Respiratory Muscles Performance Is Related to Oxygen Kinetics During Maximal Exercise and Early Recovery in Patients With Congestive Heart Failure

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Background—Dyspnea and fatigue are the main causes of exercise limitation in chronic heart failure (CHF) patients, whose peak inspiratory (Pi max ) and expiratory pressures (Pe max ) are often reduced. The aim of this study was to examine the relationship between respiratory muscle performance and oxygen kinetics.

Methods and Results—A total of 55 patients (NYHA class I to III) and 11 healthy subjects underwent cardiopulmonary exercise tests (CPET) on a treadmill. In 45 of the 55 patients (group I) and in healthy subjects (group II), pulmonary function tests, Pi max , and Pe max were measured before and 10 minutes after exercise, and oxygen kinetics were monitored throughout and during early recovery from CPET. The first degree slope of oxygen consumption (\( \dot{V}O_2 \) /t-slope) and \( \dot{V}O_2 \) half-time (T 1/2 ) were calculated. In 10 of the 55 CHF patients (group III), the measurements of Pi max were repeated 2, 5, and 10 minutes after CPET. A 10% reduction in Pi max after CPET (subgroup IA) was measured in 11 of 45 patients. In contrast, 34 of 45 CHF patients (subgroup IB) and all control subjects (group II) had Pi max >90% of baseline value after CPET. Subgroup IA patients had significantly lower peak \( \dot{V}O_2 \) (13.5 ± 2.1 versus 17.8 ± 5.6 mL · kg \(^{-1} \) · min \(^{-1} \); \( P < 0.001 \)), lower anaerobic thresholds (10.1 ± 2.4 versus 13.6 ± 4.6 mL · kg \(^{-1} \) · min \(^{-1} \); \( P = 0.003 \)) and lower \( \dot{V}O_2 \)/t-slopes (0.365 ± 0.126 versus 0.519 ± 0.227 L · min \(^{-1} \) · min \(^{-1} \); \( P = 0.008 \)) than subgroup IB patients.

Conclusions—The reduction of Pi max after exercise is associated with prolonged early recovery of oxygen kinetics, which may explain, in part, the role played by respiratory muscles in exercise intolerance in CHF patients. (Circulation. 1999;100:503-508.)

Key Words: respiratory muscles ■ heart failure ■ oxygen ■ exercise test
performance. The objective of this study was to examine the relationship between maximal respiratory mouth pressures, before and after exercise, and early recovery oxygen kinetics.

Patients and Methods
A total of 55 patients (49 men and 6 women) with CHF and 11 healthy volunteers were studied. The study was reviewed and approved by the Human Study Committee of our Institution, and informed consent was formally obtained from each participant. All subjects performed tests of maximal respiratory pressures before and after cardiopulmonary exercise tests (CPET). In 45 of the 55 patients (41 men and 4 women) with CHF (group I) and in the 11 healthy volunteers (group II), the measurements of maximal respiratory pressures were performed before and 10 minutes after the end of CPET. In the remaining 10 of the 55 patients with CHF (group III), the measurements of maximal respiratory pressures were performed before the beginning of CPET and were repeated 2, 5, and 10 minutes after the end of CPET. Table 1 lists selected characteristics pertaining to each group. All patients were clinically stable and optimally treated at the time of study. Those with recent myocardial infarction, respiratory insufficiency, or other conditions affecting exercise capacity were excluded from the study.

Pulmonary Function Tests
Each study participant had forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV-1) measured in the sitting position before exercise.

Maximal Respiratory Pressures
The measurements of maximal respiratory pressures were performed using the Vmax 229 system of pulmonary and metabolic tests (Sensormedics). The method used was similar to that described by Black and Hyatt.26 Patients were seated and breathed through a scuba-type mouthpiece attached to a 3-way valve with a small leak incorporated in the airway.26 For the measurement of Pi max, each patient was instructed to exhale to the residual volume followed by a maximal inspiratory effort through the mouthpiece. The maneuver was repeated until 3 reproducible measurements with a <5% variability had been obtained; the highest pressure measured was used for analysis. For the measurement of Pemax, each patient was instructed to inhale to total lung capacity followed by a maximal expiratory effort through the mouthpiece. During expiratory maneuvers, light pressure was applied to the cheeks to minimize the contribution of facial muscles.26

Pulmonary function tests and respiratory pressure measurements were repeated 10 minutes after the end of CPET for all study participants. However, in group III, additional respiratory pressure measurements were obtained 2 and 5 minutes after the end of CPET. Differences in maximal respiratory pressures measured before and after the exercise test were considered an index of respiratory-muscle endurance. A reduction of 10% in maximal pressures after CPET was chosen to separate 2 subgroups of patients included in group I. This arbitrary percentage was chosen because it represents twice the generally accepted intraindividual variation in measured maximal respiratory pressures. Subgroup IA includes the patients who had a reduction in Pi I max >10% between baseline value and exercise, and subgroup IB included the patients who had a Pi I max >90% of baseline value after exercise.

Cardiopulmonary Exercise Testing
CPET was performed on a treadmill. The protocol (modified Bruce or modified Naughton)27 was chosen to avoid an exercise duration longer than 15 minutes. Blood pressure measurements were obtained every 2 minutes using a standard-cuff mercury sphygmomanometer. ECG and peripheral blood O2 saturation were monitored throughout the test. Patients and normal volunteers self-graded their degree of dyspnea during CPET using the Borg scale.28 VO2, carbon dioxide output (VCO2), and air flow were measured on a breath-by-breath basis using the Vmax 229 monitor for pulmonary and metabolic studies. The system was calibrated with a standard gas of known concentration before each test. These measurements were obtained with the subject in the upright position before and during exercise and with the subject sitting in a chair during the first 10 minutes of recovery.
Baseline $V_O_2$ was calculated by averaging the measurements made for 2 minutes before the beginning of exercise.

Peak $V_O_2$ was calculated as the average of measurements made for 20 s before the end of exercise. Anaerobic threshold (AT) was determined using the V slope technique, and the result was confirmed by a graph on which the respiratory equivalent for oxygen ($VE/V_O_2$) and carbon dioxide ($VE/V_CO_2$) were plotted simultaneously against time. To evaluate $V_O_2$ kinetics during recovery in groups I and II, the first-degree slope of $V_O_2$ for the first minute of the recovery period was calculated by linear regression using an appropriate computerized statistical program. The first minute was chosen to guarantee that the measurements would reflect the alactic phase of the repayment of oxygen debt. The time required for a 50% fall from peak $V_O_2$ ($T_{1/2}$ of $V_O_2$) was also calculated. When it occurred in the middle of 2 sampling points, $T_{1/2}$ of $V_O_2$ was set at the second of these points.

In group III patients, the maximal respiratory pressure measurements were consecutively obtained 2, 5, and 10 minutes after the end of CPET. Consequently, in that group, $V_O_2$ kinetics could not be practically measured during recovery.

Patients and normal volunteers were instructed to exercise until exhaustion. Endpoints of CPET were dyspnea, fatigue, leg weakness, and chest discomfort. Subjects who terminated CPET because of dizziness or chest pain or who developed a serious arrhythmia were excluded from the study.

**Statistical Analyses**

Results are presented as mean±SD unless otherwise stated. The significance of differences between means was examined with Student’s $t$ test. Correlation between $P_i_{max}$, $P_e_{max}$, and peak $V_O_2$ were tested by Pearson’s correlation coefficient. The Mann-Whitney test was used to compare differences between groups classified according to Weber (see below).

A repeated measurement ANOVA was used to compare changes in $P_i_{max}$ measurements at different times of recovery in group III. $P<0.05$ was considered statistically significant.

**Results**

In the group I patients, the mean pulmonary capillary wedge pressure at rest was 14.4±7.3 mm Hg, and the mean left ventricular ejection fraction was 24.0±9.5%. Table 2 summarizes the results of CPET in CHF patients versus healthy subjects. Both $P_i_{max}$ and $P_e_{max}$, at rest and after exercise, were greater in controls than in CHF patients. Conversely, $T_{1/2}$ of $V_O_2$ was longer in CHF patients than in healthy volunteers. The percent change of $P_i_{max}$ or $P_e_{max}$ after exercise was not statistically different between the two groups. No control subject had a >10% reduction of $P_i_{max}$ after CPET.

In group III patients with 3 measurements of $P_i_{max}$ during recovery, a repeated measurement ANOVA showed statistically significant changes ($P=5.6, P<0.028$). A decrease was found at 2 and 5 minutes after CPET compared with preexercise values, whereas no difference was observed 10 minutes after CPET (Figure 1).

A total of 11 of the 45 group I patients (subgroup IA) had a >10% decrease in $P_i_{max}$ after CPET. Table 3 summarizes the pertinent comparisons between these 11 patients and the 34 patients whose $P_i_{max}$ did not change significantly (subgroup IB). There was no difference in preexercise $P_i_{max}$ and $P_i_{max}$% between patients in subgroups IA and IB (Table 3). Subgroup IA had lower mean peak $V_O_2$, mean $V_O_2$ at the AT, and mean $V_o_2$/t-slope. There were no significant differences between the 2 subgroups in left ventricular ejection fraction, pulmonary capillary wedge pressure, cardiac index, FEV-1%, FVC%, or FEV-1/FVC. Subgroup IA patients showed a trend toward a higher degree of dyspnea (Borg scale). Subgroup IB patients had lower mean peak $V_O_2$ (17.8±5.6 versus 26.9±4.9 mL · kg⁻¹ · min⁻¹; $P<0.001$), lower mean $V_O_2$ at the AT (13.6±4.6 versus 19.9±3.9 mL · kg⁻¹ · min⁻¹; $P<0.001$), lower mean $V_O_2$/t-slope (0.519±0.227 versus 0.889±0.327 L · min⁻¹ · min⁻¹; $P<0.005$), and greater $T_{1/2}$ (1.5±0.4 versus 1.1±0.2 minutes; $P<0.001$) compared with controls (group II).

The patients in group I were further subclassified using Weber’s scale based on peak $V_O_2$ (Borg scale). Subgroup IA had a >10% reduction in $P_i_{max}$ after CPET; however, 2 of 9 patients (22.2%) in Weber class B and 9 of 24 patients

![Figure 1. Mean and SEM of $P_i_{max}$ before CPET and 2, 5, and 10 minutes after CPET during recovery period. Statistically significant difference compared with preexercise value: *$P<0.02$, **$P<0.002$.](image-url)
(37.5%) in Weber class C/D did (Figure 2). The differences between these groups were statistically significant ($P = 0.028$). In group III, 4 patients were in class A, 2 in class B, and 4 in class C. Two of these patients failed to return to within 10% of the preexercise $P_{\text{max}}$ within 10 minutes.

A weak correlation was measured between peak $V_{\text{O}_2}$ and $P_{\text{max}}$ before CPET ($r = 0.33; P = 0.027$) in group I patients. There was no correlation between $P_{\text{max}}$ and peak $V_{\text{O}_2}$. In both patients and controls, $P_{\text{max}}$ 10 minutes after the CPET correlated significantly with $V_{\text{O}_2}/t$-slope ($r = 0.39; P = 0.003$) (Figure 3). The correlation, although weaker, was still significant when controls were removed ($r = 0.31; P = 0.039$).

**Discussion**

This study showed that the pressure-generating capacity of the respiratory muscles is not reduced 10 minutes after CPET in the majority of CHF patients. However, when a fall in $P_{\text{max}}$ does occur, it is associated with altered oxygen kinetics, i.e., the subgroup of CHF patients with $P_{\text{max}} < 90\%$ of baseline value after CPET (subgroup IA) had significantly longer recovery of basal metabolism ($V_{\text{O}_2}/t$-slope) and a significantly lower AT and peak $V_{\text{O}_2}$ than the subgroup of CHF patients whose $P_{\text{max}}$ did not decrease significantly after CPET (subgroup IB).

**Maximal Respiratory Pressures**

The maximal respiratory pressures are considered reliable indices of respiratory muscle strength.$^9,10$ Thorough coaching and patient motivation allows highly reproducible measurements.$^13$ A potential limitation of the method is that higher maximal respiratory pressures can be reached through a “learning effect.”$^13$

The design of this study, which used the

**TABLE 3. Cardiopulmonary Function and Exercise TestIndices in Patients With CHF**

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Subgroup IA</th>
<th>Subgroup IB</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{max}}, \text{ cmH}_2\text{O}$</td>
<td>82±26</td>
<td>80±27</td>
<td>83±27</td>
<td>NS</td>
</tr>
<tr>
<td>$P_{\text{max}}, %$</td>
<td>73±24</td>
<td>78±31</td>
<td>72±21</td>
<td>NS</td>
</tr>
<tr>
<td>Peak $V_{\text{O}_2}$, mL · kg$^{-1}$ · min$^{-1}$</td>
<td>16.7±5.3</td>
<td>13.5±2.1</td>
<td>17.8±5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>VE peak, L/min</td>
<td>63.6±19.9</td>
<td>58.7±15.4</td>
<td>65.3±21.1</td>
<td>NS</td>
</tr>
<tr>
<td>AT, mL · kg$^{-1}$ · min$^{-1}$</td>
<td>12.6±4.3</td>
<td>10.1±2.4</td>
<td>13.6±4.6</td>
<td>0.003</td>
</tr>
<tr>
<td>$V_{\text{O}_2}/t$-slope, L · min$^{-1}$ · min$^{-1}$</td>
<td>0.48±0.216</td>
<td>0.365±0.126</td>
<td>0.519±0.227</td>
<td>0.008</td>
</tr>
<tr>
<td>VE/$V_{\text{O}<em>2}$ ($T</em>{1/2}$)</td>
<td>55.4±12.4</td>
<td>62.2±11.1</td>
<td>53.2±12.2</td>
<td>NS</td>
</tr>
<tr>
<td>$P_{\text{CWP}}$, mm Hg</td>
<td>14.4±7.3</td>
<td>17.1±6.9</td>
<td>13.5±7.3</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24.0±9.5</td>
<td>22.4±8.7</td>
<td>24.6±9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index, L/(m$^2$ · min)</td>
<td>2.4±0.6</td>
<td>2.4±1.1</td>
<td>2.4±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Borg dyspnea scale</td>
<td>4.3±2.0</td>
<td>5.7±2.9</td>
<td>3.9±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>FEV$-1$, % predicted</td>
<td>83±15</td>
<td>81±16</td>
<td>84±15</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>90±14</td>
<td>84±15</td>
<td>91±13</td>
<td>NS</td>
</tr>
<tr>
<td>FEV$-1$/FVC, % predicted</td>
<td>76±9</td>
<td>78±8</td>
<td>75±9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are mean±SD. $P_{\text{CWP}}$ indicates pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; and NS, not significant. VE/$V_{\text{O}_2}$ ($T_{1/2}$) = ventilation per liter of oxygen uptake during the measurement of $T_{1/2} V_{\text{O}_2}$.

*Subgroup IA vs IB.
measurement of maximal respiratory pressures before exercise as baseline to evaluate the changes occurring after exercise, aimed to circumvent this potential problem because the learning effect, if existent, would have resulted in an underestimation of the $P_{\text{imax}}$ reduction after exercise. This learning effect may, thus, have accounted for the borderline ($<10\%$) reduction in $P_{\text{imax}}$ after CPET in some of our patients.

CPET is a form of endurance test for the respiratory muscles capable of producing a decline in $P_{\text{imax}}$ immediately after exercise in healthy subjects. This is also the case for CHF patients, as evidenced by the report of Mancini et al.\textsuperscript{20} who reported that the maximal respiratory pressures measured at peak exercise were lower than the values measured at rest. This reduction of $P_{\text{imax}}$ at peak or immediately after exercise most likely represents high-frequency fatigue of the respiratory muscles, because beyond 2 minutes, a gradual return to normal occurs, at least in healthy human subjects. To our knowledge, the pattern of recovery of $P_{\text{imax}}$ in CHF patients has not yet been studied.

Our finding that $P_{\text{imax}}$ was not decreased 10 minutes after exercise in the majority of CHF patients indicates that the pattern of recovery of $P_{\text{imax}}$ is similar to that observed in normal subjects.\textsuperscript{32,33} where a significant decline occurs within the first 2 minutes after CPET, with a gradual return to normal thereafter. This is further evidenced by the repeated $P_{\text{imax}}$ measurements after the end of CPET in group III patients, who showed a decrease of $P_{\text{imax}}$ at 2 and 5 minutes, but not at 10 minutes in comparison with preexercise values. However, this was not the case for all CHF patients. The large number of patients we studied allowed us to identify a subgroup of CHF patients whose $P_{\text{imax}}$ was reduced 10 minutes after CPET, which probably reflected a component of low-frequency fatigue. Was this different respiratory muscle performance associated with oxygen kinetics as hypothesized?

Oxygen Kinetics

Comparison of $P_{\text{imax}}$ and $P_{\text{emax}}$ before and after CPET in the same individuals in relation to oxygen kinetics has not been previously examined. Therefore, in this study, $P_{\text{imax}}$ and $P_{\text{emax}}$ measurements were repeated at 10 minutes into recovery from exercise. In agreement with previous findings, a weak (although statistically significant) correlation, before and after CPET, existed between $P_{\text{imax}}$ and peak $V_{\text{O}_2}$.\textsuperscript{17,34}

Assuming that the fall in $V_{\text{O}_2}$ during early recovery from exercise is linear, $V_{\text{O}_2}$ recovery in patients with CHF was examined in a linear regression model. Our measurements applied to the fast component (alactic phase) of the repayment of the oxygen debt.\textsuperscript{30} Investigators who studied the repayment of oxygen debt have used single\textsuperscript{23,35,36} and double exponential equations\textsuperscript{37} to describe the fall in $V_{\text{O}_2}$ during the recovery period. It was observed in stable workload protocols that the time constant and half-time ($T_{1/2}$) derived from it were independent of the work level.\textsuperscript{35} Recently, Cohen-Solal et al\textsuperscript{32} used the $T_{1/2}$ of $V_{\text{O}_2}$, calculated as the time required for a 50% fall in the peak $V_{\text{O}_2}$, to describe the fall in $V_{\text{O}_2}$ during recovery from exercise in patients with CHF. A close correlation was found between this $T_{1/2}$ of $V_{\text{O}_2}$ and that derived from the time constant of exponential equations.\textsuperscript{22} It was observed during graded exercise in CHF patients that $T_{1/2}$ of $V_{\text{O}_2}$ remained independent of the level of exercise as long as workload remained above 50% of maximal.

Having to choose the second point when $T_{1/2}$ of $V_{\text{O}_2}$ happens to fall between 2 sampling points is a methodological shortcoming, which may cause considerable variability in the results, particularly when using the breath-by-breath technique. We attempted to circumvent this problem by using the $V_{\text{O}_2}/t$-slope during the early recovery period.

The value of $V_{\text{O}_2}/t$-slope in the early recovery period was significantly less in subgroup IA patients than in subgroup IB patients. The association of postexercise $P_{\text{imax}}$ with oxygen kinetics is further supported by the correlation of $P_{\text{imax}}$ with $V_{\text{O}_2}/t$-slope found in our study. This may be due to the slower recovery of muscle energy stores,\textsuperscript{22} because the time course of energy stores resynthesis resembles the recovery of maximum strength after exhaustive exercise in man.\textsuperscript{24,25} The pathophysiological mechanism of the slower recovery of muscles' energy stores is not yet clear. Supinski et al,\textsuperscript{37} in an animal model of heart failure, found that the maximum phrenic arterial flow achieved during electrically induced diaphragmatic fatigue was appreciably less and the duration of postocclusive hyperemia in diaphragmatic muscle was significantly longer in animals with heart failure. Furthermore, hyperemic blood volume during the first minute after occlusion was significantly lower (ie, the time to repay the blood volume debt of the diaphragmatic muscle in animals with heart failure was prolonged). It is, therefore, tempting to speculate that an analogous vascular dysfunction occurs in the respiratory muscles of some CHF patients, which would account for the decrease in $P_{\text{imax}}$ and the slower recovery of oxygen kinetics that was observed in this study. Recent data suggest that oxygen delivery to working skeletal muscle, as evaluated by nuclear magnetic resonance and near-infrared spectroscopy, is impaired during recovery from maximal bicycle exercise in CHF patients.\textsuperscript{38,39} Moreover, Mancini et al\textsuperscript{20} found serratus anterior muscle deoxygenation during maximal bicycle exercise, consistent with respiratory muscle ischemia. At the extreme end of this dysfunction, respiratory muscle underperfusion during cardiogenic shock caused by tamponade in dogs led to diaphragmatic fatigue.\textsuperscript{40}

These observations are concordant with a significant reduction in peak $V_{\text{O}_2}$ and AT, as well as a lower $V_{\text{O}_2}/t$-slope during recovery among subgroup IA patients. This association of respiratory muscle function with indices of recovery oxygen kinetics in CHF patients has not been reported before.

Patients with CHF have several histological and biochemical changes in their striated muscles, including fewer oxidative slow-twitch fibers, impaired aerobic-oxidative capacity, and an earlier shift toward anaerobic metabolism during exercise, causing the so-called oxygen debt.\textsuperscript{41} These changes are not homogeneous throughout the CHF population, and they are not attributed to changes in muscle blood flow, but rather to intrinsic alterations in the muscle.\textsuperscript{42,43} This variability in muscle metabolism and histology\textsuperscript{38,44} may partially explain the variability in $P_{\text{imax}}$ after CPET among our patients.

In summary, respiratory muscle performance, expressed as maximal respiratory pressure after CPET, is not reduced (except transiently) in the majority of patients with heart failure. However, a long-lasting $>10\%$ decrease of maximal inspiratory pressure at late recovery was observed in CHF.
patients, with significantly lower exercise capacity and signifi-
cantly delayed recovery of resting oxygen consumption. These observations provide new insights into the pathophys-
ilogical mechanisms of respiratory muscle performance in patients suffering from CHF.

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References
7. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity and exercise capacity in patients with cardiorepi-
14. Heidja YF, Dekhuizjen P, van Herwaarden CL, Folgering HT. Effects of body position, hyperinflation, and blood gas tensions on maximal respira-
30. Margaria R, Edwards HT, Dill DB. The possible mechanisms of con-
tracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol. 1933;106:689–715.
41. Massie BM, Simonini A, Sahgal P, Wells L, Dudley GA. Relation of systemic and local muscle exercise capacity to skeletal muscle charac-
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