Increased alveolar/capillary membrane resistance to gas transfer in patients with chronic heart failure

S Puri, B L Baker, C M Oakley, J M B Hughes, J G F Cleland

Abstract

Objective—To investigate pulmonary diffusive resistance to gas exchange in patients with heart failure and healthy volunteers, assessing the relative contributions of the alveolar/capillary membrane and pulmonary capillary blood. Setting—Hospital outpatient department and pulmonary function laboratory. Patients—38 patients (mean age 60) receiving treatment with loop diuretics and angiotensin converting enzyme inhibitors for stable symptomatic heart failure of > 6 months duration (New York Heart Association (NYHA) classes II and III). Results were compared with those of 17 healthy volunteers (mean age 52). Methods—The alveolar/capillary membrane diffusive resistance and the pulmonary capillary blood volume available for physiological gas exchange were determined by the Roughton and Forster method, which measures the single breath pulmonary diffusion capacity for carbon monoxide at varying alveolar oxygen concentrations. Results—Total pulmonary diffusive resistance was higher in patients than controls. Alveolar/capillary membrane resistance formed the main component of this increase, accounting for a mean (SD) of 63% (20%) and 86% (8%) of total pulmonary diffusive resistance in patients in NYHA II and III classes respectively, compared with 53% (10%) in controls. The pulmonary capillary blood volume was not significantly different between controls and patients in NYHA class II (66 (18) ml v 61 (18) ml), but was increased in those in NYHA class III (95(46) ml, P < 0.05). Conclusion—This study confirmed impairment of pulmonary diffusion at rest in patients with chronic heart failure and identified impaired alveolar/capillary membrane function as the main factor responsible.

(Br Heart J 1994;72:140–144)

A reduction in resting pulmonary diffusing capacity to carbon monoxide (TLCO) has been previously reported in patients with chronic heart failure,1 2 but the precise aetiology of this reduction remains unclear. It has been assumed that a decrease in TLCO was not of functional significance as arterial desaturation is not prominent during exercise in patients with heart failure,3 4 and during exercise the relatively reduced cardiac output and prolonged pulmonary capillary transit time would allow increased time for gas exchange in the lung.

More recently, TLCO has been proposed as being an independent predictor of peak exercise oxygen uptake in patients with heart failure.5 Also, increasing inspired oxygen concentration during exercise has been shown to improve arterial oxygen saturation, reduce minute ventilation, and improve breathlessness.6 These data suggest that impairment of pulmonary gas exchange may be a limiting factor for exercise performance.

In patients with mitral stenosis, who also have high left atrial pressures, detailed studies of pulmonary function have been performed,7 8 including measurement of alveolar/capillary membrane diffusing capacity (Dm) and pulmonary capillary volume (Vc).9 In this group, reduction in DLCO and Dm have been shown to be associated with New York Heart Association (NYHA) functional class8 and histological lung damage.10 No such measurements of Dm and Vc have been made in patients with symptomatic heart failure. The aim of our study was to investigate pulmonary diffusive resistance (1 TLCO) to gas exchange in patients with heart failure compared with normal controls, with particular reference to the relative contributions of the alveolar/capillary membrane and pulmonary capillary blood.

Patients and methods

PATIENTS
The study was approved by the local ethics committee, and each patient gave informed consent. Patients with a history of respiratory disease or who were current smokers were excluded. Thirty six men and two women with stable symptomatic heart failure of > 6 months duration, mean age 60 (range 39–75) were studied. The mean (SD) left ventricular ejection fraction as determined by gated radionuclide ventriculography was 33% (10%). The aetiology of heart failure was ischaemic heart disease in 32 and dilated cardiomyopathy in six patients. Twenty eight patients were in NYHA class II and 10 in NYHA class III. All were receiving loop diuretic treatment, a mean (SD) frusemide equivalent dose of 45 (21) mg (assuming 1 mg of bumetanide is equivalent to 40 mg of frusemide), and angiotensin converting enzyme (ACE) inhibitors. None had needed a
Increased alveolar-capillary membrane resistance to gas transfer in patients with chronic heart failure

change in treatment in the eight weeks before the study. Three of the patients studied (all in NYHA class II) were being treated with amiodarone, and no patients were receiving other drugs that may have had an effect on the measurement of TLCO. Healthy volunteers (one woman and 16 men), mean age 52 (range 38–67), without a history of cardiopulmonary disease and with a normal physical examination were also studied.

PROCEDURE
Routine spirometry was performed to determine the forced expiratory volume in one second (FEV₁) and slow vital capacity (VC). The TLCO was measured in duplicate with a standard modified Krogh single breath technique (PK Morgan). The test gas consisted of 0-28% carbon monoxide (CO) and 14% helium (He) in air. Briefly, the patient was connected with a mouth piece and nose clip to a double bag in box system with a three way valve. After four or five tidal breaths of room air, a maximal expiration was made to residual volume and the valve was automatically switched so that the subject inhaled maximally from the bag containing the test gas mixture, a vital capacity. This was followed by a predetermined (10 s) period of breath holding at full inspiration. Leakage of gas from the patient was prevented by the closure of a shutter. A further automatic switch of the three way valve allowed the subject to exhale naturally. The first 750 ml of expired gas was discarded with collection of the next 500 ml in a second bag for subsequent gas analysis. This manoeuvre was then repeated, again in duplicate, with a test gas with a higher oxygen (O₂) concentration (0-3% CO, 10% He, 89-7% O₂). All results were corrected for the subject’s haemoglobin concentration. The alveolar partial pressure of O₂ (PₐO₂) was recorded for all TLCO measurements and was estimated from the fractional expired O₂ concentration of the same expired gas sample used for the measurement of TLCO (Servomex O₂ analyser 570A). It was assumed that the partial pressure of H₂O in the alveolus was 47 mm Hg. DM and the volume of blood available for physiological gas exchange were determined with the classic Roughton and Forster method. This method partitions pulmonary resistance capacity (1/TLCO) into its two component resistances: the diffusive resistance of the alveolar capillary membrane (1/DM) and the reactive resistance due to pulmonary capillary blood (1/θVC, where θ = the rate of reaction of CO with haemoglobin).

The Roughton and Forster equation
\[
1/\text{TLCO} = 1/D_M + 1/\theta \text{VC}
\]
links these resistances together. θ is inversely proportional to PₐO₂ as there is direct competition for haemoglobin binding sites between CO and O₂. The following equation assumes that the red cell membrane has a negligible resistance to gas exchange, and was used to find 1/θ: 1/θ = 14-6/θb × ((0-001 × PₐO₂) + 0-0134) where θb is the subject’s haemoglobin (g/dL) and PₐO₂ is measured in kPa. Therefore if TLCO is measured at different PₐO₂ values, a plot of 1/DM against 1/θ will yield a straight line with a Y intercept of 1/D_M and a gradient of 1/VC (fig 1).

STUDIES OF REPRODUCIBILITY
Repeat measurements were made at about the same time of day on two consecutive days in five controls and five patients with heart failure chosen at random.

STATISTICAL ANALYSIS
All values are expressed as mean(SD). Comparisons of results between patients with severe symptoms (NYHA class III), patients with mild to moderate symptoms (NYHA class II), and normal controls were made using the Scheffe F test (analysis of variance). A value of P < 0.05 was considered to be significant.

Results
Table 1 summarises the results of conventional lung function tests and anthropometric details of the subjects studied. The VC was reduced in patients with heart failure compared with normal controls (P < 0.05), but there was no significant increase in airflow obstruction as measured by the FEV₁/VC ratio (table 1), in keeping with previous studies.

Studies of reproducibility showed a high level of agreement between consecutive measurements of 1/D_M, having a correlation coefficient (r) of 0.99 and a coefficient of vari-

Table 1  Anthropometric details and results of routine lung function tests

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 17)</th>
<th>NYHA class II (n = 28)</th>
<th>NYHA class III (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (m)</td>
<td>1.72 (0.09)</td>
<td>1.70 (0.07)</td>
<td>1.73 (0.09)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (11)</td>
<td>79 (12)</td>
<td>77 (16)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.89 (0.18)</td>
<td>1.90 (0.16)</td>
<td>1.90 (0.23)</td>
</tr>
<tr>
<td>FEV₁/VC (%)</td>
<td>80 (9)</td>
<td>75 (9)</td>
<td>74 (9)</td>
</tr>
<tr>
<td>VC (l)</td>
<td>4.4 (0.3)</td>
<td>3.2 (0.2)*</td>
<td>2.6 (0.4)*</td>
</tr>
<tr>
<td>TLCO (mmol/min/kPa)</td>
<td>9.68 (2.02)</td>
<td>7.39 (1.51)*</td>
<td>5.22 (1.33)*</td>
</tr>
</tbody>
</table>

* P < 0.001 v controls. TLCO pulmonary diffusing capacity for carbon monoxide; FEV₁ = forced expiratory volume in one second; VC = vital capacity. Results are mean (SD).
Figure 2  Reproducibility of consecutive measurements of alveolar capillary membrane diffusive resistance (1/DM).

Figure 3  Individual results and mean value of each group for total pulmonary diffusive resistance (1/TLCO), alveolar/capillary membrane diffusive resistance (1/DM), and the percentage of total pulmonary diffusive resistance due to the alveolar/capillary membrane (100/TLCO/DM).

Table 2  Pulmonary diffusive resistance and its subdivisions

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 17)</th>
<th>NYHA class II (n = 28)</th>
<th>NYHA class III (n = 10)</th>
<th>p Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/TLCO (Pa.min.mmol⁻¹)</td>
<td>110 (20)</td>
<td>140 (30)</td>
<td>200 (60)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>1/DM (Pa.min.mmol⁻¹)</td>
<td>60 (20)</td>
<td>90 (30)</td>
<td>170 (40)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>TLCO/DM (Pa.min.mmol⁻¹)</td>
<td>53 (10)</td>
<td>63 (9)</td>
<td>86 (8)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>VC (ml)</td>
<td>66 (18)</td>
<td>61 (18)</td>
<td>95 (46)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P Values quoted are for comparisons made with the Scheffe F test for analysis of variance. TLCO, total pulmonary diffusive resistance; 1/DM, alveolar capillary membrane diffusive resistance; TLCO/DM, the percentage of total pulmonary diffusive resistance due to the alveolar capillary membrane. VC, volume of pulmonary capillary blood. Results are mean (SD).
Increased alveolar/capillary membrane resistance to gas transfer in patients with chronic heart failure

A reduction in lung volumes is well documented in patients with heart failure. If this were to be the main mechanism responsible for the increase in alveolar/capillary membrane diffusive resistance, then a significant correlation between vital capacity and TLCO/D\textsubscript{L} would be expected. Moreover, a decrease in lung volume would reduce not only DLCO, but also reduce the pulmonary capillary volume of blood available for physiological gas exchange. None of these changes were seen in our patient population, and in contrast, those patients with the greatest increase in alveolar/capillary membrane resistance also had increased pulmonary capillary blood volumes. A recent study of patients undergoing heart transplantation did not show any improvement in TLCO despite a return to normal lung volumes after transplantation, lending further support to there being an alternative explanation for raised alveolar/capillary membrane resistance to gas exchange in patients with chronic heart failure.

In a similar vein, the presence of increased ventilation/perfusion mismatch would cause a reduction in the effective surface area available for physiological gas exchange, leaving the proportion of total pulmonary diffusive resistance due to the alveolar/capillary membrane (TLCO/D\textsubscript{L}) unchanged, and the effective volume of pulmonary capillary blood reduced. This was not found to be the case in this study, suggesting that increased ventilation/perfusion mismatch is not a main cause of the increased alveolar/capillary membrane resistance seen in our patient population.

A significant determinant of pulmonary capillary volume will be the surface area of the alveolar/capillary interface available for gas exchange. This will be increased by improved ventilation/perfusion matching, and may be one factor responsible for the increase in pulmonary capillary blood volume in patients in NYHA class III—e.g., increased perfusion of the relatively over ventilated pulmonary upper lobes at rest, secondary to an increase of left atrial pressure.

In patients with mitral stenosis, raised pulmonary diffusive resistance correlates with the degree of histological pulmonary vascular damage. In animal models, a transient increase in pulmonary artery pressure has been shown to cause disruption of alveolar epithelium and pulmonary endothelium, which in the short term at least is reversible. In patients with heart failure, pulmonary capillary pressures may also be increased at rest, and increase further on exercise. This could induce stress damage of the alveolar/capillary membrane. Indeed, the earliest changes arising from a rise in pulmonary venous and capillary pressure occur in the alveolar/capillary wall, which becomes oedematous, particularly in the thicker collagen containing parts of the septum. Hyaline organisation with a mucopolysaccharide ground substance takes place. There is endothelial cell swelling, and proliferation of connective tissue (reticulin and elastin) and type II epithelial cells is seen. Raised alveolar/capillary membrane resistance may reflect the nature and magnitude of this injury. Evidence from heart transplant recipients suggests that there may be irreversible pulmonary vascular or parenchymal abnormalities as TLCO decreases despite a restoration of normal haemodynamics and lung volumes after transplantation. This population, however, represents one extreme of the heart failure spectrum. Abnormalities of pulmonary diffusing capacity, and in particular the change in alveolar/capillary membrane resistance that we have found, may be partly or totally reversible in those with less severe disease.

The importance of changes in pulmonary haemodynamics in chronic heart failure is emphasised by the fact that pulmonary hypertension has been shown to predict morbidity and mortality in patients with dilated cardiomyopathy. The inability to decrease pulmonary as well as systemic vascular resistance has been implicated both in the impairment of exercise performance and the poor clinical and sometimes hypotensive response to ACE inhibition seen in some patients with heart failure. These data would support the hypothesis that pulmonary microvascular damage and modulation of pulmonary vascular resistance are in part responsible for the exercise limitation of heart failure. Conventional measures of pulmonary haemodynamics (pulmonary artery pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance) whether at rest or on exercise, only provide a view of the pulmonary circulation over a brief period. Alveolar/capillary membrane resistance may provide a more useful and sensitive non-invasive marker for the assessment of pulmonary microvascular damage than conventional haemodynamic measures, reflecting the cumulative damage sustained throughout the course of the underlying disease process.

There is increasing evidence that impaired pulmonary function and gas exchange may contribute to the functional limitation of chronic heart failure. The results of this study support the presence of impaired function of the alveolar-capillary membrane at rest in treated stable chronic heart failure. This dysfunction is greatest in those with the most severe symptoms (NYHA class III), although there is clearly some overlap with controls in patients in NYHA class II. Whether this impairment can be modified or is of significance in the limitation of exercise performance in patients with heart failure remains unknown at present. Further investigation of alveolar/capillary membrane resistance during exercise and with progression of disease is required.

SP is supported by a Research Fellowship from the British Heart Foundation.


