Gas diffusion and alveolar–capillary unit in chronic heart failure

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KEYWORDS
Heart failure; Exercise; Lung; Oedema; Ventilation

Aims Alveolar gas diffusion (DLCO) is impaired in chronic heart failure (CHF). Diffusion depends on membrane diffusion (DM) and the amount of blood participating in gas exchange (VC). How DM, VC, and the alveolar–capillary unit behave in relationship to CHF severity is unknown.

Methods and results We measured pulmonary function, including DLCO, DM, VC, and alveolar volume (VA), in 191 CHF patients in NYHA class I–III. CHF patients were grouped accordingly to peak exercise oxygen uptake (pVO2); group <12 mL/min/kg (n = 24), group 12–16 (n = 76), group 16–20 (n = 64), and group >20 (n = 27). DLCO, DM, VC, and VA were lowest in severe CHF and were linearly related to pVO2 (DLCO, r = 0.577, P < 0.001; DM, r = 0.490, P < 0.001; VC, r = 0.216, P < 0.01; VA, r = 0.565, P < 0.01). DM/VC ratio, an index of the alveolar–capillary unit efficiency, was higher in group <12 (0.49 ± 0.39 mL/min/mmHg/mL) and >20 (0.46 ± 0.29), compared with 12–16 (0.34 ± 0.19) and 16–20 (0.35 ± 0.17).

Conclusion DLCO progressively worsens as CHF severity increases due to reduction in lung tissue participating to gas exchange (low VC and VA). In severe CHF, the few working alveolar–capillary units are the most efficient as shown by the high DM/VC. This is useful for maintaining gas exchange efficiency in severe CHF.

Introduction
It has been known for several years that lung mechanics are impaired in patients with chronic heart failure (CHF).1,2 Differently, attention has been focused on abnormalities of gas diffusion across the alveolar–capillary membrane only in the last 10 years, mainly because oxygen haemoglobin desaturation is rare in CHF.3,4 Hence, the correlation between lung diffusion abnormalities and CHF severity was considered meaningless. In the last decade, it became evident that lung diffusion abnormalities not only strongly correlate with exercise performance and CHF severity,5–7 but, most importantly, with CHF prognosis.8 Furthermore, it has been shown that improvement of lung diffusion correlates with the efficacy of some antifailure treatments.9–11

Lung diffusion is routinely measured as lung diffusion for carbon monoxide (DLCO). DLCO depends upon alveolar–capillary membrane diffusive capacity (DM) and the amount of blood, the ‘so-called’ capillary volume (VC), which flows through the ventilated alveolar–capillary units over the period of time, a few seconds, needed by the measuring technique to be carried out. Therefore, the amount of capillary blood in the lung which, for any possible reason, does not participate in gas exchange is excluded from VC measurement. In CHF, DLCO can change transiently. Indeed, an acute increase of pulmonary wedge pressure, as it happens during heavy exercise or haemodynamic instability, is associated with a reduction in DLCO, due to a lowering in DM, which is partially counterbalanced by an increase in VC.12,13 DLCO can also transiently increase, as happens during mild exercise, through an increase in VC.14 Data on DLCO subcomponents at rest in CHF patients with stable clinical condition are less clear. Indeed, a first report on a very limited number of subjects showed a VC increase in patients with severe heart failure;7 however, this finding was not confirmed in other studies.8,14,15 Furthermore, several lines of evidence suggest it is unlikely that in CHF patients with optimized treatment VC is increased: (i) DLCO abnormalities persist after heart transplant,16,17 (ii) ultrafiltration reduces lung fluid content but does not affect DLCO or its subcomponents DM and VC,17 and (iii) at Computer Tomography, lung fluids are not increased in stable maximally treated CHF patients.18 On the contrary, there are a few reasons to hypothesize that VC is reduced in CHF; among these, the increased
ventilation/perfusion mismatch which leads to ventilated area with low or no flow and to an increase of intrapulmonary shunt.\textsuperscript{19,20}

The present study was carried out to define DLCO, DM, and VC behaviours and the efficiency of the alveolar–capillary units in a large cohort of CHF patients in stable clinical conditions and different CHF severity, as defined by exercise capacity.

Methods

Study population

A total of 191 CHF subjects in stable clinical conditions fulfilled the inclusion criteria and participated in the study. Patients belong to a cohort of consecutive CHF subjects regularly followed at our heart failure unit, who were evaluated during a routine heart failure follow-up. According to the New York Heart Association (NYHA) classification 11, 91, and 89 patients were in class I, II, and III, respectively. Treatment was constant for at least 2 months, and included diuretics in 161 cases, angiotensin-converting enzyme inhibitors in 160 cases, angiotensin receptor blockers in 26 cases, beta-blocker in 74 cases, digitalis in 83 cases, amiodarone in 71 cases, antialdosteronic agents in 44 cases, antiplatelet therapy in 45 cases, anticoagulant therapy in 44 cases, and nitrates in 30 cases. At rest, 146 patients were in sinus rhythm, and 45 in atrial fibrillation.

Study inclusion criteria was CHF in NYHA class I–III, stable clinical conditions for at least 2 months, capability of performing standard pulmonary function and DLCO manoeuvres, maximal or near-maximal cardiopulmonary exercise test (CPET), previous experience with CPET in our laboratory, absence of history and/or clinical documentation of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive lung disease, significant peripheral vascular disease, exercise-induced angina, ST-segment changes, or severe arrhythmias. The study was approved by the local Ethics Committee. All patients who fulfilled the study inclusion criteria were asked to participate in the study; all accepted and provided written informed consent to the study.

CHF severity was evaluated by means of CPET. Patients were grouped according to the exercise capacity as inferred by peak \( \dot{V}O_2 \). CPETs were done on a cyclo-ergometer (Ergo 8005 Sensor Medics, Yorba Linda, CA, USA), using a personalized ramp protocol aimed at achieving peak exercise in 10 min with breath-by-breath expiratory gases and ventilation analysis (V-Max, Sensor Medics, Yorba Linda, CA, USA). The test was self-ended by the patients; however, all patients declared that they had performed what they felt to be maximal effort. Anaerobic threshold was measured with the V-slope analysis from the plot of VCO\(_2 \) vs. \( \dot{V}O_2 \) on equal scales. The anaerobic threshold value was confirmed by ventilatory equivalents and end-tidal pressures of CO\(_2\) and O\(_2\). The \( \dot{V}O_2/\text{work rate} \) relationship was evaluated throughout the entire exercise; the ventilation (VE)/VCO\(_2\) slope was calculated as the slope of the linear relationship between VE and VCO\(_2\) from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Two experts read each test independently.

Standard pulmonary tests were performed according to the American Thoracic Society criteria.\textsuperscript{21} Forced expiratory volume in 1 s (FEV\(_1\)) and forced vital capacity (FVC) normal predicted values were those reported by Quajer et al.\textsuperscript{22} DLCO was measured in the standard sitting position with the single breath constant expiratory flow technique (Sensor Medics 2200, Yorba Linda, CA, USA).\textsuperscript{23} Diffusion subcomponents, VC and DM, were also measured by applying the Roughton and Forster method.\textsuperscript{26} For this purpose, subjects inhaled gas mixtures containing 0.3\% CH\(_4\), 0.3\% CO, with three different oxygen fractions equal to 20, 40 and 60\%, respectively, and balanced with nitrogen. Alveolar volume was measured by CH\(_4\) decay slope during single breath constant expiratory flow measurements.\textsuperscript{27}

All patients underwent echocardiographic and Doppler evaluations. The presence of a restrictive pattern was evaluated by analysing, whenever possible, mitral E/A relationship, E wave slope, and pulmonary venous flow.

Statistical analysis

Data reported are mean \( \pm \) SD. Peak exercise and anaerobic threshold \( \dot{V}O_2 \) measurements are mean over 20 s. Differences among CHF groups were evaluated by multivariable analysis (ANCOVA adjusting for gender and age). Post hoc comparison between single pairs of groups were performed by t-test and resulting probabilities corrected for multiple testing by the Tukey-Cramer method. Correlations were analysed by best fit analysis, which was a linear regression analysis except when specifically stated. A \( P \)-value < 0.05 was considered as statistically significant. A sample size of 190 patients was calculated in order to assess as statistically significant a correlation coefficient of 0.2 between peak \( \dot{V}O_2 \) and VC, with an alpha value of 0.05 and a power of 80%.

Results

All subjects performed the entire heart failure evaluation protocol. Twenty-four subjects had a peak \( \dot{V}O_2 < 12 \) mL/min/kg (group 12), 76 had peak \( \dot{V}O_2 \) between 12 and 16 mL/min/kg (group 12–16), 64 had peak \( \dot{V}O_2 \) between 16 and 20 mL/min/kg (group 16–20), and 27 had peak \( \dot{V}O_2 > 20 \) mL/min/kg (group >20).\textsuperscript{21} Patients’ characteristics are reported in Table 1. Aetiology of CHF was divided cardiomyopathy due to coronary artery disease (CAD) or idiopathic cardiomyopathy (ICM): group <12, 12/12 CAD/ICM; group 12–16, 30/46; group 16–2, 17/47; group >20, 7/20, respectively. CPET results supported the finding of a progressively greater severity of the disease from group >20 to group <12. Indeed, \( \dot{V}O_2 \) at anaerobic threshold and the \( \dot{V}O_2/\text{work} \) slope were lower when the CHF severity was greater. The VE/VCO\(_2\) slope was the highest in most compromised patients.

Pulmonary function test results are reported in Table 1. Patients with severe CHF had a moderate restrictive lung disease. In the entire CHF population, FEV\(_1\) (\( r = 0.632\), \( P < 0.0001 \)) and FVC (\( r = 0.632\), \( P < 0.001 \)) were correlated with peak \( \dot{V}O_2 \) (Table 1). DLCO, DM, VA, and VC were progressively decreased as the exercise capacity reduced (Figure 1). DLCO, as % of predicted, was 64.4 \( \pm \) 17.8% in group <12, 75.2 \( \pm \) 21.7% in group 12–16, 80.3 \( \pm \) 14.7% in group 16–20, and 90.0 \( \pm \) 21.2% in group >20 (\( P < 0.01 \) vs. group <12, \( P < 0.05 \) vs. group >20). VC was lowest in group <12 (82.1 \( \pm \) 49.8 mL vs. 105 \( \pm \) 41 considering together all other CHF patients, \( P < 0.02 \)). Absolute values for DM and VC were 27.9 \( \pm \) 12.1 mL/mmHg/min and 82.1 \( \pm \) 49.8 mL in group <12, 29.1 \( \pm \) 9.8 mL/mmHg/min and 97.6 \( \pm \) 43.5 mL in group 12–16, 31.1 \( \pm \) 9.5 mL/mmHg/min and 103.9 \( \pm \) 37.3 mL in group 16–20, 42.2 \( \pm \) 11.4\textsuperscript{28} mL/mmHg/min and 111.0 \( \pm \) 42.1 mL in group >20, respectively (\( P < 0.01 \) vs. <12, \( P < 0.01 \) vs. 12–16, \( P < 0.01 \) vs. 16–20). DM/VC ratio, as shown in Figure 2 (upper panel), was higher in group <12 (0.49 \( \pm \) 0.39 mL/min/mmHg/mL) compared with group 12–16 (0.34 \( \pm \) 0.19\textsuperscript{29}) and group 16–20 (0.35 \( \pm \) 0.17\textsuperscript{29}) (\( P < 0.05 \) vs. 12). DM/VC ratio in group >20 was 0.46 \( \pm \) 0.29. DLCO, DM, and VA were linearly related to peak \( \dot{V}O_2 \) (Figure 3). VC was linearly related to peak \( \dot{V}O_2 \) with a weak relationship (Figure 3), whereas DM/VC was not linearly related to peak \( \dot{V}O_2 \), but the best fit analysis
Table 1  Clinical and functional characteristics of the study population

<table>
<thead>
<tr>
<th>Group</th>
<th>&lt;12 (n = 24)</th>
<th>12-16 (n = 76)</th>
<th>16-20 (n = 64)</th>
<th>&gt;20 (n = 27)</th>
<th>Correlation vs. peak VO(_2) (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 8</td>
<td>62 ± 7</td>
<td>59 ± 9</td>
<td>56 ± 10</td>
<td>R = -0.398, P &lt; 0.001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>18/6</td>
<td>57/19</td>
<td>52/12</td>
<td>26/1</td>
<td></td>
</tr>
<tr>
<td>Smoke (C/F/N)</td>
<td>6/7/11</td>
<td>10/35/31</td>
<td>10/32/22</td>
<td>7/8/12</td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td>2.7 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>2.3 ± 0.7(^{st})</td>
<td>2.0 ± 0.5(^{st})</td>
<td>R = -0.333, P &lt; 0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>28.3 ± 8.4</td>
<td>31.8 ± 10.1(^{t})</td>
<td>34.5 ± 8.5(^{t})</td>
<td>35.4 ± 9.1(^{t})</td>
<td>R = 0.245, P &lt; 0.01</td>
</tr>
<tr>
<td>End-diastolic volume (mL)</td>
<td>215 ± 77</td>
<td>191 ± 65</td>
<td>197 ± 67</td>
<td>213 ± 80</td>
<td>R = 0.173, P &lt; 0.05</td>
</tr>
<tr>
<td>Restrictive pattern</td>
<td>10/16</td>
<td>23/53</td>
<td>18/49</td>
<td>7/18</td>
<td></td>
</tr>
<tr>
<td>SR/AF</td>
<td>15/9</td>
<td>63/13</td>
<td>45/19</td>
<td>23/4</td>
<td></td>
</tr>
<tr>
<td>FEV(_1) (mL/min)</td>
<td>1.9 ± 0.2</td>
<td>2.4 ± 0.6(^{t})</td>
<td>2.7 ± 0.6(^{t})</td>
<td>3.0 ± 0.4(^{t})</td>
<td>R = 0.632, P &lt; 0.001</td>
</tr>
<tr>
<td>FEV(_1) as % of predicted (%)</td>
<td>73 ± 13</td>
<td>81 ± 18</td>
<td>90 ± 15(^{t})</td>
<td>98 ± 16(^{t})</td>
<td>R = 0.251, P &lt; 0.01</td>
</tr>
<tr>
<td>FVC (mL/min)</td>
<td>2.3 ± 0.4</td>
<td>3.0 ± 0.7(^{t})</td>
<td>3.3 ± 0.8(^{t})</td>
<td>3.7 ± 0.4(^{t})</td>
<td>R = 0.632, P &lt; 0.001</td>
</tr>
<tr>
<td>FVC as % of predicted (%)</td>
<td>67 ± 16</td>
<td>75 ± 14(^{t})</td>
<td>85 ± 16(^{t})</td>
<td>87 ± 18(^{t})</td>
<td>R = 0.242, P &lt; 0.01</td>
</tr>
<tr>
<td>FEV(_1)/VC</td>
<td>90 ± 15</td>
<td>84 ± 17</td>
<td>89 ± 19</td>
<td>88 ± 15</td>
<td>R = 0.032, P = NS</td>
</tr>
<tr>
<td>Peak VO(_2) (mL/min)</td>
<td>726 ± 145</td>
<td>981 ± 198(^{*})</td>
<td>1332 ± 219(^{*})</td>
<td>1678 ± 207(^{*})</td>
<td>R = 0.173, P &lt; 0.05</td>
</tr>
<tr>
<td>Peak VO(_2) as % of predicted</td>
<td>39 ± 12</td>
<td>51 ± 10(^{*})</td>
<td>65 ± 9(^{t})</td>
<td>76 ± 16(^{t})</td>
<td>R = 0.036, P &lt; 0.001</td>
</tr>
<tr>
<td>VO(_2) AT (mL/min)</td>
<td>553 ± 120</td>
<td>694 ± 183(^{*})</td>
<td>836 ± 192(^{*})</td>
<td>998 ± 191(^{*})</td>
<td>R = 0.036, P &lt; 0.001</td>
</tr>
<tr>
<td>VE/VC(_O(_2))</td>
<td>49 ± 11</td>
<td>40 ± 10(^{*})</td>
<td>32 ± 6(^{t})</td>
<td>30 ± 5(^{t})</td>
<td>R = 0.536, P &lt; 0.001</td>
</tr>
<tr>
<td>VO(_2)/Work (mL/min/watt)</td>
<td>8.0 ± 2.6</td>
<td>8.7 ± 1.5(^{t})</td>
<td>9.1 ± 1.0(^{t})</td>
<td>10.0 ± 1.2(^{t})</td>
<td>R = 0.309, P &lt; 0.001</td>
</tr>
</tbody>
</table>

C, current smoker; F, former smoker; n, non-smoker; LVEF, left ventricular ejection fraction; SR, sinus rhythm; AF, atrial fibrillation; AT, anaerobic threshold; VE, ventilation; VC\(_O\(_2\)\), carbon dioxide production. \(^{*}\)P < 0.01 vs. group <12; \(^{t}\)P < 0.05 vs. group 12-16; \(^{t}\)P < 0.01 vs. group 12-16; \(^{t}\)P < 0.05 vs. group <12; \(^{t}\)P < 0.05 vs. group 16-20, \(^{t}\)P < 0.01 vs. group 16-20. A reliable evaluation of the restrictive pattern was possible in 136/191 patients.

Figure 1  DLCO, DM, VC, and VA in the four groups of CHF patients: peak VO\(_2\) <12 mL/min/kg, peak VO\(_2\) 12–16 mL/min/kg, peak VO\(_2\) 16–20 mL/min/kg, peak VO\(_2\) >20 mL/min/kg. Patients characteristics are reported in Table 1. \(^{*}\)P < 0.01 vs. <12, \(^{t}\)P < 0.05 vs. 12-16, \(^{t}\)P < 0.01 vs. 12-16, \(^{t}\)P < 0.01 vs. 16-20, \(^{t}\)P < 0.02 vs. <12, \(^{t}\)P < 0.02 vs. groups 12-16, 16-20 and >20 combined.
well known. Our data confirm these findings but show, with intermediate CHF severity.

Mechanics impairment was due to a restrictive lung disease. This is shown by a preserved FEV1/FVC ratio with perfusion, but those working are the most efficient. The schema reported in Figure 4 helps to describe this concept. In patients with less advanced CHF (group >20), there are several efficient alveolar–capillary units at work and, in the single alveolus lung model (right side of the schema), the lung is big with almost no diffusion limitation. As the disease progresses, in group 12–16 and group 16–20, the number of alveolar–capillary units at work reduces, and the average diffusion worsens (reduced dimensions of the single alveolus model with thickening of the alveolar–capillary membrane). Finally, in patients with severe CHF (group <12), very few alveolar–capillary membrane units are at work (reached by both ventilation and perfusion), but those working are the most efficient. The schema reported in Figure 4 helps to describe this concept. In patients with less advanced CHF (group >20), there are several efficient alveolar–capillary units at work and, in the single alveolus lung model (right side of the schema), the lung is big with almost no diffusion limitation. As the disease progresses, in group 12–16 and group 16–20, the number of alveolar–capillary units at work reduces, and the average diffusion worsens (reduced dimensions of the single alveolus model with thickening of the alveolar–capillary membrane). Finally, in patients with severe CHF (group <12), very few alveolar–capillary membrane units are at work (reached by both ventilation and perfusion), but those working are the most efficient (higher DM/VC). Several reasons may explain why this happens. The geometrical shape of the alveoli is characterized by corners with different degrees. Indeed, when, during ventilation, a force on the alveolar wall is applied, the presence of the surfactant layer generates a pressure gradient between the flat alveolar surface and the alveolar corners. This pressure gradient allows fluid to flow from the surface of the alveoli to their corners, preserving the gas exchange function. For a given force applied, this pressure gradient is the biggest, the smaller the degree of the corners, making the alveoli with the smallest corners those freer of fluids along the gas exchange surface. Indeed, if the pressure at the alveolar corner is reduced,
the pressure in the interstitial space between corners of a few alveoli is also further reduced, allowing accumulation of fluids in the interstitial space. Differently, if the force allowing fluid movement from the gas exchange surface to the alveoli corners is low, as happens in the presence of alveoli with flat or large corners, fluids is accumulated in the corners, at the beginning, but does not move fast enough to the interstitial space, transforming the alveoli from a complex geometrical structure with several corners, to a more spherical one, which is more likely to be fluid-filled and, therefore, totally inefficient. 31–33 Ventilation dishomogeneity with air trapping might also account for a portion of lung which is protected from liquid filling as it happens with mechanical ventilation. 34,35 Indeed, air trapping, which might happen at rest in patients with severe CHF, 29 might further increase the geometrical alveolar interdependence described earlier. Finally, it should be noticed that data at pathology are in line with this interpretation, showing that alveolar oedema is patchy with a progressive increase in the number of alveoli filled with fluid and with few alveoli preserved keeping a normal shape. 31

In conclusion, the present study shows that DLCO, DM, VC, and VA are reduced in patients with severe CHF in stable clinical condition. The reduction of VC is a novel finding and is likely related to pulmonary vascular resistance increase, local thrombosis, microembolism, increased intrapulmonary shunt, low blood flow, and, possibly, low intravascular blood volume. The DM/VC behaviour, an index of the efficiency of the alveolar–capillary units, suggests that in severe CHF, the few alveolar–capillary units at work are those that are most efficient. This is likely the last safety mechanism to protect gas exchange...
in CHF, similar to what happens with the hyperefficient nephron unit in the failing kidney.36,37

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