Acute Saline Infusion Reduces Alveolar-Capillary Membrane Conductance and Increases Airflow Obstruction in Patients With Left Ventricular Dysfunction

Sundee Puri, MB, MRCP; David P. Dutka, MD, MRCP; B. Leigh Baker, BSc; J. Michael B. Hughes, DM, FRCP; J.G.F. Cleland, MD, FRCP, FESC

Background—Impaired alveolar-capillary membrane conductance is the major cause for the reduction in pulmonary diffusing capacity for carbon monoxide (DLCO) in heart failure. Whether this reduction is fixed, reflecting pulmonary microvascular damage, or is variable is unknown. The aim of this study was to assess whether DLCO and its subdivisions, alveolar-capillary membrane conductance (DM) and pulmonary capillary blood volume (Vc), were sensitive to changes in intravascular volume. In addition, we examined the effects of volume loading on airflow rates.

Methods and Results—Ten patients with left ventricular dysfunction (LVD) and 8 healthy volunteers were studied. DM and Vc were determined by the Roughton and Forster method. The forced expiratory volume in 1 second (FEV1), vital capacity, and peak expiratory flow rates (PEFR) were also recorded. In patients with LVD, infusion of 10 mL · kg−1 body wt of 0.9% saline acutely reduced DM (12.0±3.3 versus 10.4±3.5 mmol · min−1 · kPa−1, P<0.005), FEV1 (2.3±0.4 versus 2.1±0.4 L, P<0.0005), and PEFR (446±55 versus 414±56 L · min−1, P<0.005). All pulmonary function tests had returned to baseline values 24 hours later. In normal subjects, saline infusion had no measurable effect on lung function.

Conclusions—Acute intravascular volume expansion impairs alveolar-capillary membrane function and increases airflow obstruction in patients with LVD but not in normal subjects. Thus, the abnormalities of pulmonary diffusion in heart failure, which were believed to be fixed, also have a variable component that could be amenable to therapeutic intervention. (Circulation. 1999;99:1190-1196.)

Key Words: capillaries ■ lung ■ heart failure ■ ventricular dysfunction ■ lung diffusion

Reduction in the pulmonary diffusing capacity for carbon monoxide (DLCO) is well described in patients with chronic heart failure.1–3 The extent of the reduction in DLCO correlates independently with NYHA functional class and maximal exercise performance.4–6 Arterial oxygen desaturation on exercise, however, is uncommon in the majority of heart failure patients,7,8 indicating that mechanisms other than hypoxia per se are important in explaining the close correlation between DLCO and exercise performance.

Studies of heart transplant recipients have demonstrated that a low DLCO persists after transplantation despite the return to normal of pulmonary hemodynamics and lung volumes,9–11 suggesting that reduction of DLCO in chronic heart failure may in part reflect permanent damage to the alveolar-capillary interface. In patients with mitral stenosis, DLCO has been partitioned into its constituent parts: alveolar-capillary membrane conductance (DM) and reactive conductance θ · Vc (where θ is the rate of chemical reaction of CO with Vc, the volume of pulmonary capillary blood available for gas transfer).12 The reduction in DLCO and DM in this patient group correlates with NYHA functional class12 and the severity of histological lung damage.13 Moreover, pulmonary gas transfer may remain abnormal for up to 8 years after mitral valve replacement,14 further supporting the hypothesis that a reduction of DM may reflect structural damage of the alveolar-capillary interface.

Recent studies have demonstrated that the reduction in DLCO observed in heart failure is also due predominantly to a reduction in DM.5,6 Whether this reduction in DM is fixed, reflecting solely pulmonary microvascular damage, or has a variable component is unknown. Some workers have proposed that accumulation of subclinical interstitial edema, a potentially reversible factor, might contribute to the reduced DLCO seen in chronic heart failure.1,15,16 The aim of this study was to test the sensitivity of pulmonary gas transfer as measured by DLCO and its subdivisions to acute isotonic intravascular volume expansion in patients with significant left ventricular dysfunction (LVD) compared with normal
Subjects. In addition, because airway obstruction occurs in patients with decompensated heart failure and improves with diuretic therapy,15,17 we wished to examine the effects of acute volume loading on lung spirometry and peak expiratory flow rate (PEFR) measurements.

Methods

Subjects

This study was approved by the Hospital Ethics Committee, and all subjects gave informed written consent. Patients who were currently smoking or gave a history of respiratory disease were excluded. Ten subjects gave informed written consent. Patients who were currently smoking or gave a history of respiratory disease and with a normal physical examination were also studied. Their anthropometric and pulmonary function details are summarized in Table 1. All were ex-smokers, but none had smoked for at least 2 years before the study.

We chose patients with asymptomatic LVD as opposed to patients with symptomatic heart failure for 2 reasons: (1) to avoid the use of vasoactive medication that might confound the cardiorespiratory response to acute fluid loading and introduce iatrogenic interpatient variability and (2) because administration of intravenous 0.9% saline would be potentially more hazardous in patients with symptomatic heart failure requiring diuretic therapy.

In addition, 8 healthy volunteers (7 men, 1 woman) without a history of cardiorespiratory disease and with a normal physical examination were also studied. Their anthropometric and pulmonary function details are summarized in Table 1. Three were ex-smokers, having given up smoking >2 years previously, and the remainder were lifelong nonsmokers.

All subjects performed a screening symptom-limited maximal exercise test on an electronically controlled bicycle ergometer (Siemens EM840) with a 10-W/min incremental protocol. Respiratory gas analysis was performed on a breath-by-breath basis (Amis 2000 Respiratory Mass Spectrometer, Innovation), and the maximal oxygen consumption at peak exercise (MV\text{O}₂) was recorded (Table 1). None of the subjects studied terminated exercise for reasons other than breathlessness or fatigue.

### Pulmonary Function Testing

#### Spirometry

The forced expiratory volume in 1 second (FEV\textsubscript{1}) and vital capacity (VC) were measured with a dry-bellows spirometer (Vitalograph). The PEFR was also measured (Wright's flowmeter). The best of 3 successive measurements made was used in subsequent analysis.

#### Pulmonary Gas Transfer

DLCO was measured by the modified Krogh single-breath technique (PK Morgan). This was performed in duplicate with a test gas containing 0.28% CO, 14% He, 21% O\textsubscript{2}, and the balance nitrogen. The DLCO measurements were then repeated in duplicate with a test gas with a higher O\textsubscript{2} concentration (0.3% CO, 10% He, 89.7% O\textsubscript{2}). The alveolar partial pressure of O\textsubscript{2} (P\textsubscript{AO}₂) for all DLCO measurements was estimated from the fractional expired O\textsubscript{2} concentration of the same expired gas sample used for the measurement of DLCO (Servomex O\textsubscript{2} analyzer 570A). Dm and Vc were determined by the classic Roughton and Forster method, which is described in detail elsewhere.5,18,19 We assumed that the red cell membrane has a negligible backpressure to gas exchange (ie, that \( \lambda \), the ratio of red cell membrane permeability to that of the red cell interior, has an infinite value). We have shown this method to be reliable and highly reproducible in both normal subjects and patients with heart failure.8

### Protocol

All subjects were instructed to refrain from drinking beverages containing alcohol or caffeine for 24 hours before the study. Subjects fasted for 4 hours before the beginning of the study. An intravenous forearm cannula was inserted for blood sampling and infusion of fluids.

Blood hemoglobin concentration, body weight (after micturition), FEV\textsubscript{1}, VC, PEFR, DLCO, effective alveolar volume (V\textsubscript{A}), Dm, and Vc were measured as outlined above at baseline and 1 hour after the completion of a 30-minute infusion of 0.9% saline (the total volume infused was calculated as 10 mL · kg\textsuperscript{-1} · body wt of the individual subject undergoing study). The values obtained for DLCO and its subdivisions were corrected for hemoglobin before and after saline infusion to allow for any dilutional effect that might have occurred. Heart rate, blood pressure, and arterial O\textsubscript{2} saturation (P\textsubscript{AO}₂) by earlobe pulse oximetry were monitored at 5-minute intervals during the course of the saline infusion and at 15-minute intervals for a period of 2 hours thereafter. All patients with LVD were reassessed 24 hours after infusion and had repeat pulmonary function tests as performed during the acute saline infusion study day.

### Parallel Control Study

To assess whether there were any inherent effects of the study protocol on the variables being measured (eg, theoretical effects of CO backpressure, etc), 5 randomly chosen patients with LVD and 5 normal subjects underwent a control study using the exact same study protocol but without any infusion of saline.

### Effects of CO Backpressure on DLCO Measurements

As a result of the above control study and other measurements undertaken in our laboratory, we have found no evidence of significant CO backpressure effects on serial DLCO, Dm, or Vc measurements in normal subjects or patients with LVD under the present study protocol.

### Statistical Analysis

All values are expressed as mean±SD unless otherwise stated. Results at baseline presaline infusion and 1 hour after saline infusion were compared by paired Student’s t test analysis. Unpaired t test analysis was used to compare the data of normal subjects with those of patients with LVD. A value of \( P<0.05 \) was considered statistically significant.

### TABLE 1. Anthropometric, Clinical, and Pulmonary Function Details of the Subjects Studied

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>Patients With LVD</th>
<th>( P, ) Student’s t Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>8</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±4</td>
<td>62±10</td>
<td>NS</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.7±0.1</td>
<td>1.7±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.7±5.7</td>
<td>83.5±9.4</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area, m\textsuperscript{2}</td>
<td>1.8±0.2</td>
<td>1.9±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>Not measured</td>
<td>34±5</td>
<td></td>
</tr>
<tr>
<td>MV\textsubscript{O}₂, mL · min \textsuperscript{-1} · kg\textsuperscript{-1}</td>
<td>30±8</td>
<td>18.6±2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV\textsubscript{1} % predicted</td>
<td>105±12</td>
<td>78±13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VC % predicted</td>
<td>107±11</td>
<td>84±15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV/VC, %</td>
<td>78±8</td>
<td>76±5</td>
<td>NS</td>
</tr>
<tr>
<td>PEFR % predicted</td>
<td>104±17</td>
<td>95±20</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO % predicted</td>
<td>105±11</td>
<td>89±15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Va % predicted</td>
<td>102±14</td>
<td>80±8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DLCO/Va % predicted</td>
<td>105±12</td>
<td>111±13</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD. \( P \) by unpaired Student’s \( t \) test analysis.
Results

All subjects tolerated the infusion of 0.9% saline without side effects. The mean volume of saline infused per subject during the study was 830 ± 690 mL. This did not produce any significant change in blood pressure, heart rate, or S\textsubscript{AO2} (Table 2). Hemoglobin concentration decreased after saline infusion (from 14.3 ± 0.9 to 14.1 ± 0.7 g \cdot dL\textsuperscript{-1}, P < 0.05) but had returned to baseline values 24 hours later (14.4 ± 0.8 g \cdot dL\textsuperscript{-1}). Patients with LVD had significantly reduced values of MV\textunderscore{O2} compared with normal subjects despite being asymptomatic (Table 1).

Patients With LVD

Spirometry and PEFR

Baseline values of FEV\textsubscript{1} and VC were reduced in patients with LVD compared with normal subjects (Table 1). Saline infusion significantly reduced FEV\textsubscript{1} without any significant change in VC, thereby reducing the FEV\textsubscript{1}/VC ratio (Figure 1, Table 3). PEFR was also significantly reduced (Figure 1). Twenty-four hours later, all values had returned to baseline (Table 3).

Pulmonary Gas Transfer

Acute saline loading significantly reduced D\textsubscript{LCO} and its D\textsubscript{M} component without any significant change in pulmonary capillary volume or V\textsubscript{A} (Figures 2 and 3). The proportion of total pulmonary diffusive resistance attributable to the alveolar-capillary membrane (D\textsubscript{LCO}/D\textsubscript{M}) is 50% in normal subjects.\textsuperscript{5,20} The D\textsubscript{LCO}/D\textsubscript{M} in our study patients was higher at baseline than this value (Table 3) and increased further after saline infusion (Figure 3). All values had returned to baseline 24 hours later (Table 3).

Parallel Control Study

The results of the control study in 5 normal subjects and 5 patients with ventricular dysfunction are summarized in Table 4. No significant changes were seen in any of the pulmonary function tests measured. This would imply that the changes observed during the study conducted with acute saline infusion cannot be accounted for because of the study protocol or CO backpressure effects in our patient population.

Discussion

This study is the first to demonstrate that patients with asymptomatic LVD have significantly impaired resting lung function compared with normal subjects and that infusion of a relatively modest volume of isotonic saline (10 mL \cdot kg\textsuperscript{-1} body wt) can acutely further impair gas transfer across the alveolar-capillary membrane and increase airflow obstruction. This deterioration of pulmonary function occurs within 60 minutes after the infusion of isotonic saline and is completely reversible over a 24-hour period. No changes in pulmonary function were observed in the normal subjects. Larger and more rapid infusions of isotonic saline (25 to 30 mL \cdot kg\textsuperscript{-1} body wt infused over 20 to 30 minutes) have been shown to produce changes in pulmonary function in normal subjects,\textsuperscript{21-23} but any alterations produced are rapidly revers-

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**Table 2. Effects of Acute Saline Infusion on Blood Pressure, Heart Rate, and S\textsubscript{AO2}**

<table>
<thead>
<tr>
<th></th>
<th>Preinfusion</th>
<th>End Infusion</th>
<th>1 Hour Postinfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal subjects (n=8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66 ± 8</td>
<td>69 ± 10</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121 ± 9</td>
<td>125 ± 10</td>
<td>123 ± 10</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78 ± 6</td>
<td>75 ± 8</td>
<td>76 ± 7</td>
</tr>
<tr>
<td>S\textsubscript{AO2}, %</td>
<td>96 ± 1</td>
<td>96 ± 1</td>
<td>96 ± 1</td>
</tr>
<tr>
<td><strong>Patients with LVD (n=10)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76 ± 6</td>
<td>70 ± 8</td>
<td>74 ± 6</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128 ± 9</td>
<td>130 ± 10</td>
<td>128 ± 10</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>84 ± 6</td>
<td>80 ± 8</td>
<td>82 ± 7</td>
</tr>
<tr>
<td>S\textsubscript{AO2}, %</td>
<td>96 ± 2</td>
<td>95 ± 2</td>
<td>96 ± 2</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD.
TABLE 3. Effects of Acute Intravenous Saline Infusion on Pulmonary Function

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects (n=8)</th>
<th>Patients With LVD (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preinfusion</td>
<td>1 Hour Postinfusion</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>3.9±0.4</td>
<td>3.8±0.4</td>
</tr>
<tr>
<td>VC, L</td>
<td>4.9±0.8</td>
<td>4.8±0.9</td>
</tr>
<tr>
<td>FEV₁/VC, %</td>
<td>80±10</td>
<td>79±7</td>
</tr>
<tr>
<td>PEFR, L · min⁻¹</td>
<td>600±37</td>
<td>590±48</td>
</tr>
<tr>
<td>DLCO, mmol · min⁻¹ · kPa⁻¹</td>
<td>10.8±2.6</td>
<td>11.0±2.0</td>
</tr>
<tr>
<td>VA, L</td>
<td>6.9±0.8</td>
<td>6.7±0.9</td>
</tr>
<tr>
<td>DM, mmol · min⁻¹ · kPa⁻¹</td>
<td>19.5±5.1</td>
<td>21.0±5.0</td>
</tr>
<tr>
<td>DLCO/DM, %</td>
<td>52±9</td>
<td>51±6</td>
</tr>
<tr>
<td>Vc, mL</td>
<td>65±16</td>
<td>64±19</td>
</tr>
</tbody>
</table>

In patients with LVD, *P<0.05, †P<0.005, ‡P<0.0005 vs preinfusion values by paired Student’s t test analysis.

Saline Infusion and Pulmonary Diffusion

In the present study protocol, we found no significant change in DLCO or its subdivisions in normal subjects after saline loading. Other workers have found that saline infusion of 25 to 30 mL · kg⁻¹ body weight over 20 to 30 minutes in normal subjects increases perfusion of the lung apices and recruitment of pulmonary capillaries, resulting in a rise in DLCO but also to a reduction in its Vc component. Vc did not change significantly after saline infusion; therefore, ventilation-perfusion mismatch cannot explain the reduction in DLCO and DM.

Figure 2. Acute effects of saline infusion on alveolar-capillary membrane diffusing capacity per unit effective alveolar volume (DM/Va) and proportion of total pulmonary diffusive resistance secondary to alveolar-capillary membrane (DLCO/DM) in patients with LVD. Comparison of results between preinfusion and 1 hour postinfusion values was made by paired Student’s t test analysis.

Alveolar-Capillary Membrane Surface Area

A reduction in lung volume or an increase in ventilation-perfusion mismatch would reduce the surface area of alveolar-capillary membrane available for gas transfer. No change in VC or Va occurred in the present study after saline infusion (Table 3), and the reduction in DM persisted even when Va was accounted for (DM/Va, Figure 2), making this mechanism unlikely as a cause of the impaired pulmonary gas transfer. An increase in ventilation-perfusion mismatch would lead not only to a reduction in the DM component of DLCO but also to a reduction in its Vc component. Vc did not change significantly after saline infusion; therefore, ventilation-perfusion mismatch cannot explain the reduction in pulmonary diffusion after saline infusion.

Intrinsic Properties of the Alveolar-Capillary Interface

The alveolar-capillary interface is formed by a number of different physical layers, including the alveolar epithelium, interstitial fluid, capillary endothelium, plasma, and red cell membrane, any of which might potentially be affected by saline infusion. The development of subclinical interstitial pulmonary edema after acute myocardial infarction is well described. Clearly, saline infusion in our patient population with LVD could also lead to the accumulation of interstitial fluid. This would lead to an increase in the diffusion path length for gas exchange and thereby reduce DM.
Recent studies in the isolated rabbit lung model have shown by electron microscopy that raising pulmonary artery pressures can lead to ultrastructural fractures (also called stress failure) of the alveolar-epithelial, alveolar-capillary basement membrane, and pulmonary capillary-endothelial layers,25,26 some of which may be reversible.27 The hemodynamic consequence of rapid saline infusion in normal subjects is to acutely increase cardiac output, pulmonary artery pressure, and right atrial pressure after the infusion, with a return to baseline levels over the course of 60 minutes.23,28 Elevation of pulmonary capillary pressures is well documented in patients with LVD.29–32 Although we did not measure hemodynamics in our study, infusion of saline could have produced a further increase in pulmonary microvascular pressures sufficient to produce “stress failure” of the alveolar-capillary interface, thereby altering the intrinsic properties of the alveolar-capillary membrane and allowing the development of subsequent interstitial edema.

Saline Infusion and Airflow Obstruction
Increased airflow obstruction is well documented in patients with heart failure and pulmonary edema.15,17,24 In the present study, saline infusion acutely produced a small but significant reduction in both FEV1 and PEFR in patients with LVD (Table 3, Figure 3), but not in the normal subjects studied (Table 3). Several factors, either in isolation or in combination, could be responsible for the changes in airflow obstruction observed in patients with LVD, as follows.

**TABLE 4. Results of a Control Study Without Saline Loading in 5 Normal Subjects and 5 Patients With LVD**

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Patients with LVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Hour Postbaseline</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>3.7±0.4</td>
<td>3.6±0.4</td>
</tr>
<tr>
<td>VC, L</td>
<td>4.7±0.8</td>
<td>4.6±0.8</td>
</tr>
<tr>
<td>FEV1/VC, %</td>
<td>80±5</td>
<td>80±6</td>
</tr>
<tr>
<td>PEFR, L·min⁻¹·kPa⁻¹</td>
<td>602±38</td>
<td>583±50</td>
</tr>
<tr>
<td>Dlco, mmol·min⁻¹·kPa⁻¹</td>
<td>10.3±2.6</td>
<td>9.9±1.7</td>
</tr>
<tr>
<td>Dm, mmol·min⁻¹·kPa⁻¹</td>
<td>17.5±4.6</td>
<td>18.6±4.9</td>
</tr>
<tr>
<td>VC, mL</td>
<td>65±20</td>
<td>61±21</td>
</tr>
</tbody>
</table>

P by paired Student’s t test analysis.

**Peribronchial Compression**
Peripheral airways in the lung parenchyma lie within bronchovascular sheaths that also contain branches of the pulmonary vasculature and lymphatics. Several authors have proposed that the initial increase in airway resistance observed in experimentally induced pulmonary edema is secondary to distension of the pulmonary arteries within bronchovascular sheaths, with subsequent compression of the smaller peripheral airways.33–35 In addition, rapid infusion of 2 L of 0.9% saline in normal subjects has been shown to result in a transient reduction of indices of smaller airway flow.21

FEV1 and PEFR, however, are largely determined by the caliber of the larger airways, suggesting that this mechanism is unlikely as the major cause of any reduction observed in the present study with saline infusion. In addition, morphometric studies have failed to show any reduction in the caliber of peripheral airways in experimental pulmonary edema.36

**Bronchoconstriction**
Unmyelinated C fibers, which are present in bronchi, lung parenchyma, and pulmonary vasculature, have been proposed as stretch receptors in the interstitial space that they
occupy. In the dog model, both distension of the pulmonary vasculature and interstitial pulmonary edema independently increased C-fiber activity, leading to vagally mediated reflex bronchoconstriction. Similar changes may have been produced by saline infusion in our patient population.

**Bronchial Vessel Dilatation**

Bronchial hyperresponsiveness has been documented by several authors in patients with heart failure. Cabanes et al demonstrated that the bronchoconstrictor response to inhaled methacholine can be abolished by the action of the inhaled vasoconstrictor methoxamine in chronic heart failure. They proposed that elevation of left ventricular filling pressure in chronic heart failure causes dilatation of bronchial wall blood vessels with secondary transudation of plasma, thereby leading to an increase in airway resistance and bronchial hyperresponsiveness. Saline infusion in the patients studied could have produced elevation of pulmonary vascular pressures, with a similar effect on airway function.

**Conclusions**

This study is the first to demonstrate that measurements of pulmonary vascular pressures, with a similar effect on airway function.

**Acknowledgments**

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**References**


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