Impaired Pulmonary Diffusion During Exercise in Patients With Chronic Heart Failure

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Background—Pulmonary diffusion is impaired at rest in patients with chronic heart failure (CHF) and has been implicated in the generation of symptoms and exercise intolerance. The aim of this study was to determine whether pulmonary diffusion is impaired during exercise in CHF, to examine its relationship to pulmonary blood flow, and to consider its functional significance in relation to metabolic gas exchange.

Methods and Results—Carbon monoxide transfer factor (TLCO) and pulmonary blood flow (Qc) were measured by a rebreathe technique at rest and during steady-state cycling at 30 W in 24 CHF patients and 10 control subjects. Both patients and control subjects were able to raise TLCO and Qc during exercise. However, the patient group had a lower diffusion for a given blood flow (TLCO/Qc) both at rest (3.6±0.16 and 4.8±0.23 mL·L⁻¹·mmHg⁻¹; P<0.001) and during exercise (2.8±0.16 and 3.4±0.13 mL·L⁻¹·mmHg⁻¹ for CHF patients and control subjects, respectively; P<0.05). TLCO/Qc was related to the ventilatory equivalent for carbon dioxide (VECO₂) production at 30 W (TLCO/Qc versus VECO₂, r=−0.58, P<0.01) and to peak exercise oxygen consumption measured during a progressive test (TLCO/Qc versus VO₂peak, r=0.57, P<0.01) in these patients.

Conclusions—Patients with CHF are able to recruit reserves of TLCO and Qc during exercise. However, the TLCO/Qc ratio is consistently impaired in these patients and relates to both exercise hyperpnea and peak exercise oxygen consumption. Whether this impairment in alveolar gas exchange is reversible in CHF and therefore is a potential target for therapy has yet to be determined. (Circulation. 1999;100:1406-1410.)

Key Words: heart failure ■ exercise ■ lung ■ ventilation

In healthy subjects, pulmonary diffusion increases during exercise¹ because of absolute increases in ventilation and perfusion and improved ventilation-perfusion matching, with increased pulmonary capillary blood flow and capillary distension in ventilated areas of lung.² These factors increase the effective surface area of lung available for gas exchange. Pulmonary capillary distension may also thin the alveolar-capillary membrane, improving diffusion even further.

With increasing exercise intensity, both diffusion and perfusion continue to rise with no evidence of an upper limit,² although the increment in diffusion for a given rise in pulmonary blood flow decreases. Even after pneumonectomy, the relationship between pulmonary diffusion and pulmonary capillary blood flow is maintained; blood flow to the remaining lung increases, thereby maintaining diffusion.³ However, in patients with interstitial pulmonary fibrosis, there is impaired gas transfer across the alveolar-capillary membrane, which results in a marked reduction in diffusion for a given blood flow.⁴

In patients with chronic heart failure (CHF), pulmonary diffusion is impaired at rest⁵–⁷ and has been implicated in the generation of symptoms and exercise intolerance.⁸,⁹ Impaired diffusion in CHF is the result of a reduction in global perfusion of the lungs⁸ and a reduction in the conductance of the alveolar-capillary membrane.⁹ To date, however, pulmonary diffusion has not been measured during exercise in patients with CHF. The aim of the present study was to determine whether pulmonary diffusion impairment is present during exercise in CHF, to examine its relationship to pulmonary blood flow, and to consider its functional significance in relation to metabolic gas exchange.

Methods

Subjects
This study was approved by the local ethics committee, and all subjects gave written informed consent. Twenty-four male patients with stable, moderate to severe CHF secondary to left ventricular systolic dysfunction (clinical details are given in Table 1) and 10 healthy, age-matched, male control subjects took part in the study. Demographic details of both groups are given in Table 2. Patients with evidence of respiratory disease or recent smokers (within 12 months) were excluded. Control subjects were all nonsmokers, were
TABLE 1. Clinical Characteristics of CHF Patients

<table>
<thead>
<tr>
<th></th>
<th>CHF Patients (n=24)</th>
<th>Control Subjects (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.0±2.24</td>
<td>55.4±1.56</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174.1±1.38</td>
<td>178.1±2.73</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.8±2.63</td>
<td>86.3±3.62</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>2.69±0.11†</td>
<td>3.62±0.09</td>
</tr>
<tr>
<td>Predicted, %</td>
<td>89.0±3.8†</td>
<td>106.8±3.4</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.74±0.14‡</td>
<td>4.95±0.14</td>
</tr>
<tr>
<td>Predicted, %</td>
<td>94.6±3.5†</td>
<td>113.6±4.6</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>72.1±1.9</td>
<td>73.3±1.7</td>
</tr>
<tr>
<td>Predicted, %</td>
<td>94.4±2.6</td>
<td>94.5±2.1</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.08±0.22‡</td>
<td>7.56±0.30</td>
</tr>
<tr>
<td>Predicted, %</td>
<td>98.6±3.4†</td>
<td>114.8±3.6</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>98.0±0.14</td>
<td>97.4±0.31</td>
</tr>
<tr>
<td>TLCO, mL · min⁻¹ · mm Hg⁻¹</td>
<td>14.3±0.7‡</td>
<td>22.9±1.0</td>
</tr>
<tr>
<td>Qc, L/min</td>
<td>4.0±0.17*</td>
<td>4.8±0.20</td>
</tr>
</tbody>
</table>

IHD indicates ischemic heart disease; DCM, dilated cardiomyopathy. n=24.

on no medication, had normal physical examinations and ECGs, and were not engaged in any regular physical exercise.

Lung Function
Before entering the study, all subjects performed routine spirometry (SensorMedics Pulmonet) for determination of static and dynamic lung volumes. Data were compared with normal standards.¹⁰

Pulmonary Diffusion and Blood Flow During Exercise
Pulmonary diffusion and effective pulmonary blood flow were measured in duplicate, at rest, and during 8 minutes of upright cycle ergometry (Bosh ERG551) at a steady workload of 30 W. A rebreathe technique allowed the simultaneous measurement of carbon monoxide transfer factor (TLCO) and effective pulmonary blood flow (Qc) during exercise.² Subjects rebreathed a special gas mixture (35% oxygen, 3% sulfur hexafluoride, 0.3% acetylene, and 0.3% carbon monoxide, with the balance being nitrogen) for a period of 20 to 30 seconds at their current breathing frequency and a depth 10% to 15% higher than the preceding minute (a slightly higher ventilation is required to account for the gradual reduction in alveolar oxygen content in the closed breathing circuit). Decay rates of carbon monoxide and acetylene were measured by mass spectrometry (AMIS2000, Innovision) for calculation of TLCO and Qc, respectively. This procedure was performed in the fifth minute of exercise and repeated in the final minute if the patient was able to complete the test.

The TLCO and Qc values reported are the mean of 2 duplicate measures, except in 7 patients who could manage only a single measure in the fifth minute of exercise. In the 17 patients with duplicate measurements, the coefficient of variation for repeated measures was <5%. Analysis of the results with only the first measure of TLCO did not alter the findings of this study.

Incremental Exercise Test
After 30 minutes of recovery from steady-state exercise, all subjects performed a progressive incremental exercise test on the bicycle ergometer. Patients started with zero load warm-up, followed by 10-W/min increases until exhaustion; control subjects were provided with individually tailored work-rate increases to achieve exhaustion in 8 to 15 minutes.¹¹ Throughout exercise, metabolic gas exchange was monitored by a mass spectrometer metabolic cart (AMIS2000), heart rate was assessed by a 12-lead ECG (Siemens Megacart), and arterial oxygen saturation was estimated by earlobe pulse oximetry (Ohmeda Biox 3700e).

Statistical Analysis
All data are expressed as mean±SEM. Group comparisons were made by 1-way ANOVA, and correlations were represented by univariate linear regression analysis. Statistical significance was taken at the 95% level.

Results
Resting Pulmonary Function
Table 2 illustrates the demographic and pulmonary function details of the patient and control groups. Compared with control subjects, patients had mildly reduced lung volumes but no evidence of airflow obstruction, as demonstrated by the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC). In the patient group, there were marked reductions in TLCO (P<0.001) and Qc (P<0.02) at rest compared with control subjects. A reduction in stroke volume accounted for the impaired Qc in the patient group (50.6±2.7 and 62.6±3.3 mL for CHF patients compared with control subjects, respectively; P<0.05), with both groups showing similar resting heart rates (82.5±3.4 versus 78.3±4.3 bpm; P=NS).

Steady-State Exercise
Results at 30 W of exercise are shown in Table 3. TLCO and Qc increased during exercise both in healthy volunteers and in CHF patients. The magnitude of increase in TLCO with respect to Qc was normal in the patient group, although diffusion was reduced at any given blood flow (Figure 1). The reduced Qc during exercise was again the result of a reduction in stroke volume (65.6±4.4 versus 96.8±4.2 mL; P<0.001) and occurred despite a greater elevation of heart rate in the patient group (110.2±3.8 and 91.3±3.2 bpm; P<0.01). Oxygen consumption was similar in patients and control subjects, but the patient group had higher ventilation (VE;
P, 0.001) and a higher ventilatory equivalent for carbon dioxide production (VEVCO₂; P, 0.001). In patients with CHF, both of these measures correlated significantly with the TLCO achieved at the 30-W load (VE versus TLCO, r = 0.42, P < 0.05; VEVCO₂ versus TLCO, r = 0.65, P < 0.001).

**Pulmonary Diffusion and Effective Pulmonary Blood Flow**

The ratio of pulmonary diffusion to effective pulmonary blood flow (TLCO/Qc) provides an index of the efficiency of gas exchange across the alveolar-capillary membrane. TLCO/Qc was impaired in patients with CHF (Figure 2) compared with control subjects both at rest (3.6 ± 0.16 versus 4.8 ± 0.23 mL · L⁻¹ · mm Hg⁻¹ for CHF versus control subjects; P < 0.001) and during exercise (2.8 ± 0.16 versus 3.4 ± 0.13 mL · L⁻¹ · mm Hg⁻¹; P < 0.05). In CHF patients, the TLCO/Qc ratio at rest was predictive of both ventilatory efficiency during steady-state exercise (VEVCO₂ versus TLCO/Qc, r = −0.58, P < 0.01) and peak exercise VO₂ (Figure 3; VO₂peak versus TLCO/Qc, r = 0.57, P < 0.01).

**Maximal Exercise Test**

Table 4 shows the results of the maximal exercise test. All subjects were limited by breathlessness or fatigue, with no patient describing angina during exercise. At peak exercise, patients with CHF had markedly reduced work capacity (P < 0.001), oxygen consumption (P < 0.001), minute ventilation (P < 0.001), heart rate (P < 0.001), and oxygen pulse (P < 0.001) compared with control subjects. No significant oxygen desaturation was demonstrated by pulse oximetry. In the patient group, a significant relationship was observed between VEVCO₂ and peak VO₂ (r = −0.52, P < 0.01). The only other measured variable that correlated significantly with VO₂peak was the TLCO/Qc ratio (Figure 3).

**Discussion**

Resting TLCO, measured by a single breath maneuver that can be performed practically only at rest,¹²,¹³ has previously been reported before and 5 minutes after a maximal exercise test in patients with CHF.⁸ In that study, TLCO declined significantly after exercise, leading the authors to conclude that pulmonary diffusion had not risen during exercise. The present study demonstrates for the first time that patients with CHF are able to recruit reserves of pulmonary diffusion and pulmonary blood flow with exercise.

In health, pulmonary diffusion increases during exercise because of a rise in the effective alveolar volume, with recruitment of pulmonary capillary beds that were underperfused at rest and an improvement in alveolar-capillary membrane conductance, brought about by thinning caused by

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**Table 3. Pulmonary Diffusion and Metabolic Gas Exchange at 30 W**

<table>
<thead>
<tr>
<th></th>
<th>CHF Patients</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLCO, mL · min⁻¹ · mm Hg⁻¹</td>
<td>18.8 ± 1.0‡</td>
<td>29.5 ± 1.2</td>
</tr>
<tr>
<td>ΔTLCO (exercise to rest)</td>
<td>4.5 ± 0.6*</td>
<td>6.6 ± 0.5</td>
</tr>
<tr>
<td>Qc, L/min</td>
<td>7.0 ± 0.35†</td>
<td>8.8 ± 0.42</td>
</tr>
<tr>
<td>ΔQc (exercise to rest)</td>
<td>2.9 ± 0.29*</td>
<td>4.0 ± 0.37</td>
</tr>
<tr>
<td>VO₂sp, mL · kg⁻¹ · min⁻¹</td>
<td>9.6 ± 0.3</td>
<td>9.7 ± 0.3</td>
</tr>
<tr>
<td>VE, L/min</td>
<td>31.3 ± 1.5‡</td>
<td>21.0 ± 1.3</td>
</tr>
<tr>
<td>VEVCO₂</td>
<td>39.1 ± 1.6‡</td>
<td>30.1 ± 1.1</td>
</tr>
</tbody>
</table>

VO₂sp indicates oxygen consumption per kilogram of body weight. *P < 0.05; † P < 0.01; ‡ P < 0.001 for CHF patients vs control subjects.
pulmonary capillary distension. The relationship between pulmonary diffusion and pulmonary blood flow (TLCO/QC) has been used in other patient groups as an index of the efficiency of alveolar gas exchange. In patients who have undergone pneumonectomy, the ratio of diffusion to perfusion is maintained, with a proportionate increase in both parameters in the remaining lung. However, in patients with impaired alveolar-capillary membrane conductance, because of interstitial pulmonary fibrosis, there is a marked reduction in diffusion for a given pulmonary blood flow and an inability to raise diffusion significantly during exercise. This diffusion limitation contributes to systemic hypoxemia during exercise in that patient group. Patients with CHF have impaired alveolar-capillary membrane conductance, which relates to exercise capacity and NYHA functional class. Consistent with this is the finding in the present study that CHF patients exhibit a reduction in TLCO/QC ratio compared with normal controls (Figure 2). However, in contrast to patients with pulmonary fibrosis, CHF patients are able to recruit reserves of both diffusion and perfusion during exercise to effectively maintain arterial oxygenation.

In CHF patients who undergo heart transplantation, diffusion abnormalities and exercise intolerance persist despite an improvement in hemodynamic status. In this group, exercise may induce a systemic hypoxemia, especially in patients with abnormal pulmonary diffusion before transplantation or who have persisting pulmonary hypertension after transplantation. This would suggest that underlying impairment of alveolar-capillary membrane conductance can cause a functional hypoxemia when the pulmonary capillary transit time has been restored to normal.

Although CHF patients are able to maintain a normal arterial Po2 during exercise, it occurs at the expense of an elevation in ventilatory effort. This syndrome of exercise hyperpnea, measured as an increased ventilatory equivalent for VE/VCO2, is predictive of the peak level of oxygen consumption that a given patient can achieve during exercise. It also carries independent prognostic value. Many factors may contribute to exercise hyperpnea, including augmentation of peripheral chemosensitivity and a chemo-receptor reflex driven from within the working muscle.

In this study, we have shown a significant relationship between VE/VCO2 and TLCO and between TLCO/QC and both VE/VCO2 and peak Vo2 (Figure 3), suggesting that pulmonary diffusion limitation, particularly impaired alveolar gas exchange, may be involved in the regulation of exercise ventilation and ultimately of exercise tolerance. Although patients with CHF do not become hypoxemic during exercise, this may reflect the ability of increased ventilation, driven by a dynamic peripheral chemoreception, to maintain a normal end capillary Po2 by increasing the alveolar-arterial oxygen gradient. Further support for this view comes from the finding that hyperoxic breathing, with resulting improvement in pulmonary gas exchange and downregulation of the peripheral chemoreceptors, improves exercise tolerance and reduces exercise ventilation, with a tendency for reduced VE/VCO2 in CHF patients.

Conclusions

Patients with CHF are able to recruit reserves of pulmonary diffusion and pulmonary blood flow during exercise. However, the level of diffusion for a given blood flow is consistently reduced and relates to both exercise hyperpnea and peak exercise oxygen consumption. Whether this impairment in alveolar gas exchange is reversible in CHF and is therefore a potential target for therapy has yet to be determined.

Acknowledgment

This study was supported by a grant from the British Heart Foundation.

References


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TABLE 4. Incremental Exercise Test Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHF Patients</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>WR, W</td>
<td>79±3*</td>
<td>200±9</td>
</tr>
<tr>
<td>VO2, L/min</td>
<td>1.20±0.06*</td>
<td>2.77±0.15</td>
</tr>
<tr>
<td>VO2max, mL·kg⁻¹·min⁻¹</td>
<td>14.8±0.7*</td>
<td>32.1±1.1</td>
</tr>
<tr>
<td>VE, L/min</td>
<td>63.5±4.7*</td>
<td>101.6±4.7</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>132±2.4*</td>
<td>165±3</td>
</tr>
<tr>
<td>0₂pulse, mL/beat</td>
<td>9.3±0.6*</td>
<td>16.8±1.0</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>96.1±0.54</td>
<td>95.8±0.73</td>
</tr>
<tr>
<td>∆SpO₂ (rest to exercise)</td>
<td>−1.9±0.50</td>
<td>−1.6±0.73</td>
</tr>
</tbody>
</table>

WR indicates work rate; VO2max, oxygen consumption per kilogram of body weight; HR, heart rate; 0₂pulse, oxygen pulse (VO2/HR); SpO₂, oxygen saturation by pulse oximetry; and ∆SpO₂, change in oxygen saturation from rest to exercise. All measures were made at peak exercise.

*P<0.001 for CHF vs control.


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