Cardiorespiratory effects of inelastic chest wall restriction

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Miller, Jordan D., Kenneth C. Beck, Michael J. Joyner, A. Glenn Brice, and Bruce D. Johnson. Cardiorespiratory effects of inelastic chest wall restriction. J Appl Physiol 92: 2419–2428, 2002. First published February 15, 2002; 10.1152/japplphysiol.00394.2001.—We examined the effects of chest wall restriction (CWR) on cardiorespiratory function at rest and during exercise in healthy subjects in an attempt to approximate the cardiorespiratory interactions observed in clinical conditions that result in restrictive lung and/or chest wall changes and a reduced intrathoracic space. Canvas straps were applied around the thorax and abdomen so that vital capacity was reduced by >35%. Data were acquired at rest and during cycle ergometry at 25 and 45% of peak workloads. CWR elicited significant increases in the flow-resistant work performed on the lung (160%) and the gastric pressure-time integral (>400%) at the higher workload, but it resulted in a decrease in the elastic work performed on the lung (56%) compared with control conditions. With CWR, heart rate increased and stroke volume (SV) fell, resulting in >10% fall in cardiac output at rest and during exercise at matched workloads (P < 0.05). Blood pressure and catecholamines were significantly elevated during CWR exercise conditions (P < 0.05). We conclude that CWR significantly impairs SV during exercise and that a compensatory increase in heart rate does not prevent a significant reduction in cardiac output. O2 consumption appears to be maintained via increased extraction and a redistribution of blood flow via sympathetic activation.

DISEASES THAT CAUSE MARKED reductions in the compliance of the chest wall and volume of the thoracic cavity (e.g., kyphoscoliosis, pectus excavatum, ankylosing spondylitis) generally cause significant reductions in exercise capacity. Several studies have shown blunted cardiac output responses to exercise in these patient groups, whereas others fail to corroborate these findings (6, 20, 27, 41).

Congestive heart failure (CHF) may also involve abnormalities of cardiorespiratory interactions because of increases in cardiac size, altered pulmonary and intrathoracic (esophageal) (Pes) pressures, increased intrathoracic fluid volume, and an elevated work of breathing (22). Exercise limitation in heart failure is thought to largely be a result of cardiac dysfunction, although it is not known how much alteration in lung mechanics and enhanced cardiorespiratory interactions could contribute to the limitation (4). Our laboratory has shown previously that patients with CHF are more tachypneic, breathe at reduced lung volumes, and exhibit significant expiratory flow limitation compared with normal subjects during exercise (16). The cardiovascular sequelae of such alterations in lung and chest wall mechanics on exercise capacity are poorly defined.

In an attempt to mimic certain aspects of the above-mentioned diseases, external chest wall restriction (CWR) has been shown to lower peak exercise capacity in young, healthy subjects by 20–30% (24, 25). Explanations for these reductions in exercise capacity have focused primarily on an inefficient ventilatory pattern, an elevated work of breathing, and a heightened sensation of dyspnea. However, little data are available that characterize the cardiovascular consequences of CWR. Klineberg et al. (19) found significant reductions in cardiac output with CWR at rest, and only one other study to date has attempted to assess cardiac function during exercise with CWR in a limited number of subjects (37). To our knowledge, this is the first study to quantify the changes in breathing strategy and respiratory mechanics that occur with CWR during exercise and to examine the mechanisms by which these changes may impact cardiac function.

METHODS

Subjects. Nine normal men and one active woman between the ages of 19 and 41 yr gave written informed consent for participation in the study. All subjects were nonsmokers and did not have a history of respiratory- or cardiovascular-related problems.

Exercise. Subjects reported to the General Clinical Research Center (GCRC) for two separate visits. The first visit
consisted of an incremental cycle ergometry test to peak O\textsubscript{2} consumption (V\textsubscript{O2peak}). This visit served as a screening tool to rule out any underlying cardiovascular and pulmonary disease and for the determination of peak work capacity to adjust workloads of the follow-up study. The second visit consisted of data collection at rest and during steady-state exercise at 25 and 45% of the peak work level achieved on the initial visit. During this session, subjects were studied with and without CWR, and without CWR while mimicking the tidal volume (V\textsubscript{T}) and breathing frequency (f) observed during CWR. The latter “mimic” trial was performed to rule out a breathing pattern influence on our measurement of cardiac output. Pulmonary function, cardiac output, work performed on the lung, Pes and abdominal (gastric) pressure (Pga) production, carotid pulse tracings, and blood samples were acquired at steady state during each condition.

Visit 1. Subjects were admitted to the GCRC and had their weight and height measured. After 5 min of light cycling and stretching, the subject began the incremental cycle V\textsubscript{O2peak} test. This test involved pedaling at an initial workload of 20–35 W for 1 min, with workload increases of 20–35 W every minute thereafter until volitional fatigue (the exact workload increments were dependent on the fitness and body size of the subject).

Visit 2. After again reporting to the GCRC, subjects were instrumented with an 18-gauge retrograde hand catheter (to allow for serial venous blood sampling during each condition) and five-lead electrocardiogram (to measure heart rate). After one of the subject’s nostrils was numbed with 2% lidocaine gel, a small latex balloon attached to PE-200 tubing was inserted beyond the glottis and into the esophagus, until the tip of the balloon was 45 cm from the nares. In four of the subjects, a gastric balloon was passed through the nares simultaneously and advanced into the stomach (1, 15). These balloons allowed for the measurement of Pes and Pga changes, respectively.

After instrumentation, baseline pulmonary function tests were performed with the subject seated upright on the cycle ergometer. Subjects breathed through a low-resistance mouthpiece attached in series to a pneumotachograph mounted at a comfortable height. This height was held constant throughout the testing to minimize the effect of posture changes on the pulmonary function testing. While breathing through the mouthpiece with a nose clip in place, the subjects performed baseline forced vital capacity (VC) maneuvers until three reproducible VC measurements were recorded. The highest volume achieved during these maneuvers was used for the calculation of the target post-CWR lung volume.

At rest and during exercise, end-expiratory lung volume (EELV) was estimated from the equilibration of helium (17). Total lung capacity (TLC) was calculated by the addition of EELV to an inspiratory capacity maneuver performed during each condition. The measurement of EELV also allowed for the placement of rest and exercise tidal flow-volume loops within the maximal flow-volume loop (MFVL) for the analysis of changes in breathing patterns and to assess the degree of expiratory flow limitation (18).

For two of the subjects, the resting TLC had to be estimated from prediction equations as a result of nonphysiological resting EELV values (23). Thus the changes in TLC from the unrestricted to the restricted condition were only related to measured changes in VC rather than to a combination of inspiratory capacity and EELV in the other subjects.

Each subject’s chest wall was restricted with the use of four custom-made canvas straps (widths ranging from 10 to 15 cm) adjusted to fit just beneath the axillae and around the chest to envelop the rib cage and abdomen. The desirable degree of lung restriction was achieved by manually tightening the straps while the subject exhaled to residual volume. The extent of lung volume reduction during CWR was measured via pulmonary function tests after ~5 min of acclimatization. A 30% reduction in VC from baseline was considered the target restriction. If this level of restriction was not achieved, all four of the straps would be removed and reapplied until the subject’s VC was reduced by the desired amount.

Each condition began with the measurement of O\textsubscript{2} consumption (V\textsubscript{O2}), CO\textsubscript{2} production (V\textsubscript{CO2}), minute ventilation (ve), V\textsubscript{T}, and f by using a breathing-by-breath analysis system (Medical Graphics, St. Paul, MN). These variables were analyzed during rest and steady-state exercise. The 30-s averages of each variable were obtained after 3 min of data acquisition to ensure steady-state conditions.

When the subject was at a steady state (change in V\textsubscript{O2} < 50 ml/min over 1 min), cardiac output was measured noninvasively by using an open-circuit acetylene gas method described in detail elsewhere (17). Briefly, the subjects breathed through a mouthpiece connected to a non-rebreathing Y valve whose inspiratory port was connected to a low-resistance, low-dead space pneumatic switching valve. During the time that the subjects breathed from the apparatus, the operator switched the pneumatic valve to change the inspiratory air from room air to the cardiac output test mixture (0.7% C\textsubscript{2}H\textsubscript{2}, 21% O\textsubscript{2}, 9% He, and 69.3% N\textsubscript{2}) at the beginning of a normal inspiration. After eight breaths of data had been obtained, acquisition was stopped and data analysis was performed by using custom software (17). During resting conditions, subjects slightly augmented their f (20 breaths/min) to minimize a potential influence of the valve dead space (on the initial breath) and minimize error due to non-steady-state breathing. Cardiac output measures were acquired in duplicate during each condition.

Stroke volume (SV) during each condition was calculated by dividing the average of the two cardiac output measurements by the average heart rate. The arterial-mixed venous O\textsubscript{2} difference was calculated using the Fick equation: arterial-mixed venous O\textsubscript{2} difference = V\textsubscript{O2}/(cardiac output). Blood pressure was measured during steady-state conditions in four of the subjects by using sphygmomanometry.

Tracings of Pes and Pga were recorded for at least 1 min during each condition (rest and exercise, CWR and non-CWR), during which time subjects were encouraged not to swallow, cough, or attempt to speak. Transdiaphragmatic pressure (Pdi) was calculated from Pga – Pes. The volume signal, obtained by the digital integration of the flow signal, was corrected for any drift (i.e., unequal inspiration or expiration over time; <50 ml/min) using a computer program. The flow-resistive work performed on the lung (Wfr) was calculated by the integration of the area of the tidal breathing Pes vs. volume loops multiplied by the f to give the work performed per minute (emH\textsubscript{2}O\cdot1\textsuperscript{-min}). The calculation of the elastic work performed on the lung (Wel) during inspiration required the importation of the data into a spreadsheet program and subsequent analysis of the data by using the approach previously described by Otis (26). Briefly, this involved the integration of the area between the volume axis and a linear compliance line determined from zero-flow points over each V\textsubscript{T}. Pleural pressure (Ppi)-time and Pdi-time integrals were calculated from their respective raw data tracings and used as additional indexes of respiratory muscle work (15).

The cardiac time interval data (prejection period, left ventricular ejection time, and diastolic time) were acquired during the acquisition of the respiratory mechanics data.
This involved the simultaneous recording of the electrocardiogram (lead V5) and carotid blood velocity tracing. The carotid blood velocity tracing was obtained by placing an ultrasonic probe over the subject’s left carotid artery. The derivation of these intervals has been described in detail elsewhere (8). Additionally, the filling and emptying rates of the left ventricle were calculated by dividing the calculated SV by either the diastolic filling time or left ventricular ejection time, respectively.

Blood samples were drawn at the end of each condition. The subject was required to keep his or her hand in a heated box for at least 15 min before the drawing of any blood to ensure that it was arterialized (7). A nonheparinized saline solution was infused through the catheter at all times (except during blood draws) to prevent clotting and to keep the catheter and adjacent tubing patent. Blood samples were analyzed for blood gas content, pH, and epinephrine and norepinephrine levels.

The order in which the subject performed the CWR and nonrestricted chest wall testing was randomized and balanced during both protocols. All subjects performed protocol A, which involved the performance of the steady-state exercise under CWR, unrestricted, and mimic conditions. Four of the subjects returned to the laboratory on a third day to perform exercise in the control and CWR conditions only (protocol B), during which blood pressure and Pga were measured. At least 20 min of rest were allotted between unrestricted, CWR, and mimic conditions (the exercise was submaximal; thus the exercise from the preceding condition should not have significantly affected the resting measures of the following condition).

Statistical analysis. The data were compared by using a two-way repeated-measures analysis of variance test, followed by Tukey post hoc comparisons. Alpha was set at 0.05.

RESULTS

The characteristics of the subjects are listed in Table 1.

Changes in static lung volumes and flow rates with CWR. During resting conditions with CWR, TLC was decreased an average of 33% and resting VC decreased an average of 38% (Fig. 1, Table 2; \(P < 0.001\)) or a drop of 2.26 liters. Residual volume was also decreased at rest by an average of 23% \((P < 0.05)\). Both peak expiratory and peak inspiratory flow rates were significantly reduced \((P < 0.05)\) during CWR conditions.

Changes in breathing pattern with CWR. The resting and exercise tidal flow-volume loops plotted within the MFVL are shown in Fig. 2. At rest and at both exercise intensities, CWR reduced VT and elevated \(f\) \((P < 0.05)\), resulting in small elevations in \(V_{E}\) and \(V_{E}/V_{CO2}\) (Table 3). EELV was decreased at rest and remained reduced relative to the nonrestricted conditions throughout exercise. During CWR exercise, tidal flow rates came close to the maximal available expiratory flow rates at the highest exercise intensity but did not intersect with the MFVL because of upward shift in EELV (Fig. 2).

Table 1. Individual subject characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, m</th>
<th>Weight, kg</th>
<th>(V_{O2peak}), ml·kg(^{-1})·min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>23</td>
<td>1.55</td>
<td>53.2</td>
<td>28.73</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>24</td>
<td>1.85</td>
<td>93.2</td>
<td>49.38</td>
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<tr>
<td>3</td>
<td>M</td>
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<td>1.93</td>
<td>90.5</td>
<td>53.22</td>
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<tr>
<td>4</td>
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<td>1.70</td>
<td>84.1</td>
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<td>5</td>
<td>M</td>
<td>25</td>
<td>1.80</td>
<td>92.3</td>
<td>41.96</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>23</td>
<td>1.96</td>
<td>79.1</td>
<td>35.71</td>
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<td>7</td>
<td>M</td>
<td>25</td>
<td>1.93</td>
<td>90.9</td>
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</tr>
<tr>
<td>8</td>
<td>M</td>
<td>33</td>
<td>1.89</td>
<td>76.9</td>
<td>44.45</td>
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<tr>
<td>9</td>
<td>M</td>
<td>25</td>
<td>1.88</td>
<td>96.8</td>
<td>40.73</td>
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<td>10</td>
<td>M</td>
<td>33</td>
<td>1.79</td>
<td>78.0</td>
<td>NA</td>
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<td></td>
<td>28.1 ± 5.90</td>
<td>1.83 ± 0.12</td>
<td>83.5 ± 12.75</td>
<td>42.18 ± 7.44</td>
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</tbody>
</table>

\(V_{O2peak}\), peak \(O_2\) consumption; F, female; M, male; NA, not applicable.

Fig. 1. Static lung volumes and flow rates during control (Ctrl; solid line) and chest wall-restricted (CWR; dashed line) conditions.
Changes in the work performed on the lung with CWR. The changes in the work performed on the lung induced by the CWR are shown in Table 3. Wel was significantly reduced with CWR at the expense of slight increases in Wfr performed. Thus the total work performed on the lung (Wel + Wfr) calculated from this method was only significantly elevated during the highest level of exercise with CWR.

Changes in respiratory muscle pressure production with CWR. Changes in the Ppl-time integrals (an index of total respiratory muscle work), Pga-time integrals (an index of mean Pga), and Pdi-time integrals (an index of the work being done by the diaphragm) with CWR are shown in Table 3. The significant increases in the Pdi-time integral during all CWR conditions indicate an increase in diaphragmatic work (primarily due to an increase in Pga), which would not have been detected by measuring Pes swings alone.

Changes in gas-exchange variables with CWR. VO2, VCO2, and the respiratory exchange ratio were not significantly changed relative to control conditions at rest or during exercise with CWR (Table 4). Subjects also maintained adequate alveolar ventilation during CWR conditions, as suggested by the consistency of arterialized and end-tidal PCO2 values between CWR and control conditions.

Changes in cardiac output and its components with CWR. The CWR conditions employed in this study did not elicit a significant decrease in cardiac output during resting conditions (P = 0.074). However, CWR resulted in a significant decrease in cardiac output relative to control during both exercise conditions (Fig. 3) because of a decrease in SV and an inadequate compensatory increase in heart rate (Fig. 4). Additionally, the arterial-mixed venous O2 difference was significantly increased during all CWR conditions relative to control (P < 0.05). As expected, the mimicking of the CWR breathing pattern without the actual CWR did not elicit changes in cardiac output that were different from the control conditions (normal breathing pattern without CWR, Fig. 3), indicating that the breathing patterns elicited by CWR did not artifactually influence our measurements of cardiac output.

Because cardiac time intervals become shorter as heart rate increases, it is essential that comparisons between conditions be made at the same heart rates (8). To correct for the different heart rates between CWR and non-CWR conditions, we used the average

### Table 2. Individual changes in static lung volumes and forced expiratory lung volumes

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>TLC</th>
<th>CWR</th>
<th>FRC</th>
<th>CWR</th>
<th>RV</th>
<th>CWR</th>
<th>FVC</th>
<th>CWR</th>
<th>FEV1</th>
<th>CWR</th>
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<tbody>
<tr>
<td>1</td>
<td>5.10</td>
<td>3.86</td>
<td>2.20</td>
<td>1.55</td>
<td>1.03</td>
<td>0.94</td>
<td>4.07</td>
<td>2.92</td>
<td>2.84</td>
<td>2.17</td>
</tr>
<tr>
<td>2</td>
<td>7.37</td>
<td>4.78</td>
<td>3.01</td>
<td>1.95</td>
<td>1.03</td>
<td>0.68</td>
<td>6.34</td>
<td>4.10</td>
<td>3.80</td>
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<td>3</td>
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<td>6.70</td>
<td>4.39</td>
<td>3.67</td>
<td>2.25</td>
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<tr>
<td>4</td>
<td>6.02</td>
<td>4.89</td>
<td>2.39</td>
<td>1.58</td>
<td>1.21</td>
<td>0.83</td>
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<td>4.06</td>
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<td>3.02</td>
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<td>2.63</td>
<td>2.32</td>
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<td>4.82</td>
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<td>5.69</td>
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<td>3.76</td>
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<td>9</td>
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<td>3.45</td>
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<td>1.74</td>
<td>1.32</td>
<td>5.47</td>
<td>2.94</td>
<td>4.30</td>
<td>2.24</td>
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<tr>
<td>Mean</td>
<td>6.98</td>
<td>4.68</td>
<td>3.46</td>
<td>2.27</td>
<td>1.30</td>
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<td>5.79</td>
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<td>± SD</td>
<td>1.26</td>
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<td>1.02</td>
<td>0.41</td>
<td>0.33</td>
<td>0.36</td>
<td>0.84</td>
<td>0.67</td>
<td>0.92</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Values are given in liters. TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; Ctrl, control conditions; CWR, chest wall restriction conditions.
Table 3. Changes in work of breathing

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>25% VO2peak</th>
<th>45% VO2peak</th>
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<tbody>
<tr>
<td></td>
<td>Ctrl</td>
<td>CWR</td>
<td>Ctrl</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>13 ± 7</td>
<td>12 ± 3</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>Ve/(\dot{V})CO₂</td>
<td>47 ± 6</td>
<td>47 ± 6</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Wfr, l·cmH₂O·min⁻¹</td>
<td>63 ± 45</td>
<td>102 ± 59</td>
<td>343 ± 144</td>
</tr>
<tr>
<td>Wel, l·cmH₂O·min⁻¹</td>
<td>134 ± 61</td>
<td>93 ± 44‡</td>
<td>351 ± 148</td>
</tr>
<tr>
<td>/PpId, cmH₂O·s</td>
<td>142 ± 39</td>
<td>169 ± 52</td>
<td>332 ± 77</td>
</tr>
<tr>
<td>/Pgad, cmH₂O·s</td>
<td>140 ± 72</td>
<td>751 ± 421†</td>
<td>149 ± 48</td>
</tr>
<tr>
<td>/Pdid, cmH₂O·s</td>
<td>247 ± 71</td>
<td>866 ± 474‡</td>
<td>358 ± 87</td>
</tr>
<tr>
<td>Peak inspiratory Pes, cmH₂O</td>
<td>−11 ± 2</td>
<td>−7 ± 4</td>
<td>−14 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SD. Ve, minute ventilation; \(\dot{V}\)CO₂, CO₂ production; Wfr, flow-resistive work; Wel, elastic work performed on the lung; /PpId, pleural pressure-time integral; /Pgad, abdominal (gastric) pressure-time integral; /Pdid, transdiaphragmatic pressure-time interval; Pes, intrathoracic (esophageal) pressure; VO₂peak, peak O₂ consumption. *P < 0.05. †P < 0.01.

heart rate between the CWR and non-CWR conditions at a given workload. This average heart rate was then placed in separate regression equations derived from the plots of filling and emptying rate vs. heart rate during the CWR and non-CWR conditions. With use of this method, our data show that both left ventricular filling and emptying rates were significantly reduced at a given heart rate during CWR conditions (Fig. 5).

Changes in blood pressure with CWR. The changes in blood pressure elicited by CWR are shown in Table 5. Our data demonstrate that the changes in mean arterial blood pressure were primarily due to increases in systolic blood pressure, whereas diastolic blood pressure remained relatively unchanged from control conditions.

Neuroendocrine responses to CWR. The levels of circulating catecholamines during the non-CWR exercise conditions did not increase significantly from the resting non-CWR conditions. However, CWR did elicit significant increases in both circulating norepinephrine and epinephrine at the 45% workload compared with both the resting and 25% exercise conditions (Fig. 6).

DISCUSSION

The primary findings of this study were that CWR resulted in a 38% reduction in VC, an altered breathing pattern, and reduced cardiac output during low- to moderate-intensity exercise in healthy adults. The fall in cardiac output was due to a decline in SV because heart rate was either similar to, or higher than, that in non-CWR conditions. The mechanisms responsible for the fall in SV remain speculative but may include a reduction in preload due to reduced negative swings in Pes and augmented swings in Pga or elevations in afterload due to excessive sympathetic activation. Although the reduction in cardiac output with CWR was small at rest, it was consistent across subjects and became larger as exercise intensity increased. Interestingly, catecholamines were elevated during moderate-intensity exercise with CWR, which could optimize blood flow to the working muscles by reducing blood flow to nonactive vascular beds.

The changes in breathing pattern observed with CWR are qualitatively similar to those observed in CHF (16) and with other CWR models in the literature. These changes included significant decreases in VT and increases in f (12, 13, 24, 25). In addition to these findings, we observed a significant increase in the Wfr performed on the lung with CWR and a significant decrease in the Wel (Table 3). Furthermore, the pressure production in the abdominal cavity (Pga) was significantly elevated with CWR, resulting in marked increases in the Pdi-time integral (our index of diaphragmatic “work,” Table 3).

Reductions in cardiac output at rest with CWR have been noted previously in healthy subjects by Klineberg et al. (19). However, the influence of CWR on cardiac function during exercise has not been well characterized. In the present study, cardiac output was reduced by 10–12% and SV by 16–20% compared with control conditions, with the largest reductions occurring at the highest submaximal workload studied (45% peak workload). Our results are similar to those of Vanmeenen et al. (37), who found significant reductions in SV and cardiac output with abdominal or thoracic binding at 60 and 80% of VO₂peak in young healthy subjects. Unlike the work of Vanmeenen et al., however, we found a significant effect of exercise intensity.
on the reduction in cardiac output, with the decrement in cardiac output becoming significantly greater at higher intensities of exercise. Additionally, we observed a significant pressor response during the 45% CWR conditions compared with control conditions, whereas Vanmeenen’s group did not report an interaction between exercise intensity and mean arterial blood pressure. We also found it striking that the subjects in their study were able to exercise at 60 and 80% of their peak workload with lung volume restrictions similar to those brought about by CWR in this study (37). The majority of our subjects stated that the 45% workload in this study was near maximal during CWR conditions. Although Vanmeenen et al. did not measure changes in lung volume over time, our measurements of TLC (from the addition of EELV and inspiratory capacity) during each exercise bout ensured that the level of restriction was constant throughout all CWR testing.

The study by Vanmeenen et al. also did not account for possible artifacts in their CO₂-rebreathe measurements of cardiac output due to alterations in breathing pattern caused by CWR. In this study, we used a recently validated acetylene wash-in technique to measure cardiac output (17) and had subjects mimic the breathing pattern observed during CWR conditions to ensure that our method of measuring cardiac output was not influenced by breathing pattern alone.

Why was cardiac output decreased with CWR? It is unclear why cardiac output was decreased with CWR. Because of the difficulties associated with studying heart and lung interactions in humans, much of the past research has been accomplished with the use of mechanically ventilated animal models (3, 28, 29, 32, 34–36, 38). Most research using these models has suggested that lung inflation can significantly reduce the compliance of the ventricles via direct mechanical compression (3, 28, 29, 38). Additionally, inflation of the lungs has been shown to mechanically compress the inferior and superior vena cavae, thereby decreasing venous return (14). From these data, it is tempting to speculate that the decrease in cardiac output was due to a mechanical compression of the heart by the lungs, thus altering ventricular compliance (21). However, we find this postulate to be unlikely for two reasons.

First, the healthy lung has a very low shear modulus at lower lung volumes, making it more likely to be deformed rather than compressing or deforming another object (such as the heart) (30). Second, the animal models mentioned above used positive-pressure ventilation to inflate the lungs, which reverses the direction of the Pes change during inspiration. Thus...
the pericardial pressure measured in these studies is probably an overestimate of the force applied to the heart by the lungs during a normal, unassisted inspiration (which is determined by the shear modulus) (30). The notion that the lungs did not physically compress the heart during CWR conditions is further supported by the fact that we did not observe a clear relationship between end-inspiratory lung volume as percent TLC and the reduction in SV with CWR among our subjects. We would expect to see such a relationship if the lungs and heart were truly competing for space within the thoracic cavity.

The Pga changes associated with CWR may also have had a significant influence on cardiac output. The increase in the Pdi-time integral occurred primarily as a result of increases in Pga. Elevations in Pga (secondary to diaphragmatic contraction) have been shown to decrease venous return from the legs in humans and, in turn, to decrease the flow of blood through the inferior vena cava (36, 40). Although we did not measure

Table 5. Changes in blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>25% VO_{2peak}</th>
<th>45% VO_{2peak}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>Ctrl</td>
<td>CWR</td>
<td>Ctrl</td>
</tr>
<tr>
<td></td>
<td>118 ± 9</td>
<td>115 ± 4</td>
<td>139 ± 15</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>97 ± 9</td>
<td>80 ± 13</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>88 ± 4</td>
<td>92 ± 9</td>
<td>97 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SD. BP, blood pressure. *P < 0.05. †P < 0.01.
sure inferior vena caval flow, the observations of Wexler et al. (39) suggest that the greater oscillations in Pga (as well as an augmented mean Pga) induced by CWR may have resulted in transient decreases in inferior vena caval flow, especially during inspiration. The resultant decrease in venous return caused by this “abdominal Starling resistor” may have contributed to the decreases in cardiac output we observed (35, 36). However, it is unclear whether or not there is a critical Pga that would result in decreases in inferior vena caval flow in humans.

The changes in Ppl associated with CWR may also have played a role in the decreases in cardiac output we observed. In healthy subjects, SV appears to be more preload dependent rather than afterload dependent (5). During CWR, the peak inspiratory pressures were significantly less negative (Table 3), which would have caused a decrease in the intravascular venous return gradient via reducing the negativity of the right atrial pressure (14). However, the fact that the absolute change in Pes is smaller than the change in Pga and occurs “downstream” of the abdominal Starling resistor leads us to believe that its effects on venous return from the active tissues were minimal and that the reductions in venous return were primarily mediated by increases in Pga.

We measured changes in cardiac filling and emptying rates at rest and during exercise, and it appears that both are significantly decreased during CWR conditions. This finding suggests that SV may be decreased as a result of the inability to match venous return to the desired left ventricular outflow rate (due to increases in right atrial pressure and Pga) combined with a shorter length of filling time, resulting in a decreased preload (8).

Additionally, we examined the changes in left ventricular ejection time and diastolic filling time during the breathing cycle but found no significant differences between inspiration and expiration. This may be in part attributed to the variability of the occurrence of the cardiac cycle in relation to the respiratory cycle. It is also possible that the 30% drop in VC (and the associated fall in TLC) increases extracardiac pressure or Pga to the extent that the small additional changes associated with tidal excursions during exercise have little additional impact on venous return and ventricular function and subsequently on left ventricular filling and emptying rates.

Adaptations to constant-load exercise with a diminished cardiac output. For exercise to continue at a constant workload and constant VO$_2$ with a diminished cardiac output, O$_2$ extraction at the site of the muscle has to increase. This was demonstrated by a wider arterial-mixed venous O$_2$ difference (calculated from the Fick equation) at both exercise workloads. This pattern of increasing O$_2$ extraction in response to a diminished cardiac output is similar to that observed in patients with CHF during exercise (4).

In addition to the augmented O$_2$ extraction, the redistribution of blood flow via sympathetic activation may have helped to compensate for the decrease in cardiac output. Significant increases in circulating epinephrine and norepinephrine (Fig. 6) may have been elicited by a blood flow to metabolic rate mismatch at the site of the exercising muscles during the highest exercise intensity with CWR (31). The presence of such a “metaboreflex” in this study is supported by the observation of a significant pressor response during the highest workload (Table 5), which may have been elevated in an attempt to maintain perfusion pressure at the site of the active tissues (2, 31).

It is important to note that a growing body of evidence suggests that these metaboreflexes can originate from the respiratory muscles (11). Thus the large amount of work performed by the respiratory muscles during the CWR conditions in this study, combined with the reduced ability to increase cardiac output, may have resulted in an augmented competition for flow between the locomotor muscles and the respiratory muscles (11). The resultant sympathetic activation appeared to elicit a pressor response via systemic vasoconstriction, which is similar to that observed in the tachycardia-induced canine model of heart failure (10). The cardiovascular sequelae of this sympathoexcitation may have been exacerbated by the low-lung volume breathing pattern adapted by our subjects during CWR conditions (33). There is a growing body of evidence that a rapid, shallow breathing pattern may contribute to the excessive sympathoexcitation in patients with heart failure (9). The effect of low-lung volume breathing on sympathetic activation in other diseased states in which the chest wall is deformed or dysfunctional (e.g., pectus excavatum, ankylosing spondylitis, etc.) has yet to be determined.

Limitations. Limitations to this study include lack of a beat-to-beat analysis of SV and an inability to quantify the pressure relationships imposed by the respiratory muscles on the heart and great vessels in a human model. Without these parameters, it is difficult to determine the exact mechanisms for the reduction in cardiac output. Additionally, the measurement of inferior vena caval flow during exercise is difficult to assess noninvasively. Thus whether or not venous return in compromised by decreases in inferior vena caval flow is purely speculative.

It is also important to note that our estimates of respiratory muscle work primarily reflect the work performed on the lung and not the work done by the respiratory muscles per se. Thus the Wfr and Wel presented, along with the Ppl-time integrals, likely reflect only a fraction of the work performed by the respiratory muscles on the noncompliant rib cage during CWR conditions. However, we believe the fact that the respiratory muscles are performing a substantially greater amount of work than that portrayed by our work of breathing measures greatly increases the likelihood of the activation of the sympathetic nervous system via a metabolically mediated reflex.

An additional limitation was that EELV was not controlled for during our “mimic” trials (in which subjects mimicked both the VT and f during CWR conditions to control for the effect of breathing pattern alone
on cardiac output. Thus we cannot determine the effect of low-lung volume breathing alone on the sympathetic responses to steady-state exercise during CWR conditions.

The factors limiting exercise tolerance in patients with restrictive lung and chest wall diseases and CHF are not fully understood, and the interactions between the cardiovascular and respiratory systems during exercise are only beginning to be elucidated. Our goal was to create a human model that may augment the cardiorespiratory interactions that are similar in some respects to that which occurs in these disease states. Our data suggest that changes in intrathoracic and abdominal pressure generation along with reduced operating lung volumes may be a contributing influence to exercise intolerance in these patients. These changes may be more prominent in patients who exhibit excessive work of breathing, have more severe restrictive lung and chest wall changes, or are significantly overweight.

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