± 2\% during inspiratory loading, \( P = \) not significant).

The addition of a fixed inspiratory load significantly reduced minute ventilation primarily due to reductions in tidal volume (see Table 3), although arterial PO\(_2\) and PCO\(_2\) were not significantly altered with inspiratory loading (see Table 3). Maintaining the arterial PO\(_2\) at control levels by increasing the inspired PO\(_2\) in four of the dogs did not alter the qualitative or quantitative cardiovascular responses to inspiratory loading.

### Stimulus-Response Relationship Between Stroke Volume and Pr\(_{TP}\)

The 5-s averages of stroke volume are plotted versus the 5-s averages of integrated mouth pressure per breath for each dog.
Effects of IPPV and Inspiratory Loading on Cardiovascular Function at Rest

Healthy conditions. Neither reducing the inspiratory \( P_{\text{ITP}} \) excursion from \(-4 \pm 1 \) to \( 2 \pm 1 \) cmH\(_2\)O using 5 cmH\(_2\)O IPPV nor augmenting the inspiratory \( P_{\text{ITP}} \) excursion to \(-19 \pm 12 \) cmH\(_2\)O with a fixed inspiratory load significantly changed any of our measured cardiovascular parameters under resting conditions in healthy dogs (data not shown).

CHF conditions. Reducing the inspiratory \( P_{\text{ITP}} \) excursion from \(-6 \pm 2 \) to \( 2 \pm 2 \) cmH\(_2\)O with 5 cmH\(_2\)O IPPV significantly increased cardiac output and stroke volume by 7 \( \pm 3\% \) and 7 \( \pm 2\% \), respectively (\( P < 0.05 \) for both) in dogs with CHF. In contrast, increasing the inspiratory \( P_{\text{ITP}} \) excursion to \(-20 \pm 10 \) cmH\(_2\)O significantly reduced stroke volume by 5 \( \pm 2\% \) (\( P < 0.05 \)) in dogs with CHF, although cardiac output was maintained by a compensatory tachycardia.

DISCUSSION

This study identifies several key differences in the cardiovascular responses to changes in the inspiratory \( P_{\text{ITP}} \) excursion between healthy and severe CHF during submaximal exercise; namely, 1) removing the majority of the normally produced inspiratory \( P_{\text{ITP}} \) excursion during exercise (with 15 cmH\(_2\)O IPPV) significantly reduced stroke volume in healthy animals but resulted in significant increases in stroke volume and cardiac output in animals with CHF, 2) increasing the magnitude of the inspiratory \( P_{\text{ITP}} \) excursion had no effect on stroke volume or cardiac output in healthy animals but significantly reduced steady-state cardiac output and stroke volume in animals with CHF, 3) removing the majority of the normally produced inspiratory \( P_{\text{ITP}} \) excursion had no effect on blood flow distribution in healthy animals but significantly increased the fraction of cardiac output directed to the locomotor limb in animals with CHF, and 4) increasing the inspiratory \( P_{\text{ITP}} \) excursion (via the addition of a resistive load) significantly reduced steady-state locomotor limb blood flow and vascular conductance in both health and CHF.

Normally Produced Inspiratory \( P_{\text{ITP}} \) Excursions are Required for Normal Stroke Volume Response to Exercise in Health But Contribute to Blunted Cardiac Output Response to Exercise in CHF

In the present study, removing the majority of the normal inspiratory \( P_{\text{ITP}} \) excursion with 15 cmH\(_2\)O IPPV in healthy animals elicited rapid (onset < 10 s) reductions in stroke.
volume during submaximal exercise. These reductions in stroke volume averaged ~5% when ~70% of the normal \( P_{\text{ITP}} \) excursion was removed but ranged from 10–15% when >75% of the normal inspiratory \( P_{\text{ITP}} \) excursion was removed with 20 cmH\(_2\)O IPPV (see Fig. 7). These changes occurred despite the presence of the peripheral skeletal muscle pump forcing blood centrally. This suggests that the normally produced negative inspiratory \( P_{\text{ITP}} \) excursions participate in the maintenance of central blood volume and left ventricular preload by widening the transmural pressure gradient across the walls of the heart. Such a postulate is supported by observations in acutely instrumented anesthetized or sedated animals, where the application of relatively low levels of positive pressure ventilation (5–10 cmH\(_2\)O) elicits significant reductions in end-diastolic volume and stroke volume (20, 25).

Our changes in stroke volume are considerably smaller than those observed in anesthetized preparations, with this discrepancy likely being attributable not only to the peripheral skeletal muscle pump forcing blood centrally in our exercising animals but also due to intact, nonobtunded reflexes. Evidence for the latter comes from the observation that our healthy animals maintained cardiac output during inspiratory unloading conditions by increasing heart rate, a compensatory mechanism that serves to lower right atrial pressure and widen the pressure gradient for venous return. Thus, when the heart rate reserve is exhausted [such as during maximal exercise (14)] or reduced by anesthesia (1), our findings suggest that the heart would become considerably more dependent on the preload recruiting effect of the inspiratory \( P_{\text{ITP}} \) excursion to maintain cardiac output.

In the present study, removing the majority of the normal inspiratory \( P_{\text{ITP}} \) excursion with 15 cmH\(_2\)O IPPV in animals with CHF resulted in significant increases in stroke volume and cardiac output during submaximal exercise. These changes in stroke volume are directionally opposite to those observed in these animals while healthy and to healthy humans receiving IPPV during maximal exercise (14). This suggests that the normally produced negative inspiratory \( P_{\text{ITP}} \) excursions are detrimental to the stroke volume and cardiac output responses to exercise in CHF and are likely to impede left ventricular emptying by widening the left ventricular transmural pressure gradient. This hypothesis is supported by observations in acutely instrumented sedated pigs with pacing-induced CHF, where the application of continuous positive airway pressure (CPAP) elicits significant reductions in end-systolic volume while leaving end-diastolic volume relatively unchanged (9). However, CPAP unloads inspiration and loads expiration, thus precluding the determination of the specific effects of the normal inspiratory \( P_{\text{ITP}} \) excursions on cardiovascular function.

Fig. 4. Raw data traces showing the cardiovascular consequences of inspiratory loading in 1 representative dog while healthy (left) and after the induction of CHF (right). The x-axes are aligned to the mean value of the control conditions. Note that augmenting the inspiratory \( P_{\text{ITP}} \) excursion had no effect on stroke volume in healthy dogs but rapidly decreased stroke volume in the animals with CHF.
Can Increased Inspiratory $P_{TRP}$ Excursions Augment Venous Return and Cardiac Output?

In contrast to the effects of reducing the magnitude of the normally occurring inspiratory $P_{TRP}$ excursion, nearly doubling the magnitude of the normal inspiratory $P_{TRP}$ excursion (via the addition of an inspiratory resistive load) did not have an effect on steady-state left ventricular stroke volume, cardiac output, or heart rate during submaximal exercise in our healthy animals. Our finding that steady-state stroke volume is unaffected by more negative inspiratory $P_{TRP}$ excursions is consistent with observations made in healthy, anesthetized animals subjected to similar inspiratory loading protocols (35), although it remains unclear whether the healthy left ventricle is able to maintain stroke volume as a result of afterload insensitivity, preload recruitment, or increases in ventricular contractility under such conditions.

Several other investigations have reported that cardiac output and heart rate increase out of proportion to metabolic rate in response to a variety of inspiratory loading protocols in resting humans. Thus, these authors have concluded that exaggerated negative inspiratory $P_{TRP}$ excursions are an independent contributor to increases in venous return and cardiac output (3). However, previous reports from our laboratory and others have provided both theoretical (27, 34) and empirical (11, 24) evidence that this is not likely to be the case. More specifically, large reductions in right atrial pressure have repeatedly been shown to result in the collapse of the inferior vena cava in both dogs (11, 16) and...
humans (45), especially when abdominal pressure is elevated [as is the case with diaphragmatic descent (21)]. Additionally, even if the abdominal vascular zone conditions were appropriate for the respiratory muscle pump to increase venous return from the limbs during the inspiratory phase of a breath (44), equal and opposite reductions in locomotor limb venous return during the expiratory phase of the breath are likely to render net flow in the steady state unchanged (24). Our present findings add further support to our working hypothesis that transient increases in venous return brought about by exaggerated negative inspiratory P_{TRP} excursions cannot alter steady-state blood flow (33).

In contrast to the effects in the healthy animal, in CHF, doubling the magnitude of the normal inspiratory P_{TRP} excursion significantly reduced steady-state left ventricular stroke

Fig. 6. Effects of inspiratory loading on systemic and hindlimb vascular conductances over time \((n = 4\) dogs, average of \(3 \pm 1\) trials/dog) in healthy dogs (○) and dogs with CHF (●). Increasing the magnitude of the inspiratory pressure excursion did not have a significant effect on systemic vascular conductance in healthy or CHF animals but did significantly reduce hindlimb vascular conductance and hindlimb blood flow in both groups. *\(P < 0.05\) for each intervention vs. its own respective control. \#\(P < 0.05\) for each mean value vs. its respective control value for each time period denoted.
volume and cardiac output despite significant increases in heart rate. This strongly suggests that, unlike the healthy heart, the ability of the autonomic nervous system to compensate for increases in the transmural pressure gradient across the left ventricular free wall was very limited in these animals after the induction of CHF. Such a notion is supported by recent findings from O’Leary et al. (32) demonstrating that the inotropic left ventricular response to metaboreflex activation from the locomotor limb is markedly impaired in dogs with CHF, with these animals relying heavily on peripheral vasoconstriction to increase arterial driving pressure in response to hindlimb ischemia (4, 12).

Does a Tonically Active Respiratory Muscle “Ergoreflex” Limit Locomotor Limb Blood Flow During Submaximal Exercise in Health and CHF?

In the present study, in healthy animals, even the highest level of inspiratory unloading did not increase locomotor limb arterial blood inflow or vascular conductance. This finding agrees with previous inspiratory unloading studies from our laboratory in submaximally exercising humans (46) and supports the notion that the normal blood flow demand of the respiratory muscles does not compromise locomotor limb blood flow when respiratory muscle work is moderate and a significant cardiac reserve is present.

In contrast, in animals with CHF, when the magnitude of the inspiratory PITP excursion was reduced by ~70% with 15 cmH2O IPPV, hindlimb vascular conductance increased out of proportion to the increases in systemic vascular conductance, such that ~45% of the increase in systemic conductance occurred in the exercising hindlimb. Our animals had a cardiopulmonary response to exercise very similar to that observed in patients with CHF, namely, an excessive hyperventilatory response to exercise (36), a tachypneic and inefficient breathing pattern (2), and a blunted cardiac output response to exercise (4) (see Tables 2 and 3). This combination of excessive respiratory muscle work combined with a limited oxygen delivery is likely to be sufficient to cause the respiratory muscle metaboreflex to be tonically active (and persistently “stealing” blood flow from the locomotor limb) in CHF. This hypothesis is supported by observations in the exercising rat with CHF, where respiratory muscle blood flow is significantly elevated (29) and locomotor limb blood flow is significantly reduced (30). That there is significant sympathetically mediated constraint of locomotor limb blood flow in human submaximal exercise is supported by the observation that the acute blockade of α-adrenergic receptors significantly increases leg blood flow during submaximal treadmill exercise (19), and peak locomotor limb perfusion is only attained when a single locomotor limb is exercised (22). Although this investigation is the first to demonstrate experimentally that the normal blood flow demands of the respiratory muscles are sufficient to reduce blood flow to the exercising locomotor limbs in CHF, the relative contributions of the respiratory muscle ergoreflex, peripheral muscle ergoreflex (37, 39), carotid chemoreceptor afferent input (40, 41), and peripheral vascular dysfunction (18) to the blunted locomotor limb blood flow response to exercise in CHF are only beginning to be understood (8).

On the other hand, inspiratory loading in the present study elicited similar reductions in locomotor limb blood flow in both healthy and CHF animals that were due in large part to reductions in limb vascular conductance. Thus, it would appear that substantial increases in inspiratory muscle work (i.e., >200% of control) are sufficient enough to elicit a preferential, sympathetically mediated vasoconstriction in the exercising hindlimb in both health and CHF.

Implications for Humans

Perhaps the greatest difference between humans and quadrupeds is 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 exercis-
ing dog (38). However, we feel the directionality of this difference would favor an even larger role of the respiratory muscle pump in maintaining central blood volume in the healthy, submaximally exercising human. In the exercising dog, increases in right atrial pressure as a result of increases in \( P_{\text{TP}} \) (e.g., inspiratory unloading conditions) must overcome a driving pressure for venous return comprised of two primary forces: 1) a hydrostatic column forcing blood centrally, and 2) the peripheral skeletal muscle pump. Conversely, in the exercising human, an increase in right atrial pressure associated with inspiratory unloading must primarily overcome the driving pressure due to the peripheral skeletal muscle pump, which expends energy to force blood centrally against the hydrostatic column. Reciprocally, we believe that reductions in right atrial pressure under appropriately controlled conditions will not serve to increase venous return, since losses in peripheral venous recoil due to the central translocation of blood and increases in inferior vena caval resistance will serve to limit steady-state increases in stroke volume and cardiac output (11) [a postulate supported by observations in the maximally exercising human (14)].

As noted in the introduction, low levels of IPPV (5 cm\( \text{H}_2\text{O} \)) elicit substantial increases in exercise performance in patients with CHF (31). Interestingly, reducing the work of breathing using either a helium-oxygen mixture or IPPV does reduce sensations of locomotor limb discomfort (23). Thus our data would suggest that these improvements in exercise performance and ratings of perceived exertion are at least in part a result of increases in locomotor limb blood flow and oxygen transport (14). It is also likely that a lower level of IPPV would be required to elicit such an effect in humans, due to the fact that humans are able to voluntarily reduce their respiratory motor output and allow a given level of IPPV to reduce the inspiratory \( P_{\text{TP}} \) excursion to a greater extent. Consequently, IPPV may serve as a useful tool to facilitate the rehabilitation of patients with CHF under supervised conditions.

**Limitations**

In this investigation we did not have measurements of left ventricular volumes in our animals. Although we speculate that the improvements in cardiac function are the result of changes in \( P_{\text{TP}} \) affecting left ventricular transmural pressure (and in turn, preload or afterload), we cannot exclude the possibility that at least part of the improvements in left ventricular function resulted from changes in left ventricular contractility or through altering the mechanical interaction between the right and left ventricles (e.g., ventricular interaction during diastole) (5) and/or pericardium.

As we did not control heart rate with a pacer during the inspiratory unloading conditions in the present study, we cannot experimentally exclude the possibility that the changes in stroke volume we observed were secondary to changes in cardiac filling times (which are roughly inversely proportional to heart rate). However, evidence against changes in filling time as a primary determinant of the changes in stroke volume can be gleaned from Fig. 2, where the changes in stroke volume with inspiratory unloading in both healthy and CHF conditions are frequently dissociated from changes in heart rate (with the increase in stroke volume clearly preceding the reductions in heart rate in the CHF conditions).

A final concern is that using IPPV to reduce the magnitude of the inspiratory \( P_{\text{TP}} \) excursion does have the potential to increase pulmonary vascular resistance due to the compression of alveolar capillaries [as much as 17% in previous investigations (14)]. However, our observation in CHF animals that reducing the \( P_{\text{TP}} \) excursion increases cardiac output and stroke volume suggests that this effect did not predominate during the present study, although removing the inspiratory \( P_{\text{TP}} \) excursion without concomitant increases in pulmonary vascular resistance (e.g., with helium-oxygen gas mixtures) may have elicited even larger increases in cardiac output and stroke volume in our animals.

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