Does lung diffusion impairment affect exercise capacity in patients with heart failure?

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Objective: To determine whether there is a relation between impairment of lung diffusion and reduced exercise capacity in chronic heart failure.

Design: 40 patients with heart failure in stable clinical condition and 40 controls participated in the study. All subjects underwent standard pulmonary function tests plus measurements of resting lung diffusion (carbon monoxide transfer, TLCO), pulmonary capillary volume (VC), and membrane resistance (Dm), and maximal cardiopulmonary exercise testing. In 20 patients and controls, the following investigations were also done: (1) resting and constant work rate TLCO; (2) maximal cardiopulmonary exercise testing with inspiratory O2 fractions of 0.21 and 0.16; and (3) rest and peak exercise blood gases. The other subjects underwent TLCO, Dm, and VC measurements during constant work rate exercise.

Results: In normoxia, exercise induced reductions of haemoglobin O2 saturation never occurred. With hypoxia, peak exercise uptake (peak VO2) decreased from (mean (SD)) 1285 (395) to 1081 (396) ml/min (p < 0.01) in patients; and from 1861 (563) to 1771 (457) ml/min (p < 0.05) in controls. Resting TLCO correlated with peak VO2 in heart failure (normoxia < hypoxia). In heart failure patients and normal subjects, TLCO and peak VO2 correlated with O2 arterial content at rest and during peak exercise in both normoxia and hypoxia. TLCO, VC, and Dm increased during exercise. The increase in TLCO was greater in patients who had a smaller reduction of exercise capacity with hypoxia. Alveolar–arterial O2 gradient at peak correlated with exercise capacity in heart failure during normoxia and to a greater extent, during hypoxia.

Conclusions: Lung diffusion impairment is related to exercise capacity in heart failure.

METHODS

Patient population
Forty patients with stable heart failure (mean (SD) age 61.9 (6.4) years; 30 male, 10 female) and 40 healthy controls (57.6 (9.6) years; 28 male, 12 female) participated in the study. All the heart failure patients were in New York Heart Association (NYHA) functional class II or III and belonged to a cohort of heart failure patients regularly followed in our heart failure clinic. Heart failure aetiology was: ischaemic cardiomyopathy (15), idiopathic (11), alcoholic (7), HIV related (4), and related to antitumour drugs (3). Exclusion criteria included: a left ventricular ejection fraction > 35% by echocardiography, the presence of periodic breathing during exercise, primary pulmonary disease, unstable angina, recent myocardial infarction, and artificial pacemakers. Ten patients were active smokers, 20 were previous smokers (defined as patients who quit smoking more than five years ago), and 10 were active smokers, 20 were previous smokers (defined as patients who quit smoking more than five years ago), and 10 active smokers, 20 were previous smokers (defined as patients who quit smoking more than five years ago), and 10 previous smokers (defined as patients who quit smoking more than five years ago).
had never smoked. Treatment was stable and included: digitalis (13), diuretics (34), ACE inhibitors (29), angiotensin 1 blockers (8), β blockers (18), and amiodarone (18).

Healthy controls were chosen from patients’ relatives and hospital employees or their friends. Eighteen were smokers, eight were previous smokers, and 14 never smoked. None was involved in regular exercise programmes.

The study was approved by the local ethics committee and all subjects provided their written informed consent.

Pulmonary function evaluation
Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured in triplicate and calculated according to the American Thoracic Society criteria, using a mass flow sensor (2200 Sensor Medics, Yorba Linda, California, USA). Maximum voluntary ventilation (MVV) was assumed to be either MVV measured in 12 seconds or FEV₁ × 40, whichever was higher. Predicted values are from Quanjer and colleagues, and Jones. TlCO was measured with the single breath constant expiratory flow technique. TlCO data are reported as absolute values or as a percentage of predicted. Molecular diffusion of carbon monoxide across the alveolar-capillary membrane (Dm) and pulmonary capillary blood volume (Vc) were measured according to the method of Roughton and Forster. TlCO, Dm, and Vc are linked by the following equation:

\[
\frac{1}{TlCO} = \frac{1}{Dm} + \frac{1}{\theta Vc}
\]

where θ is the rate of reaction of carbon monoxide with haemoglobin and is inversely proportional to Pao₂ in the alveolar air (Pao₂). Therefore subjects inspired a gas mixture with 0.3% CH₄, 0.3% CO, and 0.3% C₂H₂ balanced with nitrogen with three different O₂ fractions equal to 20%, 40%, and 60%, respectively. This procedure allows measurement of TlCO at different Pao₂ values, thereby causing TlCO to vary and enabling calculation of Dm and Vc graphically.

Cardiopulmonary exercise testing
Maximal cardiopulmonary exercise tests (Vmax 29C, Sensor Medics) were done on a cycle ergometer (Ergometrics-800, Sensor Medics) using a personalised ramp protocol aimed at achieving peak exercise in around 10 minutes. These samples were used to measure haemoglobin concentrations, oxygen and carbon dioxide tensions, CaO₂, and pH (ABL 520, Radiometer, Copenhagen, Denmark). PaO₂ was determined from the equation:

\[
PaO₂ = ([Bp (mm Hg) - 47] × FiO₂ - PacO₂/R)
\]

where Bp = barometric pressure, FiO₂ = oxygen inspired fraction, PacO₂ = arterial carbon dioxide partial pressure, and R = respiratory gas exchange ratio.

Study design
The first part of the protocol was the same for all subjects. Both patients and control subjects underwent standard pulmonary function tests, resting TlCO, Dm, and Vc measurements (in the sitting position) and an incremental cardiopulmonary exercise test. At least one cardiopulmonary exercise test was performed before the formal study to familiarise the subjects with the techniques and procedures. Subjects were then randomly allocated into two groups, A and B, each comprising 20 heart failure patients and 20 normal controls.

Investigations in group A
In group A, TlCO was also measured with the subjects sitting on the ergometer and after three and five minutes of light exercise (20% of the maximum workload achieved). The cardiopulmonary exercise tests, with an FiO₂ of 21% and 16%, were done on the following days. The order of the two tests was randomised and a resting interval of more than six hours was allowed between each test.

Investigations in group B
In group B, only one cardiopulmonary exercise test was performed to assess exercise capacity while the subjects were breathing room air. TlCO, Dm, and Vc were measured with the subjects sitting on the cycle ergometer and during light exercise (20% of maximum workload achieved) which lasted around five minutes.

Statistical analysis
Data are presented as mean (SD). Correlations were obtained by linear regression analysis and the best fit method. Differences were evaluated by analysis of variance (ANOVA) and the unpaired t test, applying the Bonferroni correction for multiple comparisons as appropriate. Multivariate stepwise regression model (SPSS 9.0) was used to identify independent predictors of TlCO and peak exercise oxygen consumption (peak VO₂). All variables with a univariate probability value of p < 0.05 were included.

RESULTS
Pulmonary function and exercise capacity (all subjects)
Results of the pulmonary function tests were consistent with a mild restrictive defect in the heart failure patients (table 1). Compared with the normal controls, resting TlCO was reduced in the heart failure group owing to a reduction in Dm with a normal Vc (table 1). Vo₂ at peak exercise and at anaerobic threshold was 1285 (376)/800 (140) and 1866 (540)/1010 (290) ml/min in patients and controls, respectively (p < 0.01 for both conditions). Oxygen pulse at peak exercise was 10.0 (2.7) and 12.5 (3.5) ml/beat in patients and normal subjects, respectively (p < 0.05). In heart failure patients (fig 1, upper panel) but not in normal subjects (lower panel) resting TlCO was significantly correlated with normoxic peak Vo₂. To avoid

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Standard pulmonary function and lung diffusion tests in the whole study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure patients (n=40)</td>
<td>Normal controls (n=40)</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>86 (20)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>74 (12)</td>
</tr>
<tr>
<td>FEV₁ / FVC</td>
<td>115 (15)</td>
</tr>
<tr>
<td>MVV (% pred)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>TlCO (ml/min/mm Hg)</td>
<td>19.9 (5.5)</td>
</tr>
<tr>
<td>TlCO (% pred)</td>
<td>77 (19)</td>
</tr>
<tr>
<td>Dm (ml/min/mm Hg)</td>
<td>29.0 (10.6)</td>
</tr>
<tr>
<td>Vc (ml)</td>
<td>103.8 (40.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). *p < 0.01 v normal controls.

Dm, molecular diffusion for carbon monoxide across the alveolar-capillary membrane; FENV, forced expiratory volume in one second; FVC, forced vital capacity; MVV, maximum voluntary ventilation; pred, TlCO, lung transfer capacity for carbon monoxide; Vc, capillary blood volume.
confounding by variables such as age, sex, or anthropometric measurements, both resting TLCO and peak VO₂ are reported as per cent of predicted normal values.

**Exercise capacity in hypoxic condition (group A)**

With normoxia, peak exercise VO₂ was 1285 (395) and 1861 (563) ml/min in patients and controls, respectively. The maximum work rate achieved was 101 (36) W in the patients and 163 (54) W in the controls. With hypoxia (FiO₂ = 16%), peak VO₂ reduced to 1081 (396) in patients and to 1771 (457) in normal subjects, respectively (p < 0.01 and p < 0.05 v normoxic condition); the maximum work rate was reduced to 87 (34) W in patients and to 157 (52) W in normal subjects (p < 0.01 and p < 0.05 v normoxic condition). With hypoxia, in both patients and normal subjects ventilation was increased at rest and throughout the test compared with normoxic levels, but not at peak exercise (table 2). Resting TLCO was correlated with peak VO₂ obtained under hypoxic conditions (fig 2), with an R value greater than in normoxic conditions (0.725 and 0.619, respectively). Resting TLCO, DM, and VC did not predict the reduction in exercise capacity with hypoxia, either in patients or in controls.

**Blood gas values and exercise capacity in normoxic and hypoxic conditions**

Haemoglobin concentration, PO₂, SaO₂, CaO₂, alveolar po₂, and ΔPa[AO₂] at rest and peak exercise in normoxic and hypoxic conditions are reported in table 4; each datum is the mean of three measurements. In the normoxic condition PO₂, CaO₂, alveolar po₂, and ΔPa[AO₂] increased during exercise in both patients and normal controls. With hypoxia the resting data were comparable between the normal subjects and the patients. At peak exercise, PO₂ and SaO₂ decreased compared with resting values in both patients and normal controls.

**Figure 1** Peak VO₂ during normoxia v resting lung transfer capacity for carbon monoxide (TLCO) (reported as per cent of predicted) in heart failure patients (upper panel, n = 40) and healthy controls (lower panel, n = 40).

**Figure 2** Peak VO₂ during hypoxia v resting lung transfer capacity for carbon monoxide (TLCO) (both reported as per cent of predicted) in heart failure patients (upper panel, n = 20) and healthy subjects (lower panel, n = 20) (group A). In chronic heart failure, the correlation between TLCO and peak VO₂ increased further during hypoxia.

**Table 2** Ventilation, tidal volume, and respiratory rate at rest and on peak exercise under normoxic and hypoxic conditions in patients with heart failure (n = 20) and normal controls (n = 20) (group A)

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Peak exercise</td>
</tr>
<tr>
<td>Heart failure patients</td>
<td>11 (2)</td>
<td>58 (18)*</td>
</tr>
<tr>
<td>Ventilation (l/min)</td>
<td>0.6 (0.1)</td>
<td>1.6 (0.4)*</td>
</tr>
<tr>
<td>Tidal volume (l)</td>
<td>19 (4)*</td>
<td>37 (7)</td>
</tr>
<tr>
<td>Respiratory rate (beats/min)</td>
<td>15 (4)</td>
<td>34 (5)</td>
</tr>
<tr>
<td>Normal controls</td>
<td>10 (2)</td>
<td>69 (19)</td>
</tr>
<tr>
<td>Ventilation (l/min)</td>
<td>0.6 (0.1)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>Tidal volume (l)</td>
<td>15 (4)</td>
<td>34 (5)</td>
</tr>
<tr>
<td>Respiratory rate (beats/min)</td>
<td>15 (4)</td>
<td>34 (5)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

* p < 0.01 v normal controls; † p < 0.01 v normoxia.
in both patients and normal controls are reported in table 6. The correlations between peak \( V_O^2 \) and \( CaO_2 \) and haemoglobin were significant in patients and controls in all the conditions studied.

The \( \Delta P[A–aO_2] \) value in the patients was greater at rest with normoxia than in the normal controls (table 4). However, the increase at peak exercise was greater in the controls than in the patients (14.4 (6.4) vs 5.8 (10.0) mm Hg, \( p < 0.01 \)). With hypoxia the increase in the \( \Delta P[A–aO_2] \) value from rest to peak was 11.9 (5.9) mm Hg and 15.9 (9.1) mm Hg in patients and in normal subjects, respectively (NS). There was a significant correlation between resting TLCO and \( \Delta P[A–aO_2] \) at peak exercise in normoxia and at rest and peak exercise in hypoxia in patients but not in normal subjects (table 7). Adjusting \( \Delta P[A–aO_2] \) for peak \( V_O^2 \) strengthened this correlation at peak exercise in the patients, and made it evident in the normal subjects (table 7). Best fit analysis showed that a curvilinear relation significantly improved the correlation of \( \Delta P[A–aO_2] \), adjusted for peak \( V_O^2 \), with TLCO in both normoxic (fig 5, upper panel) and hypoxic conditions (fig 5, lower panel).

**DISCUSSION**

This study contains several observations aimed at elucidating the complex interplay between lung diffusion abnormalities and impairment of exercise capacity in patients with heart failure.

In the first place, our study confirms that in patients with heart failure, resting TLCO correlates with peak \( V_O^2 \). Although we were only able to show a correlation and not a cause–effect link, we believe that a causal relation between impaired TLCO and reduced exercise capacity exists; indeed when the physiological impact of TLCO reduction is increased, as with hypoxia, the correlation between TLCO and peak \( V_O^2 \) is high.

Second, our study provides evidence that in heart failure patients, even though resting and peak exercise \( SaO_2 \), \( PaO_2 \), and \( CaO_2 \), are in the normal range, their values correlate with TLCO, that TLCO increases during exercise as a result of increases in both \( V_C \) and \( DM \), and that patients who have the greatest capability to increase their TLCO during exercise are those who have the smallest reduction in exercise capacity with hypoxia.

Finally, in both normoxic and hypoxic conditions, the value of the \( \Delta P[A–aO_2] \) differences is related to TLCO, so when oxygen flow across the alveolar capillary membrane has to increase, as with exercise, or is impaired, as in hypoxia, the \( \Delta P[A–aO_2] \) difference increases more the lower the resting TLCO value.

The patients we studied belong to a cohort of subjects regularly followed in our heart failure clinic. They were in stable clinical condition and, as in several previous reports, results of standard pulmonary function tests and TLCO showed mild restrictive lung disease and impairment of diffusion. As previously reported, TLCO impairment at rest correlates with exercise capacity. However, even if several pieces of evidence suggest a link between TLCO and exercise capacity, the physiological meaning of this correlation remains controversial because, in contrast with patients with pulmonary disease.

### Table 3: CO transfer (TLCO) subcomponents during submaximal exercise (group A, 20 heart failure patients and 20 normal controls)

<table>
<thead>
<tr>
<th>Heart failure subjects</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td><strong>5th minute</strong></td>
</tr>
<tr>
<td>DM (ml/min/mm Hg)</td>
<td>29.1 (8.4)*</td>
</tr>
<tr>
<td>DM/Va</td>
<td>5.4 (1.3)*</td>
</tr>
<tr>
<td>VC (ml)</td>
<td>109 (42)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

* \( p < 0.01 \) vs normal controls; † \( p < 0.01 \) vs values at rest.

exercise induced haemoglobin desaturation is rare in patients with heart failure. A cardiopulmonary exercise test with a reduced O2 fraction is a safe test used to assess exercise capacity at moderate altitude.22 With hypoxia, peak VO2 and maximum work rate were reduced in both heart failure patients and normal controls. It is noteworthy that the correlation between TLCO and exercise capacity was high in the patients and normal controls. It is noteworthy that the correlation between TLCO and exercise capacity was high in the patients and normal controls.

In normal subjects we found a correlation between TLCO and haemoglobin and CaO2, measured at peak exercise, suggesting that in hypoxia CaO2 becomes a relevant determinant of exercise capacity. The observed reduction of PO2 and SaO2 is countervalued by an increase in haemoglobin concentration, which serves to obviate an undesirable reduction of CaO2 during exercise. Two explanations for the decrease in arterial P O2 at peak exercise with hypoxia are likely. In the first place, there could be a hypoxia induced increase in pulmonary shunting because of hypoxic pulmonary vasoconstriction enhancing the ventilation–perfusion mismatch; secondly, the pulmonary

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### Table 4  Haemoglobin concentration, PO2, SaO2, CaO2, and PaCO2 at rest and during peak exercise under normoxic and hypoxic conditions (group A, 20 heart failure patients and 20 normal controls)

<table>
<thead>
<tr>
<th></th>
<th>Normoxia Rest</th>
<th>Normoxia Peak exercise</th>
<th>Hypoxia Rest</th>
<th>Hypoxia Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>14.0 (1.5)</td>
<td>14.9 (1.6)*</td>
<td>14.3 (1.4)</td>
<td>15.0 (1.4)*</td>
</tr>
<tr>
<td>PO2 (mm Hg)</td>
<td>86 (6)</td>
<td>99 (11)*</td>
<td>68 (9)*</td>
<td>61 (8)*</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>97.2 (0.8)</td>
<td>97.7 (2.2)*</td>
<td>94.9 (2.0)</td>
<td>92.1 (3.1)*</td>
</tr>
<tr>
<td>CaO2 (ml/100 ml)</td>
<td>18.3 (2.0)</td>
<td>19.5 (2.2)*</td>
<td>18.1 (1.9)</td>
<td>18.5 (2.3)*</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (0.03)</td>
<td>7.40 (0.04)*</td>
<td>7.46 (0.05)</td>
<td>7.44 (0.04)*</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>100 (8)</td>
<td>119 (5)*</td>
<td>79 (4)*</td>
<td>84 (4)*</td>
</tr>
<tr>
<td>PaA–PaO2 (mm Hg)</td>
<td>14.7 (7.6)</td>
<td>20.5 (10.0)*</td>
<td>11.1 (8.8)</td>
<td>23.0 (7.8)*</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>36.8 (4.5)</td>
<td>33.3 (5.5)*</td>
<td>31.2 (4.1)</td>
<td>32.1 (4.4)</td>
</tr>
</tbody>
</table>

Data were obtained from means of three samples.

Values are presented as mean (SD).

*p<0.05 v rest; †p<0.05 v normoxia.

CaO2, arterial oxygen content; PaA–PaO2, alveolar–arterial pressure difference for oxygen; Hb, haemoglobin; PaCO2, arterial carbon dioxide tension; PaO2, arterial oxygen pressure; PO2, arterial oxygen tension; SaO2, haemoglobin saturation with oxygen.

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### Table 5  Correlations between resting carbon monoxide transfer (TLCO) and haemoglobin oxygen saturation, arterial oxygen content, haemoglobin, and arterial oxygen tension (group A, 20 heart failure patients and 20 normal controls)

<table>
<thead>
<tr>
<th></th>
<th>SaO2</th>
<th>CaO2</th>
<th>Hb</th>
<th>PO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoxia, rest</td>
<td>R=0.633, p&lt;0.01</td>
<td>R=0.438, p=0.06</td>
<td>R=0.394, NS</td>
<td>R=0.674, p&lt;0.01</td>
</tr>
<tr>
<td>Normoxia, peak exercise</td>
<td>R=0.503, p&lt;0.02</td>
<td>R=0.499, p&lt;0.03</td>
<td>R=0.483, p&lt;0.05</td>
<td>R=0.478, p&lt;0.02</td>
</tr>
<tr>
<td>Hypoxia, rest</td>
<td>R=0.479, p&lt;0.03</td>
<td>R=0.503, p&lt;0.03</td>
<td>R=0.425, NS</td>
<td>R=0.417, p&lt;0.06</td>
</tr>
<tr>
<td>Hypoxia, peak exercise</td>
<td>R=0.54, p&lt;0.01</td>
<td>R=0.50, p&lt;0.03</td>
<td>R=0.476, p&lt;0.03</td>
<td>R=0.54, p&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SaO2</th>
<th>CaO2</th>
<th>Hb</th>
<th>PO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoxia, rest</td>
<td>R=0.140, NS</td>
<td>R=0.645, p&lt;0.01</td>
<td>R=0.655, p&lt;0.01</td>
<td>R=0.148, NS</td>
</tr>
<tr>
<td>Normoxia, peak exercise</td>
<td>R=0.216, NS</td>
<td>R=0.688, p&lt;0.01</td>
<td>R=0.690, p&lt;0.01</td>
<td>R=0.164, NS</td>
</tr>
<tr>
<td>Hypoxia, rest</td>
<td>R=0.210, NS</td>
<td>R=0.678, p&lt;0.01</td>
<td>R=0.684, p&lt;0.01</td>
<td>R=0.192, NS</td>
</tr>
<tr>
<td>Hypoxia, peak exercise</td>
<td>R=0.087, NS</td>
<td>R=0.563, p&lt;0.01</td>
<td>R=0.603, p&lt;0.01</td>
<td>R=0.148, NS</td>
</tr>
</tbody>
</table>

Data were obtained from means of three samples.

CaO2, arterial oxygen content; Hb, haemoglobin; PO2, arterial oxygen tension; SaO2, haemoglobin saturation with oxygen.
capillary transit time could be too short for a reduced alveolar $P_{O_2}$ to achieve an equilibrium between alveolar and capillary $P_{O_2}$ pressures. Indeed with hypoxia the A–a $O_2$ gradient increased compared with normoxia, both at rest and during peak exercise (table 6). An inadequate exercise induced increase in ventilation during hypoxia is unlikely because $P_{CO_2}$ levels did not increase.

Smith and colleagues recently showed that $T_{LCO}$ increases during light exercise in heart failure patients. Our findings are consistent with that report and provide new information about the cause of the exercise induced increase in $T_{LCO}$. $T_{LCO}$ depends on membrane diffusion capacity and capillary volume, and both were increased during exercise in our heart failure patients and normal controls. The increase in VC is likely to be caused by pulmonary vessel recruitment. The exercise induced increase in DM is more difficult to understand. The increase in DM during exercise confirms that DM is not a fixed value but can increase. This observation is in line with the suggestion that $T_{LCO}$ should be used as an antifailure treatment target. It is not possible to measure $T_{LCO}$ or its components reliably at peak exercise when haemoconcentration can further increase $T_{LCO}$ by increasing the surface of the alveoli in contact with the red blood cells. We measured $T_{LCO}$ during light exercise (around 20% of the maximum workload achieved) and therefore we cannot say whether this value represents the maximum possible increase in $T_{LCO}$ or not. We used a light workload to show that $T_{LCO}$ can be increased and that at the same increment of work rate the increase in $T_{LCO}$ correlates with the capacity of the subjects to adjust to exercise under hypoxic conditions. Indeed we showed that patients who increase $T_{LCO}$ most during exercise are those with the least reduction in hypoxia induced exercise capacity—meaning that the increase in $T_{LCO}$ during exercise can be viewed as a compensatory mechanism.

**Conclusions**

While none of the present evidence, when considered in isolation, proves a causal role of $T_{LCO}$ impairment in the reduced

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### Table 6 Correlations of peak oxygen consumption with haemoglobin saturation with oxygen, arterial oxygen content, haemoglobin, and arterial oxygen tension (group A, 20 heart failure patients and 20 normal controls)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Heart failure patients (n=20)</th>
<th>Normal controls (n=20)</th>
</tr>
</thead>
</table>
| $S_aO_2$                | $R=0.515$, 
$p<0.02$                  | $R=0.315$, 
NS                |
| $C_aO_2$                | $R=0.509$, 
$p<0.02$                  | $R=0.597$, 
$p<0.01$              |
| Hb                      | $R=0.474$, 
$p<0.05$                  | $R=0.615$, 
$p<0.01$              |
| $P_{O_2}$               | $R=0.549$, 
$p<0.01$                  | $R=0.603$, 
NS                |

Data were obtained from means of three samples.

Ca$O_2$, arterial oxygen content; Hb, haemoglobin; $P_{O_2}$, arterial oxygen tension; $S_aO_2$, haemoglobin saturation with oxygen.

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### Table 7 Correlation between resting carbon monoxide transfer ($T_{LCO}$) and alveolar–arterial pressure difference for oxygen (group A, 20 heart failure patients and 20 normal controls)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Heart failure patients (n=20)</th>
<th>Normal controls (n=20)</th>
</tr>
</thead>
</table>
| $\Delta[P(A-aO_2)/V_{O_2}]$, normoxia, rest | $R=0.439$, 
$p=0.06$                  | $R=0.06$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, normoxia, peak exercise | $R=0.516$, 
$p<0.02$                  | $R=-0.211$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, hypoxia, rest | $R=-0.502$, 
$p<0.02$                  | $R=-0.106$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, hypoxia, peak exercise | $R=-0.625$, 
$p<0.01$                  | $R=-0.207$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, normoxia, rest | $R=-0.384$, 
NS                  | $R=-0.022$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, hypoxia, peak exercise | $R=-0.720$, 
$p<0.01$                  | $R=-0.488$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, normoxia, rest | $R=-0.431$, 
$p=0.06$                  | $R=0.049$, 
NS                |
| $\Delta[P(A-aO_2)/V_{O_2}]$, hypoxia, peak exercise | $R=-0.794$, 
$p<0.01$                  | $R=-0.791$, 
$p<0.01$                |

$\Delta[P(A-aO_2)/V_{O_2}]$, alveolar–arterial pressure difference for oxygen; $V_{O_2}$, oxygen uptake.
exercise capacity of patients with heart failure, collectively the following findings strongly suggest that its role is indeed causal:

- the resting TlCo correlates with exercise capacity and that this correlation is increased with hypoxia
- a low but “normal” arterial haemoglobin content, SaO₂, and CaO₂ are associated with reduced exercise performance in heart failure patients
- a reduced capacity to increase TlCo during submaximal effort correlates with the reduction of exercise capacity with hypoxia
- if resting TlCo is low at peak exercise with hypoxia, then the ∆P[A–ao₂] difference shows the greatest oxygen gradient.

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REFERENCES

IMAGES IN CARDIOLOGY
Subaortic stenosis caused by two discrete membranes

A 15 year old girl presented with fatigue and dyspnoea on exertion. She had an ejection murmur at the left sternal border. A chest radiograph showed cardiomegaly and the ECG showed left ventricular hypertrophy with a strain pattern. The echocardiogram confirmed left ventricular hypertrophy, with outflow obstruction caused by subaortic stenosis at two separate levels, one immediately proximal to the aortic valve appearing as a fibrous ridge (upward arrow) and the other as a discrete membrane. Cardiac catheterisation confirmed two discrete intracavitary pressure gradients. Subaortic stenosis is usually caused by a discrete membrane or fibromuscular ridge and may very rarely be due to a fibrous tunnel involving the whole left ventricular outflow tract. Obstruction caused by two separate but very discrete membranes as occurred in our patient also appears to be very rare. At operation both obstructions were resected and the patient made a good recovery. She will, however, require long term follow up as recurrence of subaortic stenosis after surgical treatment is known to occur in a proportion of cases.

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