Respiratory Muscle Function and Dyspnea in Patients With Chronic Congestive Heart Failure

Donna M. Mancini, MD; David Henson, MD; John LaManca, PhD; and Sanford Levine, MD

Background. Patients with heart failure (HF) frequently experience exertional dyspnea. Using near-infrared spectroscopy, we have previously demonstrated accessory respiratory muscle deoxygenation during exercise in these patients by monitoring changes in light absorption at 760–800 nm.

Methods and Results. To investigate whether low-frequency respiratory muscle fatigue occurs, we performed supramaximal bilateral transcutaneous phrenic nerve stimulation before and after maximal bicycle exercise in 10 patients with HF (age, 62±10 years; ejection fraction, 18±7%) and six normal subjects (age, 50±8 years). Maximal rates of contraction and relaxation, peak twitch tension, and maximal transdiaphragmatic pressure (Pdi) were derived before and after exercise from analysis of six to 12 twitches obtained at functional residual capacity. Pdi, time in inspiration (Ti), time per breath (TTOT), respiratory gases, ratings of perceived dyspnea and fatigue, and 760–800 nm near-infrared spectroscopy absorbency changes of the serratus anterior muscle were measured throughout exercise. The tension time index (TTdi) of the diaphragm was derived. In both normal and HF subjects, all parameters of diaphragmatic function (i.e., maximal rates of contraction and relaxation, peak twitch tension, and maximal Pdi) were unchanged before and after exercise. Mean Pdi was comparable at rest (normal, 3.7±1; HF, 5.8±2.9 cm H2O; p=NS) but significantly greater in patients with HF at peak exercise (normal, 12.1±3; HF, 18.3±6.6 cm H2O; p<0.05). TT/TOT of both groups was similar at rest and throughout exercise. TTdi was significantly greater at rest (normal, 0.01±0.01; HF, 0.03±0.02; p<0.05) and at peak exercise (normal, 0.03±0.02; HF, 0.10±0.03; p<0.04) in patients with HF. Significant accessory respiration muscle deoxygenation was noted only in patients with HF (peak exercise: normal, −1±3; HF, 28±15 arbitrary units; p<0.01). Linear correlation analysis was performed between ratings of perceived dyspnea and parameters of pulmonary and diaphragmatic function. Significant correlations were observed between ratings of perceived dyspnea and maximal inspiratory and expiratory pressure, the TTdi of the diaphragm, near-infrared absorption changes, and forced expiratory volume in 1 second (FEV1) (all r>0.5; p<0.05). Thus, respiratory muscle strength, work, and oxygenation were significantly correlated with the degree of dyspnea.

Conclusions. We conclude that low-frequency diaphragmatic muscle fatigue does not occur despite accessory respiratory muscle deoxygenation during exercise in patients with HF. However, diaphragmatic work as assessed by the TTdi is dramatically increased in patients with HF and approaches levels previously shown to generate fatigue. The sensation of dyspnea appears closely related to respiratory muscle function. (Circulation 1992;86:909–918)

Key Words • heart failure, congestive • exercise • dyspnea

Patients with heart failure are frequently limited in their activities of daily living by exertional dyspnea. The mechanism underlying dyspnea remains unclear. Early lactic acidosis, ventilation perfusion abnormalities, activation of pulmonary juxta-capillary receptors, altered arterial Pco2 control of ventilation, chronic fibrotic changes, and increased work of breathing are some proposed mechanisms.1–5

One hypothesis for dyspnea is that the reduced cardiac output that occurs during exercise in patients with heart failure results in respiratory muscle ischemia and, ultimately, respiratory muscle fatigue.6 Using near-infrared spectroscopy, a noninvasive technique based on the optical properties of hemoglobin,7,8 we recently demonstrated significant accessory respiratory muscle deoxygenation during bicycle exercise in patients with heart failure but not in age-matched control subjects.9 This finding suggests that respiratory muscle underperfusion occurs in these patients. The present study was undertaken to investigate whether this muscle underperfusion results in low-frequency respiratory muscle fatigue.

Accordingly, we performed supramaximal bilateral transcutaneous phrenic nerve stimulation before and immediately after maximal bicycle exercise in heart failure and normal subjects. This technique provides an objective assessment of diaphragmatic fatigue that is independent of patient effort.10,11 We reasoned that if patients with heart failure developed respiratory muscle fatigue with maximal exercise, then the maximal transdiaphragmatic pressure as well as the maximal rate of contraction and relaxation of each stimulation would be reduced.

Furthermore, we sought to investigate the relation between parameters of respiratory muscle function and

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ratings of perceived dyspnea\textsuperscript{12} during submaximal exercise. Increased activity of the respiratory muscles and/or muscle weakness rather than fatigue may be sufficient to evoke the sensation of dyspnea. Therefore, if respiratory muscle function was an important determinant of dyspnea, we reasoned that significant correlations would be observed between parameters of respiratory function and ratings of perceived dyspnea measured during exercise.

### Methods

**Patient Population**

Nine men and one woman with an average age of 62±10 years were studied. Etiology of heart failure was coronary artery disease in six patients and dilated cardiomyopathy in four patients. Four patients had undergone prior coronary artery bypass surgery. One patient was in New York Heart Association functional class IV, five patients were in class III, two patients were in class II, and two patients were in class I congestive heart failure. Left ventricular ejection fraction averaged 18±7%. All patients were receiving digoxin, diuretics, and angiotensin converting enzyme inhibitors. Average height was 68±4 in., and average weight was 173±27 lb. Body surface area averaged 1.93±0.20 m\(^2\). None of the patients had a prior history of lung disease, kyphoscoliosis, or recent respiratory infections. Four patients never smoked. Six patients were ex-smokers (average pack-years, 17±13) who had stopped smoking a mean of 11.0 years before the study (range, 4–22 years). Patients limited by angina or claudication were excluded from the study.

Six normal male subjects with an average age of 50±7 years (\(p<0.05\) versus heart failure) also participated in the study. Average height was 70±4 in., and average weight was 175±31 lb. Body surface area averaged 1.96±0.22 m\(^2\). All subjects had no significant past medical history. All subjects were currently nonsmokers. Three subjects never smoked; three subjects had a past history of smoking (12–9 pack-years) but had stopped smoking a mean of 5 years (range, 1–13 years) before study. All subjects had a normal physical examination, ECG, and pulmonary function tests.

The protocol was approved by the Committees on Studies Involving Human Beings at the Philadelphia Veterans Administration Center and the Hospital of the University of Pennsylvania. Written informed consent was obtained from all subjects.

**Experimental Protocol**

Pulmonary function tests were obtained in all subjects on a separate day than that of the exercise studies. Two exercise studies were then performed in a 1-week period. The first exercise study (i.e., study 1) was performed with near-infrared absorption and respiratory gas measurements. The second exercise study (i.e., study 2) was performed with transcutaneous phrenic nerve stimulation before and after exercise. All exercise tests were performed with subjects in the fasting state.

**Study 1.** Upon arrival in the exercise laboratory, maximal inspiratory and expiratory pressures were measured in triplicate. Near-infrared fiberoptic light guides were placed on the sixth intercostal space, the anterior axillary line over the serratus anterior muscle, an accessory inspiratory muscle. The subjects were then positioned upright on a Monarch exercise bicycle ergometer, and they breathed through a three-way Hans Rudolph valve into a SensorMedics (Anaheim, Calif.) metabolic cart for respiratory gas analysis. Arterial saturation was monitored using an Ohmeda ear oximeter.

After a 3-minute rest period, subjects performed maximal bicycle exercise. Exercise was begun at a workload of 0 W and increased by 25-W increments every 3 minutes to symptom-limited maximum. Blood pressure was measured by cuff sphygmomanometry at the end of each work load. Respiratory gases, arterial saturation, heart rate, and near-infrared spectra were monitored throughout exercise. Borg scale ratings of perceived dyspnea and fatigue\textsuperscript{12} were obtained at the end of each work load. At peak exercise, maximal inspiratory and expiratory pressures were again measured.

Near-infrared spectroscopy noninvasively assesses skeletal muscle oxygenation. Both oxygenated and deoxygenated hemoglobin absorb light at 800 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.\textsuperscript{7a} The difference in absorption at 760–800 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 was the muscle deoxygenation. A negative value represents hyperoxygenation. The 800-nm absorption curve was used to assess total hemoglobin concentration and, thus, changes in blood volume.

**Study 2.** On a separate day, all subjects arrived at the Philadelphia Veterans Medical Center Pulmonary Exercise Laboratory in the fasting state. Costal diaphragmatic and ECG electrodes were applied. Esophageal and gastric balloons were inserted after the nares were anesthetized. Transcutaneous supramaximal bilateral phrenic nerve stimulation was performed with the subject seated in a chair with lung volume fixed at functional residual capacity. Two series of six stimulations were performed. Another series of stimulations was repeated with the subject performing a Muller maneuver. Subjects then performed bicycle exercise as previously described with transdiaphragmatic pressure and ventilatory measurements. Transcutaneous supramaximal bilateral phrenic nerve stimulation was repeated within 3–5 minutes after exercise.

Patients were prepared for supramaximal bilateral phrenic nerve stimulation in the following manner. A pair of surface-stimulating electrodes (TECA, model 9523-4, Pleasantville, N.Y.) with a cathode diameter of 8 mm were initially applied to the skin surface on the posterior border of the sternomastoid muscle at a position midway between the clavicular head and the mandibular angle. The stimulating electrodes were adjusted to deliver constant current square-wave electrical pulses of 100-\(\mu\)sec duration; the current to each electrode could be independently adjusted to a maximum of 50 mA. The frequency of electrical stimulation.
was adjusted to deliver one stimulation per second (1 Hz).

The diaphragmatic action potential (i.e., M wave) was used to determine electrode position and current required for supramaximal phrenic nerve stimulation. A pair of 16-mm diameter (Beckman, model 651524, Fullerton, Calif.) skin electrodes were placed in the seventh intercostal space midway between the anterior axillary and midaxillary line on each side of the thorax. Each electrode was attached to a preamplifier (TECA, model PA63T) connected to an oscilloscope monitor (TECA, model M). Stimulating electrodes were repositioned on each side of the neck until the largest possible M wave from each of the hemidiaphragms was obtained; these positions were then marked on the neck. These marks served as reference points for postexercise stimulations. To obtain maximum M wave amplitude, the stimulating current was increased until no further increment in M wave amplitude could be elicited; to ensure supramaximal stimulation, the current was then increased by another 20%.

Because changes in lung volume can affect diaphragmatic twitch parameters, all diaphragmatic stimulations were carried out with the subject relaxed at functional residual capacity as measured by spirometry. Before administering each series of approximately six stimulations, the spirometer mouthpiece was occluded at the end of a normal breath, i.e., functional residual capacity; therefore, each series of phrenic nerve stimulations was performed at essentially the same lung volume. A minimum of two series were performed before and after exercise.

Changes in thoracoabdominal configuration can also affect diaphragmatic twitch parameters; therefore, each patient assumed a standard seated posture while leaning against the back of a rigid chair with each arm positioned on an armrest. Finally, each patient was instructed to look straight ahead to ensure standard head position.

M waves from each hemidiaphragm were digitized at a rate of 512 Hz and analyzed by interactive computer program (PDP 11/73, Digital Equipment, Maynard, Mass.). For each M wave, the computer algorithm computed peak-to-trough amplitude (i.e., M wave height) as well as the integrated area of the full-wave rectified signal (i.e., M wave area).

The changes in transdiaphragmatic pressure elicited by each phrenic nerve stimulation (peak twitch tension) was defined as the maximum increase in twitch tension developed over a 10-msec time interval. Maximum rate of contraction was defined as the maximum rate of twitch tension development over a 10-msec time interval. Maximum rate of relaxation was defined as the maximum rate of twitch tension relaxation over a 10-msec time interval; one-half relaxation time (T1/2) was defined as the time required for decay of the peak twitch tension to one-half its value. Criteria used to reject analysis of diaphragmatic twitches were the same as those previously described.11

Each subject's transdiaphragmatic pressure maximum was determined using the twitch interpolation technique of Bellemare and Bigland-Ritchie.12 Briefly, this technique involves the superimposition of diaphragmatic twitches elicited by supramaximal bilateral phrenic nerve stimulation upon voluntary diaphragmatic contraction (i.e., while performing a Muller maneuver). As more diaphragmatic motor neuron units are progressively voluntarily recruited during the Muller maneuver, fewer are available for recruitment by phrenic nerve stimulation; therefore, the peak twitch tension elicited by each stimulus becomes smaller as the voluntary transdiaphragmatic pressure approaches maximum (Figure 1). Indeed, if the subject is able to achieve transdiaphragmatic pressure maximum and, therefore, recruit every motor neuron unit, no additional peak twitch tension can be elicited by phrenic nerve stimulation. However, because many patients are either unable or unwilling to achieve transdiaphragmatic pressure maximum defined in this manner (i.e., twitch transdiaphragmatic pressure maximum), it must be derived by extrapolating the linear relation between peak twitch tension and voluntary transdiaphragmatic pressure to a peak twitch tension of 0 cm H₂O. Both twitch transdiaphragmatic pressure maximum as well as voluntary transdiaphragmatic pressure maximum were used to assess diaphragmatic function after exercise.

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Top to bottom: Stimulus onset, right and left costal diaphragmatic electromyograms (EMGs), mass action potential of the diaphragm (M waves), and ECG spikes at a constant functional residual capacity (FRC); transdiaphragmatic (Pdi) twitches superimposed on a voluntary diaphragmatic contraction. A single twitch at functional residual capacity is illustrated at the far right.
TABLE 1. Pulmonary Function Tests in Heart Failure Subjects and Normal Patients

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (n=6)</th>
<th>Percent predicted</th>
<th>Heart failure patients (n=10)</th>
<th>Percent predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
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<tr>
<td>FVC (l)</td>
<td>5.2±0.9</td>
<td>115±15</td>
<td>3.2±0.8*</td>
<td>86±22</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>3.9±0.8</td>
<td>104±18</td>
<td>2.3±4.7*</td>
<td>79±23</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>74±5</td>
<td>...</td>
<td>73±8</td>
<td>...</td>
</tr>
<tr>
<td>Maximum voluntary ventilation (l)</td>
<td>145±21</td>
<td>122±18</td>
<td>89±19*</td>
<td>88±17</td>
</tr>
<tr>
<td>Maximal inspired pressure (cm H₂O)</td>
<td>101±14</td>
<td>86±10</td>
<td>81±23</td>
<td>76±15</td>
</tr>
<tr>
<td>Maximal expired pressure (cm H₂O)</td>
<td>184±46</td>
<td>81±19</td>
<td>161±49</td>
<td>80±21</td>
</tr>
<tr>
<td>Lung volumes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung capacity (l)</td>
<td>7.4±1.1</td>
<td>113±12</td>
<td>5.0±0.8*</td>
<td>85±14</td>
</tr>
<tr>
<td>Functional residual capacity (l)</td>
<td>3.9±0.4</td>
<td>109±15</td>
<td>2.7±0.5*</td>
<td>81±19</td>
</tr>
<tr>
<td>Residual volume (l)</td>
<td>2.1±0.5</td>
<td>106±26</td>
<td>1.7±0.5</td>
<td>84±16</td>
</tr>
<tr>
<td>Diffusing capacity (ml/min/mm Hg)</td>
<td>31.5±3.4</td>
<td>97±9</td>
<td>20.9±7.5*</td>
<td>74±16</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.
*p<0.05 normal versus heart failure.

Measurement of esophageal, gastric, and transdiaphragmatic pressures was performed at rest, during, and after exercise. Esophageal pressure and gastric pressure were directly measured by 100-110-cm catheters custom fitted with 10-cm latex balloons according to the method of Milic-Emili. Transdiaphragmatic pressure was derived by electrical subtraction of esophageal pressure from gastric pressure.

During bicycle exercise, the subjects breathed through a mouthpiece connected to a specially modified two-way nonrebreathing valve (Hans Rudolph, Kansas City, Mo.). The subject inspired air through an inspiratory pneumotachograph (model 3800, Hans Rudolph) connected to a variable reluctance pressure transducer (model MP45-871, Validyne Engineering, Northridge, Calif.).Expired gas was directed through the expiratory valve into the expiratory pneumotachograph (model 3800, Hans Rudolph) and then into a 6-l mixing chamber. Ventilatory frequency, inspiratory time per breath, and the duty cycle, i.e., fraction of breathing cycle spent in inspiration, were derived from these signals. The time-tension index of the diaphragm as defined by Bellemare was derived for each breath as the product of the duty cycle and the mean transdiaphragmatic pressure divided by the maximal voluntary transdiaphragmatic pressure.

Statistical Analysis
Data from patients with heart failure and normal subjects at rest and during exercise were compared with Student’s nonpaired and paired t tests or two-way repeated-measures ANOVA as appropriate. The relations between variables were examined by linear regression analysis. A value of p<0.05 was considered significant. Data are expressed as mean±SD.

Results
Pulmonary Function Tests
The results of the pulmonary function tests obtained in normal and heart failure subjects are listed in Table 1. Pulmonary function tests were normal in the control group. However, in patients with heart failure, lung volumes, maximal voluntary ventilation, expiratory flow rates, and diffusing capacity were significantly reduced. Ratio of FEV₁ to forced vital capacity was normal in both groups. Maximal inspiratory and expiratory pressures tended to be reduced in patients with heart failure, although this did not achieve statistical significance.

Exercise Measurements
At rest, patients with heart failure had comparable heart rates (normal, 82±11; heart failure, 86±15 beats per minute), mean arterial blood pressure (normal, 96±6; heart failure, 90±10 mm Hg), oxygen consumption (normal, 4.2±0.8; heart failure, 3.4±1.3 ml/kg/min), respiratory quotients (normal, 0.78±0.05; heart failure, 0.77±0.08), and arterial saturation (normal, 97±1%; heart failure, 97±1%) when contrasted to the normal subjects (all p=NS). At peak exercise, heart rate (normal, 167±11; heart failure, 136±18 beats per minute), mean arterial blood pressure (normal, 140±9; 150±11; heart failure, 130±18; 140±20 mm Hg), oxygen consumption (normal, 8.5±1.5; heart failure, 8.0±1.0 ml/kg/min), respiratory quotients (normal, 0.85±0.05; heart failure, 0.78±0.08), and arterial saturation (normal, 97±1%; heart failure, 97±1%) were significantly reduced.

FIGURE 2. Bar graphs showing maximal inspiratory and expiratory pressures before and at peak exercise in normal subjects and heart failure patients (CHF) (mean±SEM).
heart failure, 114±18 mm Hg), and oxygen consumption (normal, 33±11; heart failure, 15.6±5.9 ml/kg/min) were significantly reduced in patients with heart failure (all p<0.05). Both groups achieved comparable respiratory exchange ratio consistent with maximal or near-maximal exertion (normal, 1.09±0.15; heart failure, 1.03±0.15).

At rest, patients with heart failure had a significantly decreased maximal expiratory pressure and tended to have a reduced maximal inspiratory pressure when contrasted to normal subjects. At peak exercise, patients with heart failure and normal subjects exhibited significant decreases in maximal inspiratory and expiratory pressures (Figure 2).

**Near-Infrared Spectroscopy**

At all exercise work loads, 760–800 absorption changes were significantly greater in heart failure subjects than in normal subjects (peak exercise: normal, −3±6; heart failure, 28±5 arbitrary units; p<0.001). This indicates that during exercise, patients with heart failure develop progressive deoxygenation of their serratus anterior muscle. No significant change occurred in the 800-nm signal throughout exercise in either normal or heart failure subjects, indicating total blood volume was unchanged during exercise. Representative near-infrared absorption spectra at rest and during exercise in a normal subject and a heart failure patient are illustrated in Figure 3.

**Bilateral Transcutaneous Phrenic Nerve Stimulation**

In three patients, we were unable to complete the phrenic nerve stimulation protocol. One patient became exhausted after the initial phrenic nerve stimulation protocol and could not exercise. In two patients, we were unable to transcutaneously stimulate the phrenic nerve, probably due to excess adipose tissue.

Phrenic nerve stimulation was successfully performed in seven patients with heart failure and six control subjects. The M wave amplitude, i.e., peak to trough height and M wave integrated area of the right and left hemidiaphragms, were comparable before and after exercise in both normal and heart failure subjects (Table 2). Thus, the degree of diaphragmatic stimulation was comparable in each group before and after exercise.

To verify that phrenic stimulation was performed at functional residual capacity, esophageal pressure measured at the end of a normal breath through a spirometer was compared with the esophageal pressure at the time of phrenic nerve stimulation in all subjects. Esophageal pressure was −7.0±1.3 cm H2O at the end of a
normal breath and $-7.0 \pm 1.2$ cm H$_2$O at the time of phrenic nerve stimulation ($p=NS$).

Results of the diaphragmatic twitch measurement data are presented in Table 3. Preexercise peak twitch tension, maximal rate of contraction, maximal rate of relaxation, and $T_{1/2}$ were comparable for the two groups. No significant change in any parameter occurred after exercise in both groups.

Figure 4 illustrates the derivation of maximal twitch transdiaphragmatic pressure in a normal subject and a heart failure patient before and after exercise. Resting maximal twitch transdiaphragmatic pressure was comparable between both groups. After exercise, maximal twitch transdiaphragmatic pressure was unchanged. Voluntary transdiaphragmatic pressure maximum was also unchanged after exercise in both (Table 3).

**Transdiaphragmatic Pressure Measurements**

Transdiaphragmatic pressure measurements were performed in nine patients. At rest (normal, 0.28±0.07; heart failure, 0.32±0.04) and peak exercise (normal, 0.44±0.07; heart failure, 0.45±0.03), the duty cycle (the time in inspiration divided by the time per breath) was comparable between both groups ($p=NS$). Transdiaphragmatic pressure tended to be higher at rest (normal, 3.7±1.0; heart failure, 5.8±2.9 cm H$_2$O, $p=NS$) and was significantly greater at peak exercise (normal, 12.1±3.0; heart failure, 18.6±6.6 cm H$_2$O; $p<0.05$) in patients with heart failure than in normal control subjects. The tension time index was increased at rest and throughout exercise in patients with heart failure compared with normal subjects (Figure 5). This was primarily due to increased transdiaphragmatic pressures as the duty cycle was comparable between groups. The tension time index was significantly correlated with near-infrared absorption changes in patients with heart failure ($r=0.69, p<0.0001$).

**Ratings of Perceived Dyspnea and Fatigue**

Dyspnea was the primary limiting symptom in two patients and three normal subjects. However, during exercise, all subjects experienced dyspnea and fatigue, which was equal in intensity at both absolute and normalized (percent peak Vo$_2$) work loads. In patients with heart failure, Borg ratings of fatigue and dyspnea were significantly greater than for normal subjects at the same absolute work load but comparable for work loads normalized for percent peak Vo$_2$ (Table 4).

To investigate what objective variable best predicts dyspnea, Borg scale readings at a fixed exercise work load, i.e., 25 W, were correlated with parameters of pulmonary and diaphragmatic function. A significant negative correlation was observed between both parameters of respiratory muscle strength, i.e., maximal inspiratory and expiratory pressures and Borg Scale recordings. Significant correlations were also observed with FEV$_1$, near-infrared absorption changes, and the tension time index of the diaphragm. Thus, parameters of respiratory muscle strength, work, oxygenation, and air flow were critical variables for determining dyspnea (Table 5).

**Discussion**

Dyspnea is a frequently limiting symptom in patients with heart failure, yet the mechanism underlying dyspnea remains unclear. The respiratory muscles have been proposed to be key modulators of this sensation.$^{17,18}$ Indeed, a unified mechanism for dyspnea based

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**Table 2. Comparison of the M Wave Height and Area of Left and Right Phrenic Nerve Before and After Exercise in Normal Subjects and Heart Failure Patients**

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Heart failure patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before exercise</td>
<td>After exercise</td>
</tr>
<tr>
<td>M wave height (arbitrary units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1.6±1.2</td>
<td>1.6±1.2</td>
</tr>
<tr>
<td>Right</td>
<td>2.2±1.1</td>
<td>2.3±1.4</td>
</tr>
<tr>
<td>M wave area (arbitrary units)$^{2}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>16.8±8.5</td>
<td>18.3±10.8</td>
</tr>
<tr>
<td>Right</td>
<td>24.3±12.0</td>
<td>25.2±12.1</td>
</tr>
</tbody>
</table>

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**Table 3. Summary of Twitch Measurement Data in Normal Subjects and Patients With Heart Failure Before and After Maximal Bicycle Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Heart failure patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before exercise</td>
<td>After exercise</td>
</tr>
<tr>
<td>PTT (cm H$_2$O)</td>
<td>18.8±9.3</td>
<td>18.4±10.1</td>
</tr>
<tr>
<td>MRC (cm H$_2$O/mssec)</td>
<td>0.42±0.27</td>
<td>0.39±0.29</td>
</tr>
<tr>
<td>MRR (cm H$_2$O/mssec)</td>
<td>$-0.18\pm0.09$</td>
<td>$-0.18\pm0.08$</td>
</tr>
<tr>
<td>$T_{1/2}$ (mssec)</td>
<td>75.3±23.5</td>
<td>83.0±37.8</td>
</tr>
<tr>
<td>Twitch Pdi max (cm H$_2$O)</td>
<td>106±32</td>
<td>101±37</td>
</tr>
<tr>
<td>Voluntary Pdi max (cm H$_2$O)</td>
<td>104±22</td>
<td>98±25</td>
</tr>
</tbody>
</table>

PTT, peak twitch tension; MRC, maximum rate of contraction; MRR, maximum rate of relaxation; Twitch Pdi max, maximum transdiaphragmatic pressure using the interpolation technique of Bellemare and Bigland-Ritchie; $T_{1/2}$ (mssec), half time of recovery; Voluntary Pdi max, volitional maximum transdiaphragmatic pressure.
on respiratory muscle function is that breathlessness occurs when the activity of the respiratory muscles are increased and/or the respiratory muscles are weak. Usually, skeletal muscles are not viewed as a sensory organ but simply a mechanical system. However, muscles have the capacity to sense effort, tension, displacement, and fatigue via tendon organs, muscle spindles, joint receptors, and small nerve endings. Varying respiratory muscle strength will result in differences in perception of load and dyspnea, whereas vagal blockade will not.19-22

Respiratory muscle function has not been well studied in patients with chronic congestive heart failure. Only one prior report described inspiratory muscle weakness in patients with mitral valve disease.23 In our study, we sought to investigate respiratory muscle function and perfusion in patients with heart failure. Specifically, we sought to investigate whether low-frequency respiratory muscle fatigue occurs after exercise in these patients. We have previously demonstrated accessory respiratory muscle deoxygenation during bicycle exercise in patients with heart failure through the application of near-infrared spectroscopy. We thus hypothesized that respiratory muscle ischemia may occur, producing low-frequency diaphragmatic fatigue.6

TABLE 4. Borg Scale Ratings of Dyspnea and Fatigue at Absolute Work Loads and at Work Loads Normalized for Peak VO2 in Normal Subjects and Heart Failure Patients

<table>
<thead>
<tr>
<th>Borg scale ratings</th>
<th>Dyspnea</th>
<th>Fatigue</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Work load (W)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>6.8±0.8</td>
<td>10.4±1.9*</td>
</tr>
<tr>
<td>50</td>
<td>7.3±1.5</td>
<td>12.3±2.6*</td>
</tr>
<tr>
<td>75</td>
<td>9.2±1.7</td>
<td>14.3±2.0*</td>
</tr>
<tr>
<td>Peak VO2 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-50</td>
<td>10.5±2.8</td>
<td>9.1±2.2</td>
</tr>
<tr>
<td>-75</td>
<td>12.8±2.2</td>
<td>11.1±1.2</td>
</tr>
<tr>
<td>100</td>
<td>16.7±2.0</td>
<td>16.6±1.4</td>
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*p<0.05 normal vs. heart failure.
To test this hypothesis, we used the technique of low-frequency bilateral transcutaneous phrenic nerve stimulation before and after maximal exercise. Diaphragmatic fatigue can be demonstrated if, under identical conditions of 1) electrical stimulation intensity (assessed by stability of the diaphragmatic action potentials or M waves), 2) lung volume (measured by spirometry), and 3) thoracoabdominal configuration, a reduction in transdiaphragmatic pressure development (i.e., peak twitch tension) occurs after an intervention (in this case, bicycle exercise). The significant advantage of bilateral phrenic nerve stimulation over voluntary generation of transdiaphragmatic pressure is that phrenic nerve stimulation is not influenced by patient motivation or by the phenomenon of central fatigue.10,11,13

With bilateral transcutaneous phrenic nerve stimulation, we were unable to demonstrate low-frequency diaphragmatic fatigue in either age-matched normal subjects or patients with heart failure after maximum bicycle exercise. Peak twitch tension, maximal rates of contraction, and relaxation, half time of recovery, and twitch transdiaphragmatic pressure maximum were unchanged after exercise in both normal and heart failure subjects. Failure to demonstrate respiratory muscle fatigue is not surprising, as fatigue should imply eminent respiratory muscle failure. In addition, most of our subjects terminated exercise due to leg fatigue rather than dyspnea. Prior attempts to demonstrate limb fatigue in patients with heart failure by decreased muscle strength and/or electromyelographic changes were similarly difficult.24

In this study, we demonstrated a significant reduction in maximal inspiratory and expiratory pressures at peak exercise in both normal subjects and heart failure patients, which is consistent with high-frequency fatigue. These findings are similar to Davies et al,25 who demonstrated a reduction in maximal inspiratory and expiratory pressures in heart failure patients but not normal subjects after treadmill exercise. Our inability to detect high-frequency fatigue via phrenic nerve stimulation may have been due to the 3–5-minute time delay in recording measurements after exercise. Alternately, these reductions in maximal inspiratory and expiratory pressures may be due to mechanisms other than peripheral muscle fatigue, i.e., inability (central fatigue) or unwillingness of the subjects to generate maximal effort shortly after maximal exercise.

The work of the diaphragm as assessed from the tension time index was significantly greater in patients with heart failure at rest and throughout exercise compared with normal subjects. This index is calculated for each breath and is the product of the duty cycle and the ratio of the mean transdiaphragmatic pressure to maximal transdiaphragmatic pressure.15 It approximates the oxygen consumption of the diaphragm. The significant increase in the tension time index resulted primarily from increased transdiaphragmatic pressure as the duty cycle was comparable between both groups. Although diaphragmatic fatigue is thought to occur when the tension time index reaches a ratio of 0.15 or greater,15 this fatiguing ratio in ischemic muscle is probably lower. Furthermore, the high tidal volumes, breathing frequency, and minute ventilation associated with exercise may further lower the fatigue threshold.26 In six of nine patients, the tension time index at end exercise was ≥0.1 and thus approached fatiguing levels.

Increase in diaphragmatic oxygen consumption would imply an increase in oxygen extraction and/or perfusion. In humans, it is technically impossible to monitor diaphragmatic blood flow. However, via use of the near-infrared spectrometer, we are now able to monitor accessory respiratory muscle perfusion.9 In this study, accessory respiratory muscle deoxygenation was again demonstrated in all patients with heart failure but not in normal control subjects. This response correlated significantly with the progressive increase in the tension time index. This suggests that the near-infrared absorbency changes of the accessory respiratory muscle provides an indirect monitor of diaphragmatic oxygenation. Furthermore, these findings imply that in patients with heart failure, the decreased cardiac output response to exercise results in increased oxygen extraction to maintain respiratory muscle function.

Perceived ratings of dyspnea assessed by the Borg scale correlated significantly with parameters of respiratory muscle strength, muscle oxygenation, diaphragmatic work, and airflow (FEV1). Our results are in agreement with previous investigators,17 who have emphasized the importance of both air flow and respiratory muscle strength in patients with lung disease. Our results extend these observations with the addition of muscle oxygenation data.

Our findings suggest that respiratory muscle function is critical for the genesis of dyspnea. Thus, the metabolic and histochemical characteristics of these muscles gain in importance. Previous studies using 31P magnetic resonance spectroscopy have demonstrated metabolic abnormalities in patients with heart failure in limb skeletal muscle characterized by decreased oxidative capacity and earlier shift to glycolytic metabolism.27–29 Intrinsic skeletal muscle abnormalities and generalized muscle atrophy have also been described in patients with heart failure.30–33 Skeletal muscle metabolic and histochemical changes are probably not confined to the limb musculature but likely involve the respiratory muscles as well. Diaphragmatic muscle atrophy has been described in chronically ill patients and in patients with chronic obstructive lung disease who have lost weight.34,35 Thus, intrinsic respiratory muscle changes may also occur in patients with heart failure and contribute to the generation of dyspnea.
Study Limitations

Bicycle exercise primarily provides a stress for the quadriceps muscle; therefore, one might anticipate development of limb muscle fatigue before the onset of respiratory muscle fatigue. Treadmill exercise may have been preferable. In addition, we did not select patients whose primary limitation to exercise was dyspnea or patients with grossly abnormal ventilation during exercise.

Monitoring of the crural diaphragmatic electromyography may have provided additional information concerning the fatigue state of the diaphragm (i.e., comparison of preexercise and postexercise diaphragmatic electromyography with respect to high-to-low ratio and centroid and median frequencies). However, it is unclear whether changes in diaphragmatic electromyography have any clinical relevance because they are often transient (lasting only minutes), unlike the reduction of diaphragmatic force associated with low-frequency diaphragmatic fatigue, which can last for many hours.\(^\text{10}\)

The use of bilateral phrenic nerve stimulation to assess diaphragmatic function makes several assumptions, which we have addressed in previous studies.\(^\text{11}\) One basic assumption of this technique is the constancy of the diaphragmatic action potentials (i.e., M waves) recorded from each hemidiaphragm during preexercise and postexercise bilateral phrenic nerve stimulation reflected the same number of motor neuron units recruited with each stimulation. Most subjects had constancy of both M wave amplitude and area during preexercise and postexercise measurements. One subject with an increase in M wave amplitude during postexercise measurements developed diaphragmatic fatigue after exercise that was not masked by lack of constancy of diaphragmatic stimulation.

Clinical Implications

This study demonstrates greatly increased diaphragmatic work and accessory respiratory muscle deoxygenation in patients with heart failure. Furthermore, it suggests that respiratory muscle function is critical in the perception of dyspnea. How chronic therapeutic interventions affect respiratory muscle function has not been studied in patients with heart failure. Only aerobic training\(^\text{36}\) and cardiac transplantation\(^\text{37}\) have been shown to ameliorate the excessive ventilatory response to exercise in these patients. Respiratory muscle training\(^\text{38}\) and nutritional supplementation\(^\text{39}\) have been shown to improve respiratory muscle function and dyspnea in patients with chronic obstructive lung disease; patients with heart failure may also achieve symptomatic relief with isolated respiratory muscle training and/or nutritional supplementation. Therapeutic agents that enhance diaphragmatic perfusion such as aminophylline may also be beneficial.\(^\text{40}\)

Although our study demonstrates an association among respiratory muscle strength, oxygenation, and work with dyspnea, it does not prove a causal effect. Only a modification of respiratory muscle function with alleviation of dyspnea will demonstrate whether respiratory muscle function is a key determinant of this sensation. Future studies involving therapeutic approaches to improve respiratory muscle function and/or perfusion are warranted.

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