Acute Unloading of the Work of Breathing Extends Exercise Duration in Patients With Heart Failure

DONNA MANCINI, MD, LISA DONCHEZ, RN, SANFORD LEVINE, MD*


Objectives. This study investigated whether maximal exercise performance can be improved by acutely decreasing the work of breathing in these patients.

Background. Exertional dyspnea is a frequent limiting symptom in patients with heart failure. It may result from increased work of breathing.

Methods. Fifteen patients with heart failure and nine age-matched normal subjects underwent two maximal exercise tests. Subjects exercised twice in randomized, single-blind manner using room air (RA) and a 79% helium/21% oxygen mixture (He). Respiratory gas analysis, Borg scale recordings of perceived dyspnea and near infrared spectroscopy of an accessory respiratory muscle were obtained during exercise.

Results. In normal subjects there was no significant difference in peak oxygen uptake (\(V_\text{O}_2\)) (mean \(\pm\) SD) RA 38 \(\pm\) 8 vs. He 35 \(\pm\) 7 ml/kg per min), exercise duration (RA 724 \(\pm\) 163 vs. He 762 \(\pm\) 123 s) or peak minute ventilation (RA 97 \(\pm\) 27 vs. He 97 \(\pm\) 28 liters/min, all \(p = NS\)). Only three of nine control subjects thought that exercise with the He mixture was subjectively easier. In contrast, patients with heart failure exercised an average of 146 s longer with the He mixture (RA 868 \(\pm\) 293 vs. He 1,014 \(\pm\) 338, \(p < 0.01\)). Peak \(V_\text{O}_2\) (RA 19 \(\pm\) 4 vs. He 18 \(\pm\) 5 ml/kg per min) and peak minute ventilation (RA 53 \(\pm\) 12 vs. He 53 \(\pm\) 15 liters/min) were unchanged (both \(p = NS\)). The respiratory quotient at peak exercise was lower with the He mixture (RA 1.05 \(\pm\) 0.08 vs. He 0.98 \(\pm\) 0.06, \(p < 0.05\)). Thirteen of the 15 patients thought that exercise with the He mixture was subjectively easier (\(p < 0.02\) vs. control group).

Conclusions. In patients with heart failure, pulmonary factors, including respiratory muscle work and airflow turbulence, contribute to limiting exercise performance. Therapeutic interventions aimed at attenuating work of breathing may be beneficial.

(J Am Coll Cardiol 1997;29:590–6)
©1997 by the American College of Cardiology

In patients with heart failure, changes in pulmonary function occur as a consequence of chronic venous pulmonary hypertension. This abnormal hemodynamic function results in decreased lung compliance and an increase in airflow resistance, both of which are major components of the work of breathing (1–3). During exercise, the work of breathing is further increased because of the excessive ventilatory response, with a further increase in pulmonary pressures. Previous studies (4,5) have demonstrated an increase in the metabolic cost of breathing in patients with heart failure at rest and during exercise compared with that in normal control subjects. This elevated work of breathing probably contributes to the exertional dyspnea so characteristic of these patients.

Although exertional dyspnea is a major clinical symptom in these patients, it is presumed that exercise is limited by central or peripheral factors and not lung function. However, some previous studies (6,7) have suggested a pulmonary limitation to maximal exercise performance in some patients with heart failure. Cabanes et al. (7) demonstrated an improvement in both submaximal and maximal exercise performance after inhalation of methoxamine in patients with heart failure limited by dyspnea, presumably by a decrease in airflow resistance. Selective respiratory muscle function has also been shown (8) to improve exercise performance in these patients.

In the present study, we investigated the effect of acutely unloading the work of the respiratory muscles on exercise capacity and the sensation of dyspnea in patients with heart failure. We accomplished this by exercise using helium, an inert, nonabsorbable gas with a density 70% less than that of room air (9,10). Although helium is 10% more viscous than air, its lower density has been shown (9,10) to decrease airflow turbulence in both the large and small bronchial airways by maintaining laminar flow. We hypothesized that if exercise performance was limited in part by the metabolic costs of breathing, then exercise capacity would be improved during exercise with the normoxic helium mixture in patients with heart failure. Similarly if dyspnea were predominantly a consequence of the work of breathing, then the sensation of dyspnea during exercise would also be less.
Methods

Patients. Fifteen patients with heart failure participated in the study (13 men, 2 women; mean [± SD] age 52 ± 10 years, range 37 to 62; mean left ventricular ejection fraction 19 ± 11%). Twelve patients had cardiomyopathy, and only three had coronary artery disease. Body surface area averaged 1.88 ± 0.19 m².

Nine age-matched control subjects (three women, six men, mean age 49 ± 13 years, range 41 to 53) also participated. Body surface area was 1.87 ± 0.23 m². Both groups were comparable with regard to height and weight.

Standard pulmonary function tests, including lung volumes, flow rates and respiratory muscle strength, were performed in all subjects. Forced expired volume in 1 s divided by forced expired volume was comparable between the heart failure group and normal subjects. Respiratory muscle strength tended to be lower in patients with heart failure, although this did not achieve statistical significance (Table 1). Respiratory muscle strength was assessed by measuring maximal mouth pressures. Maximal inspiratory pressure was measured at residual volume, whereas maximal expiratory pressure was assessed at total lung capacity. Maximal inspiratory and expiratory pressures were recorded in triplicate or until a stable value was achieved (11).

The protocol was approved by the Human Studies Committee at Columbia Presbyterian Hospital. Written informed consent was obtained from all subjects.

Study protocol. Maximal symptom-limited treadmill exercise tests were performed twice in a 1-week period in randomized, single-blinded fashion. One test was performed using room air and the other a normoxic helium mixture (79% helium/21% oxygen). Patients exercised according to the modified Naughton protocol and control subjects by the Bruce protocol. All subjects had undergone a previous exercise test.

Subjects reported to the exercise laboratory in the fasting state. Near infrared light guides were applied to the sixth right intercostal space over the serratus anterior muscle to monitor accessory respiratory muscle oxygenation. Subjects were connected to a metabolic cart (Medical Graphics Cardio O₂) through a disposable pneumotach. Metabolic measurements, heart rate, blood pressure and pulse oximetry were monitored throughout exercise. Borg scale recordings of perceived dyspnea were obtained during the last minute of each work load and at the end of exercise. At the completion of both studies, the subject was asked which test, if any, was easier.

The metabolic cart was calibrated for volumetric analysis before the exercise tests using either room air or helium. The density of helium is 0.43 mg/liter standard temperature and pressure, dry (STPD). In contrast, the density of room air is 1.12 mg/liter STPD.

The normoxic helium mixture was connected by a quick release valve to a 100-liter Douglas bag fitted with two Hans Rudolph valves connected in series to a third Hans Rudolph valve coupled to a disposable pneumotach. The expired gas was vented into the atmosphere. This experimental design was used for both exercise tests, with a sham setup used during the room air test. Subjects were not permitted to speak during testing or 2 min into recovery because of the change in the tonal quality of the voice with helium.

Near infrared spectroscopy. Accessory respiratory muscle oxygenation was monitored using near infrared spectroscopy. We previously used this technique to noninvasively monitor skeletal muscle oxygenation (12–15). Both oxygenated and deoxygenated hemoglobin absorb light at 850 nm, whereas primarily deoxygenated hemoglobin absorbs light at 760 nm. Therefore, by monitoring the difference in absorption noted at these two wavelengths, it is possible to assess changes in hemoglobin oxygenation. The difference in absorption at 760 to 850 nm was used to assess serratus anterior muscle oxygenation. All studies were performed using the same gain settings on the spectrometer. Absorption changes were then expressed as arbitrary units of deviation from a stable baseline. The higher the arbitrary unit, the greater the muscle deoxygenation. A negative value represents an increase in oxygenation.

Statistical analysis. Data from patients and normal subjects were compared with Student paired or unpaired t tests, as appropriate. Relation between variables were examined by linear regression analysis. Chi-square analysis was used to examine nonnumeric differences between groups. A value of p < 0.05 was considered significant. Data are expressed as mean value ± SD.

Results

Exercise tests. The results of metabolic and ventilatory measurements for the normal subjects and patients with heart failure are shown in Table 2 and Figure 1. During rest, the respiratory quotient was significantly lower during helium (He) inhalation in both normal subjects (room air [RA] 0.81 ± 0.05 vs. He 0.74 ± 0.04, p < 0.05) and patients with heart failure (RA 0.84 ± 0.08 vs. He 0.76 ± 0.05, p < 0.05). No other hemodynamic, metabolic or ventilatory variable was affected.
by helium inhalation. The inspiratory duty cycle (i.e., the time in inspiration divided by the total time per breath) was similar during helium inhalation in both normal subjects (RA 0.49 ± 0.05 vs. He 0.50 ± 0.08, p = NS) and patients with heart failure (RA 0.45 ± 0.03 vs. He 0.45 ± 0.03, p = NS).

With exercise, peak oxygen uptake (Vo2) and minute ventilation remained unchanged in both tests in normal subjects and patients with heart failure. As with the rest data, the respiratory quotient at end-exercise was significantly lower in normal subjects, the respiratory quotient was reduced from 1.18 to 1.11 and from 1.05 to 0.98 in patients with heart failure (both p < 0.05). The duty cycle at peak exercise was not significantly different in normal subjects (RA 0.48 ± 0.02 vs. He 0.47 ± 0.02, p = NS) and patients with heart failure (RA 0.45 ± 0.03 vs. He 0.45 ± 0.03, p = NS).

Exercise duration measured in seconds for the individual subjects is shown in Figure 2. The exercise duration in normal subjects remained unchanged (Δ + 38 ± 66 s). However, in patients with heart failure, a significant increase in exercise duration was observed. Exercise duration increased an average of 2.4 min, from 869 to 1,013 s (Δ + 144 ± 147 s).

Near infrared spectroscopy. Minimal 760- to 850-nm absorption occurred during exercise in normal subjects. Near infrared data from a normal subject during exercise using room air and helium is illustrated in Figure 2. The 760- to 850-nm signal (i.e., the difference signal) shows minor changes with exercise.

In contrast, patients with heart failure demonstrated sustained accessory respiratory muscle deoxygenation with exercise that was ameliorated with exercise with helium (Fig. 3). When the 760- to 850-nm deflection was quantitated in arbitrary units, the maximal deflection for the patients with heart failure tended to be lower at peak exercise during the helium test, but this did not achieve statistical significance. However, if the near infrared signal is recorded at the same time point (i.e., maximal exercise duration of the test using room air), then accessory muscle deoxygenation is significantly reduced during the helium study (Fig. 4).

Ratings of perceived dyspnea. Perceived dyspnea at each level of exercise in the patients with heart failure during exercise with room air and the normoxic helium mixture is illustrated in Figure 5. Although perceived dyspnea tended to be lower with helium inhalation, these curves were not statistically different. However, 13 of the 15 patients with heart failure stated that the exercise test with helium was significantly easier than that with room air, whereas only three of the nine normal subjects were able to detect a difference (p < 0.05). Six of the patients were limited by dyspnea during exercise with room air; however, only two patients remained limited by dyspnea during the helium study (p = NS).

Table 2. Hemodynamic, Metabolic and Ventilatory Response to Exercise in Normal Subjects and Patients With Heart Failure Breathing Room Air and Helium During Rest and Exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>V̇O₂ (ml/kg per min)</td>
</tr>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Room air</td>
<td>82 ± 15</td>
<td>95 ± 11</td>
</tr>
<tr>
<td>Helium</td>
<td>78 ± 11</td>
<td>93 ± 13</td>
</tr>
<tr>
<td>CHF group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Room air</td>
<td>86 ± 14</td>
<td>82 ± 13</td>
</tr>
<tr>
<td>Helium</td>
<td>86 ± 14</td>
<td>86 ± 14</td>
</tr>
</tbody>
</table>

*p < 0.05 room air versus helium. Data presented are mean value ± SD. BP = blood pressure; HF = heart failure; HR = heart rate; RQ = respiratory quotient; V̇E = minute ventilation; V̇O₂ = oxygen consumption.

Figure 1. Exercise duration during exercise with room air and helium in the individual normal subjects and patients with heart failure. CHF = congestive heart failure.

![Figure 1](image-url)

![Figure 2](image-url)

![Figure 3](image-url)

![Figure 4](image-url)

![Figure 5](image-url)
**Discussion**

In the present study, we demonstrated that in normal subjects, acute unloading of the work of breathing using a normoxic helium mixture minimally affected exercise performance. Peak VO2, exercise duration and the sensation of dyspnea during exercise was unaffected in normal subjects. These findings support a cardiovascular limitation to exercise performance in normal humans. In contrast, in patients with heart failure there was a significant increase in exercise duration, a subjective decrease in exertional dyspnea and a lessening of accessory respiratory muscle deoxygenation. Therefore, in patients with heart failure, pulmonary factors appear to contribute to the limitation of peak exercise performance.

**Exercise response to helium.** Previous investigators have examined the exercise response of normal healthy adults while breathing a normoxic helium mixture (16–18). Some investigators have demonstrated an increase in exercise ventilation and peak VO2 in young healthy subjects, whereas others have not found any improvement in exercise performance. In our study, we were unable to demonstrate any improvement in exercise performance in the normal subjects while inhaling the normoxic helium mixture. Unlike some of the previous studies, we did not humidify the helium/oxygen mixture, which may have contributed to our inability to detect any significant differences. However it is more likely that in the absence of significant pulmonary pathology, exercise performance is not affected by the inhalation of a lighter density gas.

In patients with obstructive lung disease who exhibit an increased resistance to airflow, exercise performance may be improved using helium/oxygen mixtures. Improvement in rest indexes of lung function have been shown in some studies (19–21). However, Bradley et al. (20) demonstrated no improvement in submaximal exercise performance in 7 patients with advanced chronic obstructive pulmonary disease. Similarly, Martin et al. (21) failed to demonstrate any improvement in peak VO2, maximal minute ventilation or exercise duration in 11 pediatric patients with cystic fibrosis despite an improvement in resting spirometry. Estimates of perceived dyspnea were not obtained during those studies (21).

Similar to previous studies, we did not demonstrate an improvement in peak VO2 or peak minute ventilation during exercise with the normoxic helium mixture in patients with heart failure. However, we were able to demonstrate a significant improvement in exercise duration as well as a subjective decrease in the overall sensation of dyspnea during exercise in these patients. Our ability to detect this may have been related to differences in the exercise protocols. We used a steady state protocol rather than rapid incremental protocols (20,21).

**Possible mechanisms.** There are several possible explanations for the improved exercise performance in the patients with heart failure. Improvement could result as a consequence of decreased lung work from the lower density gas mixture. Although the work of breathing was not directly measured, minute ventilation during the exercise with room air and with

---

Figure 2. Near infrared absorption spectra during exercise with room air and helium in a normal subject.
the normoxic helium mixture was similar. Given the substantial differences in gas density of the two gases, work of breathing must have been reduced. Besides a simple mass effect, the improvement in exercise performance may have resulted from a decrease in airflow turbulence, with subsequent decrease in airflow resistance and work of breathing. Previously, Cabanes et al. (6) demonstrated bronchial hyperresponsiveness secondary to metacholine challenge in patients with heart failure. This bronchial hyperresponsiveness could be prevented by pretreatment with methoxamine. Pretreatment with methoxamine improved submaximal and maximal exercise performance in patients with heart failure limited by dyspnea. Cabanes et al. hypothesized that the improvement in exercise performance was related to a diminished airflow resistance. Our findings are concordant with these previous studies. Furthermore, our study extends the findings of Cabanes et al. because our study was not limited to patients who terminated exercise specifically from dyspnea.

Another possible hypothesis to explain our results could be

Figure 4. Bar graphs demonstrating 760- to 850-nm absorption in arbitrary units for patients with heart failure at end-exercise during inhalation of room air and at 850 s from the start of exercise and at peak exercise during inhalation of helium.

Figure 5. Comparison of perceived dyspnea at each level of treadmill exercise during exercise with room air and helium in patients with heart failure.
that with a decrease in the work of breathing, there is a shunting of blood from the lungs to the exercising limbs. In several previous studies, we demonstrated accessory respiratory muscle deoxygenation during exercise in patients with congestive heart failure from systolic dysfunction and valvular disease. In the latter study, after mitral valvuloplasty with a significant increase in valve area, respiratory muscle deoxygenation was attenuated. In the present study, we again demonstrated a progressive, sustained increase in respiratory muscle deoxygenation during exercise in the patients with heart failure. Peak 760- to 850-nm absorption tended to be lower during exercise with the normoxic helium mixture and was significantly reduced at comparable time points during exercise. This may represent a shift in blood flow such that more cardiac output is available to the limb musculature. This proposed shift in blood flow distribution could result in the ability to perform more work. The lessening of accessory respiratory muscle deoxygenation during exercise in patients with heart failure supports this theory, although without leg flow measurements this remains purely speculative. The lower respiratory quotient at end-exercise in the patients with heart failure also suggests that less anaerobic work is being performed by the respiratory muscles and all working muscles.

Although patients with heart failure were able to accurately distinguish between the two gas mixtures and consistently report a greater alleviation of dyspnea, this subjective change could not be quantitated during exercise by use of the Borg scale. This unidimensional measure was probably not sensitive enough to capture the qualitative difference perceived by the patients. One of the most difficult challenges in clinical medicine has been to design an adequate tool that assesses dyspnea. The great number of approaches to quantitating dyspnea implies that there is no ideal measurement for this multidimensional sensation.

Study limitations. A major limitation of the study was the single-blinded design. The investigator could have subconsciously encouraged the patient more when the helium/oxygen mixture was administered. However, the normoxic helium mixture was delivered through a closed system that required careful surveillance to ensure consistent delivery of the gas. At high work loads, the gas reservoir would be rapidly exhausted, thus, the investigators’ tendency was to terminate exercise sooner rather than later because of anxiety over possible inadequate gas delivery.

This study is also limited in that work of breathing measurements were not obtained during the exercise tests. However, by simple mass effects as well as probable decreases in airflow resistance in both groups, the work of breathing should be less. Our results may have been underestimated because the patients studied were limited by both exertional dyspnea and fatigue. Had we selected patients limited primarily by exertional dyspnea, we might have detected greater improvement during testing with the normoxic helium mixture.

Our failure to humidify the gas mixture may have also negatively affected our results because bronchoconstriction can be caused by the dryness of the gas. However, this would have a similar effect in both patients with heart failure and normal subjects.

Clinical implications. In patients with heart failure, the metabolic costs of breathing affects exercise performance. During exercise with the normoxic helium mixture where the work of breathing is less, patients can perform more exercise. Thus, in these patients there appears to be a pulmonary limitation to peak exercise performance. Alternatively, with a reduced work of breathing, blood flow may be redistributed to the limb muscles rather than the ventilatory muscles. More work can be performed at the same oxygen cost. Therapeutic approaches directed at reducing the work of breathing should improve exercise performance in these patients. Aggressive diuresis with significant reduction in lung water should and does improve both submaximal and maximal exercise performance. Bronchodilation with beta-agonists that decrease airflow resistance similarly should and does improve submaximal and maximal exercise performance (22). Finally, in patients with marked end-stage heart failure who are receiving treatment with home oxygen therapy, a normoxic helium mixture may provide greater relief.

In this study we also observed that the sensation of dyspnea in patients with heart failure is only slightly modified by acutely decreasing ventilatory muscle work. Previous studies (23) in posttransplant recipients have revealed an alleviation of exertional dyspnea despite an absence of reduction in diaphragmatic work. We also showed (24) in a small group of patients that selective respiratory muscle training ameliorates exertional dyspnea but does not diminish the work of breathing. Thus, all these studies suggest that ventilatory muscle work is not the predominant signal for the sensation of dyspnea. Other mechanisms, such as chemoreceptor activation, airflow resistance or muscle perfusion, alone or in combination, may be the primary determinant for this sensation.

References