Exercise-Induced Pulmonary Edema in Heart Failure

Piergiuseppe Agostoni, MD, PhD; Gaia Cattadori, MD; Michele Bianchi, MD; Karlman Wasserman, MD, PhD

Background—In heart failure (HF) patients, exercise may increase pulmonary capillary hydrostatic pressure and thereby generate pulmonary edema. If pulmonary edema developed, alveolar-capillary membrane conductance (Dm), measured immediately after exercise, would decrease. To test this hypothesis, we measured Dm before and at 2 and 60 minutes after exercise.

Methods and Results—We studied 10 HF patients with exercise-induced periodic breathing, 10 with peak VO2 ≤15 mL · min⁻¹ · kg⁻¹ (severe HF), 10 with VO2=15 to 20 mL · min⁻¹ · kg⁻¹ (moderate HF), and 10 normal subjects (control). Using the Roughton-Forster technique, we measured carbon monoxide diffusion capacity (DLCO) and its components, capillary blood volume (Vc) and Dm, at rest and 2 and 60 minutes after exercise. At rest, DLCO and Dm were lowest in periodic breathing and highest in control subjects. Dm decreased in periodic breathing, severe HF, and moderate HF (−7.83±3.98, −5.57±2.03, and −3.85±3.53 mL · min⁻¹ · mm Hg⁻¹, respectively; P<0.01) at 2 minutes after exercise but not in control subjects. Vc increased in all groups at 2 minutes and remained elevated at 60 minutes only in periodic breathing. Dm/Vc was decreased in periodic breathing, severe HF, and moderate HF at 2 minutes but not in control subjects. Dm and Dm/Vc remained low at 60 minutes only in periodic breathing.

Conclusions—Dm decreases after exercise in HF patients but not in control subjects, which suggests a decrease in conductance across the alveolar-capillary barrier, as with pulmonary edema. The reductions were most marked in HF patients with periodic breathing and less reduced in less severe HF. (Circulation. 2003;108:2666-2671.)

Key Words: heart failure ■ exercise ■ edema ■ lung

In patients with left ventricular failure during exercise, pulmonary vascular pressure increases more markedly than in normal subjects. Indeed, the left ventricle dilates early and significantly during exercise because of an increase in venous return, systemic arterial pressure, catecholamine levels, and central blood volume and failure of the heart to keep up with increased cardiac work that results from an increased heart rate and shortened diastolic period. Therefore, leakage of fluid from the pulmonary vasculature into the pulmonary interstitium could be enhanced depending on the increase in transcapillary fluid pressure. The amount of pulmonary extravascular fluid is a function of the balance between pulmonary capillary fluid filtration and fluid removal from the pulmonary interstitium. The potential for developing exercise-induced pulmonary edema as a result of an increase in transcapillary fluid pressure should depend on the level of exercise performed and the severity of heart failure (HF).

Fluid should be reabsorbed from the interstitial space and alveolus when transcapillary fluid pressure decreases in exercise recovery. The time to remove the exercise-induced increase in pulmonary edema, when exercise is terminated, should depend on the reversal of the exercise-induced pressure elevation and the quantity of fluid transudated during exercise. A more prolonged recovery time should take place in more compromised patients. To test this hypothesis, we measured carbon monoxide diffusion capacity (DLCO) and its components, with particular attention to specific membrane conductance (Dm), before exercise and 2 minutes and 1 hour after exercise in HF patients and a matched group of normal subjects. Our objective was to determine whether membrane conductance (Dm) was reduced during the postexercise period in HF compared with normal control subjects, and if so, whether its decrease was related to the severity of HF.

Methods

Study Population

Thirty patients with chronic HF and 10 healthy volunteers participated in the study. Patients belonged to a cohort of HF subjects regularly followed up at our HF unit. All subjects were evaluated previously by cardiopulmonary exercise testing (CPET) in our laboratory. Study inclusion criteria for chronic HF patients were New York Heart Association class II or III; optimized, individually tailored drug treatment; stable clinical conditions for at least 2 months as confirmed by absence of relevant edema, stable body weight, and urinary output; capability of performing a CPET; and absence of history or clinical documentation of pulmonary embolism or primary valvular heart disease, pericardial disease, severe obstructive lung disease, significant peripheral vascular disease, exercise-induced angina, ST changes, or severe arrhythmias. Heart failure patients were grouped according to the following criteria: (1)

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periodic breathing (PB), defined as presence of exercise-induced periodic oscillation in ventilation, $\dot{V}O_2$, and $\dot{V}CO_2$ and the gas exchange ratio; (2) severe HF, defined as HF patients with peak $\dot{V}O_2 < 15 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ without oscillatory gas exchange; and (3) moderate HF, defined as HF patients with peak $\dot{V}O_2$ between 15 and $20 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. Patients with peak $\dot{V}O_2 > 20 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ were not included in the study. Normal subjects, consisting of hospital personnel and patients’ relatives, served as controls. All had previous experience with CPET in our laboratory. Subjects’ characteristics are reported in Table 1. Left ventricular ejection fraction was evaluated by echocardiography (Table 1). The study was approved by the local ethics committee. All subjects provided written informed consent to participate in the study.

### Lung Diffusion

All subjects were evaluated by standard pulmonary function tests, which included DLCO measured with the single breath–constant inspiratory flow technique (Sensor Medics 2200).6 Diffusion subcomponents, capillary volume (VC) and Dm, were also measured by application of the Roughton and Forster method.7 For this purpose, subjects inspired gas mixtures containing 0.3% CH₄ and 0.3% CO₂ with 3 different oxygen fractions equal to 20%, 40%, and 60%, respectively, and balanced with nitrogen.

### CPET Ramp Protocol

A CPET in which work rate was increased in a ramp pattern after 3 minutes of rest and 3 minutes of unloaded cycling was performed on a cycle ergometer (Ergo 800S Sensor Medics). Expiratory O₂, CO₂, and ventilation (VE) were measured breath by breath. A 12-lead ECG was also recorded from which heart rate was obtained (V-Max, Sensor Medics). The patients were strongly encouraged to perform a maximal test, but they determined when their symptoms were so severe that it was necessary to stop cycling. At the end of the test, the patient was asked to indicate the major symptom that led to his or her stopping the exercise. Specifically, we inquired about chest pain, fatigue, and dyspnea. The rate of work rate increase during testing was decided on the basis of the patient’s clinical condition and the results of previous tests. The aim was to achieve peak exercise in 10 minutes. If test duration was >12 or <8 minutes, the test was repeated the next day with the work rate increase adjusted as needed. Peak exercise was considered the highest $\dot{V}O_2$ achieved. Anaerobic threshold was measured with the V-slope analysis from the plot of $\dot{V}CO_2$ versus $\dot{V}O_2$ on equal scales.8 The anaerobic threshold value was confirmed by ventilatory equivalents (increase of $\dot{V}E/\dot{V}CO_2$ and end-tidal pressure (increase of end-tidal $\dot{V}O_2$ with constant end-tidal $\dot{PCO}_2$). The $\dot{V}O_2$/work rate relationship was evaluated throughout the entire exercise, during the ramping period, after elimination of the increase in work rate during the first 45 seconds to account for the time constant for the $\dot{V}O_2$ response to the work rate increase.9 The $\dot{V}E$ versus $\dot{V}CO_2$ slope was calculated as the slope of the linear relationship between $\dot{V}E$ and $\dot{V}CO_2$ from the beginning of loaded exercise to the end of the isocapnic buffering period. Two experts independently read each test, and the results were averaged.

### CPET Constant Work-Rate Protocol

A constant work rate CPET was also performed. The work rate of the constant work rate CPET was selected as that which gave a $\dot{V}O_2$ approximately midway between peak exercise and the anaerobic threshold, according to the following formula:

$$\dot{WR}_C = (\text{PeakWR} - \text{ATWR})/2 + \text{ATWR}$$

where $\dot{WR}_C$ is work rate of the constant work rate test, PeakWR is peak exercise work rate, ATWR is anaerobic threshold work rate, and 0.75 is the average calculated time constant, in minutes, for $\dot{V}O_2$ in response to work rate increase.9 The patients were asked to perform the constant work rate test for 10 minutes.

### Study Design

#### Day 1

All subjects underwent careful clinical evaluation, assessment of resting pulmonary function, and a learning session for DLCO measurements. Afterward, each subject underwent a CPET with ramp protocol to group patients according to HF severity and to obtain data to calculate the work rate for the constant work rate protocol to be used on day 2.

#### Day 2

Patients underwent a 10-minute CPET constant work rate protocol. DLCO, DM, and VC were measured while subjects were sitting on the cycle ergometer before the constant work rate CPET and 2 to 8 minutes (referred to as 2 minutes or “early”) and 1 hour later. If the DLCO measurements for the 3 $\text{Fi}_2O_2$ tests did not fit the theoretical 3-point linear analysis between $\text{I} / \text{DLCO}$ and $\text{Fi}_2O_2$, measurements were repeated.

### Statistical Analysis

Data reported are mean±SEM. Intragroup and intergroup differences were evaluated by ANOVA followed by unpaired or paired t test as appropriate. Differences from zero were evaluated by difference analysis.

### Results

Two patients stopped the exercise because of dyspnea, whereas all other reasons for stopping were because of fatigue (patients with exercise-induced chest pain were excluded from the study). Results of the CPET ramp protocol are reported in Table 2. HF severity was greatest in PB patients and lowest in moderate HF patients. Peak $\dot{V}O_2$, $\dot{V}O_2$ at anaerobic threshold, and peak work rate achieved were lowest in PB patients and increased progressively with less severe

### Table 1. Descriptive Characteristics of HF Patients and Normal Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PB</th>
<th>Severe HF</th>
<th>Moderate HF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.3±1.2</td>
<td>63.2±2.9</td>
<td>57.8±4.3</td>
<td>60.5±2.2</td>
</tr>
<tr>
<td>Gender male/female</td>
<td>9/1</td>
<td>8/2</td>
<td>9/1</td>
<td>9/1</td>
</tr>
<tr>
<td>Etiology</td>
<td>5 IDC/5 CAD</td>
<td>6 IDC/4 CAD</td>
<td>9 IDC/1 CAD</td>
<td>...</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3±0</td>
<td>2.6±0.2</td>
<td>2.3±0.2</td>
<td>...</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.2±2.6</td>
<td>171.4±2.0</td>
<td>174.0±2.1</td>
<td>174.9±3.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.7±4.8</td>
<td>80.3±4.5</td>
<td>81.3±3.9</td>
<td>76.1±3.9</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>26.1±3.4*</td>
<td>34.8±3.8*</td>
<td>31.9±2.4*</td>
<td>70±1.8</td>
</tr>
</tbody>
</table>

IDC indicates idiopathic dilated cardiomyopathy; CAD, coronary artery disease; and NYHA, New York Heart Association. Data are mean±SEM. *P<0.01 vs control.
HF to normal values for normal subjects (Table 2). The increases in exercise capacity from PB patients to severe HF patients to moderate HF patients and finally to normal subjects were significant.\(^{10-13}\)

The ΔVO\(_2\)/Δwork rate relationship likewise increased progressively from the lowest values in PB patients to normal values of 9.9 mL·min\(^{-1}·W\(^{-1}\) in normal subjects. Thus, PB patients had the greatest decrease in O\(_2\) utilization, and this deficit became less with less severe HF.\(^9\)

The slope of VE versus V\(_{CO2}\), a strong HF prognostic indicator independent of peak VO\(_2\),\(^{14,15}\) was significantly elevated in PB patients, elevated but to a smaller degree in severe HF patients, and normal in moderate HF patients and normal subjects (Table 2). The work rate of the constant work rate exercise was lower the greater the severity of the disease (Table 3).

The constant work rate CPET lasted, as programmed, for 10 minutes in all but 7 patients (2 PB patients, 3 severe HF patients, and 2 moderate HF patients); in these patients, constant CPET lasted at least 8 minutes. The VO\(_2\) reached at the end of the constant work rate exercise (Table 3) was approximately equal to the peak VO\(_2\) measured in the ramp protocol (Table 2).

At rest, DL\(_{CO}\) and DM were highest in normal subjects, whereas they were lowest in PB patients (Figure 1). VC and DM/VC were similar among all 4 groups at rest, with a considerable intragroup data dispersion (Figure 1).

At early (2 to 8 minutes) and late (1 hour) recovery from constant work rate exercise, DL\(_{CO}\) did not change significantly. Normal subjects had increased DL\(_{CO}\) shortly after exercise (Figure 2). DM decreased in all HF subjects immediately after exercise, in contrast to normal subjects (Figure 3). The reduction was most marked in PB patients. At 1 hour, DM remained low only in PB patients (Figure 3). VC increased in all groups immediately after exercise, with a greater increase in moderate HF patients (Figure 4). One hour after exercise, VC remained elevated only in PB patients (Figure 4). Immediately after exercise, DM/VC decreased in all HF groups but was unchanged in normal subjects (Figure 5). The reduction was greatest in PB patients (P<0.02 versus moderate and severe HF patients). DM/VC remained reduced at 1 hour into recovery only in PB patients (Figure 5).

**Discussion**

Physiological evidence of exercise-induced pulmonary edema, evaluated as changes in the membrane component of diffusion capacity, are present in HF subjects and, to a greater extent, in HF patients with PB. Apparently, complete reabsorption of lung edema fluid needs more than 1 hour for DM and DM/VC to return to preexercise levels in HF patients with PB who undergo exercise. Normal individuals do not develop postexercise reductions in DM or Dm/VC.

HF patients were grouped according to peak VO\(_2\) or to the presence of exercise-induced PB. The latter group had more severe HF as suggested by several findings, including (1) higher New York Heart Association class, (2) lower resting DL\(_{CO}\) and DM, (3) lower peak VO\(_2\) and VO\(_2\) at anaerobic threshold, (4) lower work rate achieved, (5) lower ΔVO\(_2\)/Δwork rate relationship, and (6) higher VE versus V\(_{CO2}\) slope. Although the New York Heart Association classification has been the most used HF classification in clinical medicine for many years,\(^\text{16}\) other physiological measures of HF prognosis have been correlated with exercise capacity, including peak VO\(_2\), VO\(_2\) at anaerobic threshold, work rate achieved,\(^\text{10-13}\) ΔVO\(_2)/Δwork rate relationship (an indicator of efficiency of oxygen delivery to peripheral muscles), and finally, the slope of VE versus V\(_{CO2}\) from unloaded cycling to the ventilatory compensation point, an indicator of the efficiency of ventila-

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**TABLE 2. Results of CPET Ramp Protocol**

<table>
<thead>
<tr>
<th></th>
<th>PB</th>
<th>Severe HF</th>
<th>Moderate HF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(_2) peak, mL/min</td>
<td>816.9±68*†††</td>
<td>1103.1±88‡‡‡</td>
<td>1483.7±98§</td>
<td>2430.4±186</td>
</tr>
<tr>
<td>VO(_2) peak, mL·kg(^{-1}·min(^{-1})</td>
<td>11.1±1.1†††</td>
<td>13.7±0.9‡‡‡</td>
<td>18.2±0.7‡</td>
<td>31.8±1.4</td>
</tr>
<tr>
<td>VO(_2) % of predicted</td>
<td>40.6±3.2‡‡‡</td>
<td>53.7±4.3</td>
<td>64.3±3.0</td>
<td>108.4±5.1</td>
</tr>
<tr>
<td>VO(_2) sat, mL/min</td>
<td>595.2±45.5*†††</td>
<td>824.5±55.0</td>
<td>956.3±90.8</td>
<td>1585.8±127.8</td>
</tr>
<tr>
<td>Workload peak, W</td>
<td>54.2±7.5*†††</td>
<td>84.1±9.8§</td>
<td>117.1±9.8§</td>
<td>201.2±15.2</td>
</tr>
<tr>
<td>ΔVO(_2)/Δworkload, mL·min(^{-1}·W(^{-1})</td>
<td>7.4±0.6§§</td>
<td>8.2±0.4∥</td>
<td>8.9±0.4∥</td>
<td>9.9±0.2</td>
</tr>
<tr>
<td>VC/VC(_{O2})</td>
<td>46.6±4.0†††</td>
<td>36.6±3.0§§</td>
<td>29.9±1.3</td>
<td>27.4±1.2</td>
</tr>
</tbody>
</table>

*‡ indicates anaerobic threshold. Data are mean±SEM.

\(^*P<0.01\) vs severe HF; †P<0.05 vs severe HF; ‡P<0.01 vs moderate HF; §P<0.05 vs moderate HF; †§P<0.01 vs control.

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**TABLE 3. Results of CPET Constant Work Rate Protocol**

<table>
<thead>
<tr>
<th></th>
<th>PB</th>
<th>Severe HF</th>
<th>Moderate HF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(<em>2) (</em>{peak}), mL/min</td>
<td>803±72*§§</td>
<td>1138±112§§</td>
<td>1536±148§</td>
<td>2346±134</td>
</tr>
<tr>
<td>Workload (_{peak}), W</td>
<td>36.5±5.7*§§</td>
<td>66.4±8.9§§</td>
<td>90.7±9.2§</td>
<td>160.4±10.5</td>
</tr>
<tr>
<td>RQ(_{peak})</td>
<td>1.01±0.03</td>
<td>1.02±0.03</td>
<td>1.02±0.02</td>
<td>1.05±0.02</td>
</tr>
</tbody>
</table>

VO\(_2\) indicates highest VO\(_2\) measured during constant work rate exercise; RQ, respiratory quotient at end of exercise.

\(^*P<0.01\) vs severe HF; †P<0.01 vs moderate HF; ‡P<0.05 vs moderate HF; §P<0.01 vs control.
It appears that DLCO, particularly the change in the Dm component with exercise, can be included among predictors of HF severity and prognosis. To induce pulmonary edema, we asked all subjects to perform a high work rate constant CPET that was intended to last 10 minutes. Indeed, the work rate chosen was between the anaerobic threshold and peak exercise. Almost all subjects performed 10 minutes of exercise at this level. V˙O₂ was similar to peak V˙O₂ measured with the ramp-protocol CPET. Shortly after heavy exercise, DLCO increased in normal subjects owing to increases in both VC and Dm, albeit the latter was only a trend. DLCO did not change in HF patients shortly after exercise. This observation is consistent with the fact that unlike chronic lung disease patients and elite athletes, desaturation of hemoglobin is rarely observed during exercise in stable HF patients and normal subjects. Several facts may explain why hemoglobin desaturation is not observed in patients with HF during exercise: (1) the reduction in Dm is relatively small, (2) the pulmonary transit time for red blood cells is slow, and (3) VC increases. Indeed, in HF, the observed reduction of Dm is accompanied by an increase in VC (Figure 4) so that DLCO remains constant. The exercise-induced increase in VC is presumably due to pulmonary vessel recruitment. This occurred to a lesser degree in patients with more severe HF, which suggests a limited capability to recruit pulmonary vessels in patients with severe HF. A significant reduction of DLCO was observed in subjects with exercise-induced PB and severe HF 1 hour after exercise (Figure 2). This was due to persistence of a reduced Dm with a smaller VC increase compared with the early recovery measurement.
edema with exercise is greater in patients with PB. It had been proposed that HF patients with PB are likely functioning on the descending limb of the Starling curve; therefore, they would be more readily subject to increases in pulmonary capillary pressure and exercise-induced pulmonary edema when venous return increases with exercise.\(^2\)

Patients with exercise-induced PB apparently reabsorb pulmonary edema in recovery relatively slowly, so that even after 1 hour, DM remained reduced. This supports the widely held perspective that HF patients with PB are among the most severe HF patients and likely need prolonged observation after exercise. Because exercise-induced PB is detectable from the beginning of exercise, disappearing as work rate is increased above the anaerobic threshold, assessment of HF in this group does not require a maximal effort exercise test to properly classify the severity of HF in these patients.\(^26\)

In conclusion, we found that DM and Dm/Vc decreased transiently after heavy-intensity exercise in HF patients but not in control subjects. This decrease in conductance across the alveolar-capillary barrier is consistent with development of exercise-induced pulmonary edema. The reductions were transient but were most marked and longer lasting in HF patients with an exercise-induced PB or oscillatory breathing pattern.

References

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