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.)
periodic breathing (PB), defined as presence of exercise-induced periodic oscillation in ventilation, \( V_O_2 \), and \( V_CO_2 \) and the gas exchange ratio; (2) severe HF, defined as HF patients with peak \( V_O_2 < 15 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) without oscillatory gas exchange; and (3) moderate HF, defined as HF patients with peak \( V_O_2 \) between 15 and 20 \( \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \). Patients with peak \( V_O_2 > 20 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) 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 calculated as the difference between the end-diastolic volume and the end-systolic volume, divided by the end-diastolic volume.

<table>
<thead>
<tr>
<th>TABLE 1. Descriptive Characteristics of HF Patients and Normal Subjects</th>
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<tr>
<td></td>
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<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Gender, male/female</td>
</tr>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>NYHA class</td>
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<tr>
<td>Height, cm</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Ejection fraction, %</td>
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</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.

The CPET ramp protocol was used on day 2. 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.

**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 \( V_O_2 \) approximately midway between peak exercise and the anaerobic threshold, according to the following formula:

\[
W_Rc = (\text{PeakWR} - \text{ATWR}) / 2 + \text{ATWR}
\]

where \( W_Rc \) is work rate of the constant work rate test, PeakWR is exercise peak work rate, \( \text{ATWR} \) is anaerobic threshold work rate, and \( 0.75 \times \text{ramp work rate}/\text{minute} \), and 0.75 is the average calculated time constant, in minutes, for \( V_O_2 \) response to work rate increase.† 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 V C 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 FiO 2 tests did not fit the theoretical 3-point linear analysis between 1/DLCO and FiO 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 \( V_O_2 \) at anaerobic threshold, and peak work rate achieved were lowest in PB patients and increased progressively with less severe
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 Δ\(\dot{V}_\text{O}_2/\Delta\text{work rate}\) relationship likewise increased progressively from the lowest values in PB patients to normal values of 9.9 mL \(\cdot\) min \(^{-1}\) \(\cdot\) W \(^{-1}\) in normal subjects. Thus, PB patients had the greatest decrease in \(\dot{V}_\text{O}_2\) utilization, and this deficit became less with less severe HF.\(^9\)

The slope of \(\dot{V}_\text{E}\) versus \(\dot{V}_\text{CO}_2\), a strong HF prognostic indicator independent of peak \(\dot{V}_\text{O}_2\),\(^{14,15}\) was significantly elevated in PB patients, elevated 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 \(\dot{V}_\text{O}_2\) reached at the end of the constant work rate exercise (Table 3) was approximately equal to the peak \(\dot{V}_\text{O}_2\) measured in the ramp protocol (Table 2).

At rest, DLCO and DM were highest in normal subjects, whereas they were lowest in PB patients (Figure 1). \(V_c\) 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, DLCO did not change significantly. Normal subjects had increased DLCO 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). \(V_c\) increased in all groups immediately after exercise, with a greater increase in moderate HF patients (Figure 4). One hour after exercise, \(V_c\) 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 \(\dot{V}_\text{O}_2\) 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 DLCO and DM, (3) lower peak \(\dot{V}_\text{O}_2\) and \(\dot{V}_\text{CO}_2\) at anaerobic threshold, (4) lower work rate achieved, (5) lower Δ\(\dot{V}_\text{O}_2/\Delta\text{work rate}\) relationship, and (6) higher \(V_c\) versus \(\dot{V}_\text{CO}_2\) slope. Although the New York Heart Association classification has been the most used HF classification in clinical medicine for many years,\(^{16}\) other physiological measures of HF prognosis have been correlated with exercise capacity, including peak \(\dot{V}_\text{O}_2\), \(\dot{V}_\text{O}_2\) at anaerobic threshold, work rate achieved,\(^{10-13}\) Δ\(\dot{V}_\text{O}_2/\Delta\text{work rate}\) relationship (an indicator of efficiency of oxygen delivery to peripheral muscles), and finally, the slope of \(\dot{V}_\text{E}\) versus \(\dot{V}_\text{CO}_2\) from unloaded cycling to the ventilatory compensation point, an indicator of the efficiency of ventila-

### 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>(\dot{V}_{\text{O}_2}) \text{max}; mL/min</td>
<td>816.9±68*‡</td>
<td></td>
<td></td>
<td>1103.1±88‡</td>
</tr>
<tr>
<td>(\dot{V}_{\text{O}_2}) \text{max}; mL \cdot \text{kg}^{-1} \cdot \text{min}^{-1}</td>
<td>11.1±1.1†</td>
<td></td>
<td></td>
<td>13.0±0.9†</td>
</tr>
<tr>
<td>(\dot{V}_{\text{O}_2})% of predicted</td>
<td>40.6±3.2*‡</td>
<td></td>
<td></td>
<td>53.7±4.3</td>
</tr>
<tr>
<td>(\dot{V}_{\text{O}_2}); mL/min</td>
<td>595.2±48.5*‡</td>
<td></td>
<td></td>
<td>824.5±55.0</td>
</tr>
<tr>
<td>Workload\text{const.}; W</td>
<td>54.2±7.5*‡</td>
<td></td>
<td></td>
<td>84.1±9.8§</td>
</tr>
<tr>
<td>(\Delta\dot{V}_{\text{O}_2}/\Delta\text{workload}); mL \cdot \text{min}^{-1} \cdot \text{W}^{-1}</td>
<td>7.4±0.6§</td>
<td></td>
<td></td>
<td>8.2±0.4</td>
</tr>
<tr>
<td>(V_c/\dot{V}_\text{CO}_2);</td>
<td>46.6±4.0*‡</td>
<td></td>
<td></td>
<td>36.6±3.0</td>
</tr>
</tbody>
</table>

\(\Delta T\) indicates anaerobic threshold. Data are mean±SEM.

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

### 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>(\dot{V}_{\text{O}_2}); mL/min</td>
<td>803±72*‡§</td>
<td>1138±112§</td>
<td>1536±148§</td>
<td>2346±134</td>
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<tr>
<td>Workload\text{const.}; 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>(R\text{Q});</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>

\(\dot{V}_\text{O}_2\) indicates highest \(\dot{V}_\text{O}_2\) measured during constant work rate exercise; \(R\text{Q}\), 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. VO2 was similar to peak VO2 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.

![Figure 1](image1.png)  
**Figure 1.** DLCO, DM, VC, and DM/VC at rest and 2 minutes and 1 hour after exercise in different groups. *P<0.02 vs rest; $P<0.05$ vs rest; &P<0.02 vs control; £P<0.02 vs severe HF; DP<0.02 vs moderate HF. Recov indicates recovery.

![Figure 2](image2.png)  
**Figure 2.** DLCO changes from rest in different groups (2-minute recovery and 1-hour recovery). *P<0.01 vs rest. Per Br indicates periodic breathing (PB); Sev, severe; Mod, moderate; and Recov, recovery.

![Figure 3](image3.png)  
**Figure 3.** Membrane conductance (DM) changes from rest in different groups; symbols and abbreviations as in Figure 2. *P<0.01 vs rest.
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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