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

P G Agostoni, M Bussotti, P Palermo, M Guazzi

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

Abbreviations: Cao2, arterial oxygen content; Dm, membrane resistance; \( \Delta P[A-aO_2] \), alveolar–arterial oxygen pressure gradient; FEV1, forced expiratory volume in one second; Fio2, inspired oxygen fraction; FVC, forced vital capacity; MVV, maximum voluntary ventilation; Paco2, systemic arterial oxygen tension; Sao2, haemoglobin saturation with oxygen; TLCO, carbon monoxide transfer; VC, pulmonary capillary blood volume; VO2, oxygen uptake
had never smoked. Treatment was stable and included: diabetics (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 highest. Predicted values are from Quanjer and colleagues, and Jones. 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 θ 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. Sensor Medics), using a personalised ramp protocol aimed at achieving peak exercise in around 10 minutes. These samples were used to measure haemoglobin and is inversely proportional to PO2 in the alveolar air.

To avoid

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**Table 1 Standard pulmonary function and lung diffusion tests in the whole study population**

<table>
<thead>
<tr>
<th></th>
<th>Heart failure patients (n=40)</th>
<th>Normal controls (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 [% pred]</td>
<td>86 (20)*</td>
<td>114 (21)</td>
</tr>
<tr>
<td>FVC [% pred]</td>
<td>74 (12)*</td>
<td>106 (12)</td>
</tr>
<tr>
<td>FEV1 / FVC</td>
<td>115 (15)</td>
<td>108 (10)</td>
</tr>
<tr>
<td>MVV [ % pred]</td>
<td>85 (20)</td>
<td>118 (17)</td>
</tr>
<tr>
<td>Tlco [ml/min/mm Hg]</td>
<td>19.9 (5.5)*</td>
<td>28.0 (6.1)</td>
</tr>
<tr>
<td>Tlco [% pred]</td>
<td>77 (19)*</td>
<td>108 (17)</td>
</tr>
<tr>
<td>Dm [ml/min/mm Hg]</td>
<td>29.0 (10.6)*</td>
<td>45.4 (12.8)</td>
</tr>
<tr>
<td>Vc [ml]</td>
<td>103.8 (40.8)</td>
<td>103.3 (38.2)</td>
</tr>
</tbody>
</table>

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
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) ml/min in normal subjects, respectively (p < 0.01 and p < 0.05 vs normoxic condition); the maximum work rate was reduced to 87 (34) W in patients and 157 (52) W in normal subjects (p < 0.01 and p < 0.05 vs 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 PaO₂, and PaA–PaO₂ 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 and SaO₂ 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.

**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></th>
<th>Hypoxia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest (l/min)</td>
<td>Peak exercise</td>
<td>Rest (l/min)</td>
<td>Peak exercise</td>
</tr>
<tr>
<td>Heart failure patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation</td>
<td>11 (2)</td>
<td>58 (18)*</td>
<td>28 (6)†</td>
<td>57 (19)*</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>0.6 (0.1)</td>
<td>1.6 (0.4)*</td>
<td>1.3 (0.2)*†</td>
<td>1.6 (0.4)*</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>19 (4)*</td>
<td>37 (7)</td>
<td>21 (4)*</td>
<td>36 (7)</td>
</tr>
<tr>
<td>Normal controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation</td>
<td>10 (2)</td>
<td>69 (19)</td>
<td>28 (5)†</td>
<td>72 (18)</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>0.6 (0.1)</td>
<td>2.1 (0.6)</td>
<td>1.5 (0.3)†</td>
<td>2.3 (0.6)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>15 (4)</td>
<td>34 (5)</td>
<td>18 (3)</td>
<td>32 (8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

* p < 0.01 vs normal controls; † p < 0.01 vs normoxia.
Hypoxic conditions; resting T LCO was also weakly correlated to the relation between resting T LCO and (1) SaO₂, (2) CaO₂, and (3) haemoglobin and CaO₂, measured during normoxia and hypoxia both at rest and at peak exercise. None of the heart failure patients showed significant (>3%) haemoglobin desaturation either at rest or peak exercise in normoxic conditions (mean SaO₂ at rest 97.2 (0.8)%, range 94.7–98.4%; mean SaO₂ at peak exercise 97.5 (1.4)%, range 93.2–99.0%).

In the first place, our study confirms that in patients with heart failure, resting T LCO correlates with peak VO₂. Although we were only able to show a correlation and not a cause-effect link, we believe that a causal relation between impaired T LCO and reduced exercise capacity exists; indeed when the physiological impact of T LCO reduction is increased, as with hypoxia, the correlation between T LCO and peak VO₂ is high.

Second, our study provides evidence that in heart failure patients, even though resting and peak exercise SaO₂, PO₂, and CaO₂ are in the normal range, their values correlate with T LCO, that T LCO increases during exercise as a result of increases in both VC and DM, and that patients who have the greatest capability to increase their T LCO 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 ΔP[A–aO₂] differences is related to T LCO, so when oxygen flow across the alveolar capillary membrane has to increase, as with exercise, or is impaired, as in hypoxia, the ΔP[A–aO₂] difference increases more the lower the resting T LCO 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 T LCO showed mild restrictive lung disease and impairment of diffusion. As previously reported, T LCO impairment at rest correlates with exercise capacity. However, even if several pieces of evidence suggest a link between T LCO and exercise capacity, the physiological meaning of this correlation remains controversial because, in contrast with patients with pulmonary disease,

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

<table>
<thead>
<tr>
<th></th>
<th>Heart failure subjects</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest 5th minute</td>
<td>Rest 5th minute</td>
</tr>
<tr>
<td>DM (ml/min/mm Hg)</td>
<td>29.1 (8.4) *</td>
<td>46.9 [14.0]</td>
</tr>
<tr>
<td>DM/VA</td>
<td>5.4 [1.3] *</td>
<td>8.0 [2.1]</td>
</tr>
<tr>
<td>VC (ml)</td>
<td>109 (42)</td>
<td>104 [39]</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). *p < 0.01 v normal controls; †p < 0.01 v 3rd minute value; ‡p < 0.01 v 5th minute value; ¶p < 0.01 v 5th minute value.
Exercise induced haemoglobin desaturation is rare in patients with heart failure. A cardiopulmonary exercise test with a reduced \( O_2 \) fraction is a safe test used to assess exercise capacity at moderate altitude. With hypoxia, peak \( V_{O_2} \) and maximum work rate were reduced in both heart failure patients and normal controls. It is noteworthy that the correlation between \( T_{LCO} \) and exercise capacity was high in the hypoxic tests (fig 2), a condition where \( T_{LCO} \) impairment is likely to become more important. In normal subjects we found a correlation between \( T_{LCO} \) and \( \text{CaO}_2 \) probably mediated by haemoglobin. In heart failure patients, in contrast, resting \( T_{LCO} \) correlated with arterial \( \text{SaO}_2 \), \( P_{O_2} \), and \( \text{CaO}_2 \) both at rest and during peak exercise in normoxic conditions; this suggests that in patients who are not able to increase their cardiac output adequately during exercise, the \( \text{CaO}_2 \) at rest and its increase during exercise became relevant determinants of oxygen delivery (and therefore of exercise capacity) (table 3).

Accordingly, even if the \( \text{SaO}_2 \), arterial \( P_{O_2} \), and \( \text{CaO}_2 \) values which we measured in the normoxic condition are within the so-called “normal range” (table 4), values at the lower end of this range are functionally relevant. In other words, it makes a difference for a heart failure patient whether they have a haemoglobin of 12 mg/dl or 15 mg/dl, or an \( \text{SaO}_2 \) of 94% or 98%. Furthermore, our data confirm the role of an increase in haemoglobin as a determinant of exercise capacity.

To our knowledge, blood gas analyses during exercise in hypoxia have not previously been reported in patients with heart failure. In normal subjects as well as in heart failure patients, the \( \text{CaO}_2 \) measured at peak exercise, suggesting that in hypoxia \( \text{CaO}_2 \) becomes a relevant determinant of exercise capacity. The observed reduction of \( P_{O_2} \) and \( \text{SaO}_2 \) is counterbalanced by an increase in haemoglobin concentration, which serves to obviate an undesirable reduction of \( \text{CaO}_2 \) during exercise. Two explanations for the decrease in arterial \( P_{O_2} \) 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

### Table 4. Haemoglobin concentration, \( P_{O_2} \), \( \text{SaO}_2 \), \( \text{CaO}_2 \), and \( PaCO_2 \) 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>( \text{Hb} ) (g/dl)</td>
<td>14.1 (1.4)</td>
<td>14.3 (1.5)</td>
<td>14.2 (1.5)</td>
<td>15.2 (1.3)</td>
</tr>
<tr>
<td>( P_{O_2} ) (mm Hg)</td>
<td>86 (6)</td>
<td>93.4 (2.0)</td>
<td>88 (2.0)</td>
<td>90.8 (2.5)</td>
</tr>
<tr>
<td>( \text{SaO}_2 ) (%)</td>
<td>97.8 (0.6)</td>
<td>98.5 (0.6)</td>
<td>96.2 (1.6)</td>
<td>97.8 (0.5)</td>
</tr>
<tr>
<td>( \text{CaO}_2 ) (ml/100 ml)</td>
<td>18.3 (2.0)</td>
<td>20.5 (1.0)</td>
<td>18.1 (1.9)</td>
<td>18.5 (2.3)</td>
</tr>
<tr>
<td>( \text{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>( PaCO_2 ) (mm Hg)</td>
<td>100 (8)</td>
<td>110 (5)</td>
<td>97.4 (6.1)</td>
<td>106 (5)</td>
</tr>
<tr>
<td>( [A-\text{aO}_2] ) (mm Hg)</td>
<td>4.3 (6.5)</td>
<td>18.6 (5.6)</td>
<td>3.0 (5.3)</td>
<td>20.4 (4.9)</td>
</tr>
<tr>
<td>( \text{PaCO}_2 ) (mm Hg)</td>
<td>36.9 (3.3)</td>
<td>33.9 (3.8)</td>
<td>30.6 (4.2)</td>
<td>30.5 (4.0)</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD).

* \( p < 0.05 \) vs rest; † \( p < 0.05 \) vs normoxia.

\( \text{CaO}_2 \), arterial oxygen content; \( [A-\text{aO}_2] \), alveolar–arterial pressure difference for oxygen; \( \text{Hb} \), haemoglobin; \( PaCO_2 \), arterial carbon dioxide tension; \( \text{PaO}_2 \), alveolar oxygen pressure; \( P_{O_2} \), arterial oxygen tension; \( \text{SaO}_2 \), haemoglobin saturation with oxygen.

### Table 5. Correlations between resting carbon monoxide transfer (\( T_{LCO} \)) 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>( \text{SaO}_2 )</th>
<th>( \text{CaO}_2 )</th>
<th>( \text{Hb} )</th>
<th>( P_{O_2} )</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=0.653 ), ( 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=0.417 ), ( p=0.06 )</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=0.06 )</td>
</tr>
<tr>
<td>Hypoxia, peak exercise</td>
<td>( R=0.541 ), ( p&lt;0.01 )</td>
<td>( R=0.300 ), ( p&lt;0.03 )</td>
<td>( R=0.476 ), ( p&lt;0.03 )</td>
<td>( R=0.541 ), ( p&lt;0.01 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal controls</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<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.

\( \text{CaO}_2 \), arterial oxygen content; \( \text{Hb} \), haemoglobin; \( P_{O_2} \), arterial oxygen tension; \( \text{SaO}_2 \), 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 $A-aO_2$ 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 
$P_aCO_2$ 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 $V_C$ is 
likely to be caused by pulmonary vessel recruitment. The 
exercise induced increase in $D_m$ is more difficult to under-
stand. The increase in $D_m$ during exercise confirms that $D_m$ 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 haemoco-
centration 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></th>
<th>$S_aO_2$</th>
<th>$C_aO_2$</th>
<th>$Hb$</th>
<th>$P_{O_2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart failure patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoxia, rest</td>
<td>$R=0.515$, $p&lt;0.02$</td>
<td>$R=0.509$, $p&lt;0.02$</td>
<td>$R=0.474$, $p&lt;0.05$</td>
<td>$R=0.569$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Normoxia, peak exercise</td>
<td>$R=0.333$, NS</td>
<td>$R=0.557$, $p&lt;0.01$</td>
<td>$R=0.561$, $p&lt;0.01$</td>
<td>$R=0.340$, NS</td>
</tr>
<tr>
<td>Hypoxia, rest</td>
<td>$R=0.243$, NS</td>
<td>$R=0.478$, $p&lt;0.04$</td>
<td>$R=0.462$, $p&lt;0.05$</td>
<td>$R=0.187$, NS</td>
</tr>
<tr>
<td>Hypoxia, peak exercise</td>
<td>$R=0.462$, $p&lt;0.04$</td>
<td>$R=0.542$, $p&lt;0.01$</td>
<td>$R=0.538$, $p&lt;0.02$</td>
<td>$R=0.525$, $p&lt;0.02$</td>
</tr>
<tr>
<td><strong>Normal controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoxia, rest</td>
<td>$R=0.315$, NS</td>
<td>$R=0.597$, $p&lt;0.01$</td>
<td>$R=0.615$, $p&lt;0.01$</td>
<td>$R=0.003$, NS</td>
</tr>
<tr>
<td>Normoxia, peak exercise</td>
<td>$R=0.143$, NS</td>
<td>$R=0.674$, $p&lt;0.01$</td>
<td>$R=0.696$, $p&lt;0.01$</td>
<td>$R=0.434$, NS</td>
</tr>
<tr>
<td>Hypoxia, rest</td>
<td>$R=0.306$, NS</td>
<td>$R=0.539$, $p&lt;0.02$</td>
<td>$R=0.662$, $p&lt;0.02$</td>
<td>$R=0.315$, NS</td>
</tr>
<tr>
<td>Hypoxia, peak exercise</td>
<td>$R=0.291$, NS</td>
<td>$R=0.532$, $p&lt;0.02$</td>
<td>$R=0.677$, $p&lt;0.01$</td>
<td>$R=0.231$, NS</td>
</tr>
</tbody>
</table>

Data were obtained from means of three samples. 
$C_aO_2$, arterial oxygen content; $Hb$, haemoglobin; $P_{O_2}$, arterial oxygen tension; $S_aO_2$, haemoglobin saturation 
with oxygen.

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

$r = 0.80$

$r = 0.85$

![Figure 5](http://www.heartjnl.com)

**Figure 5** Correlation between alveolar–arterial $O_2$ differences at peak exercise divided by peak $V_{O_2}$ ($\Delta [P(A-aO_2)]/peak V_{O_2}$) v resting 
diffusing capacity for carbon monoxide ($T_{LCO}$) in normoxia (upper 
panel) and hypoxia (lower panel).
exercise capacity of patients with heart failure, collectively the following findings strongly suggest that its role is indeed causal:

- the resting $T_LCO$ correlates with exercise capacity and that this correlation is increased with hypoxia
- a low but “normal” arterial haemoglobin content, $S_aO_2$, and $CaO_2$, are associated with reduced exercise performance in heart failure patients
- a reduced capacity to increase $T_LCO$ during submaximal effort correlates with the reduction of exercise capacity with hypoxia
- if resting $T_LCO$ is low at peak exercise with hypoxia, then the $\Delta[P_A-o_2]$ difference shows the greatest oxygen gradient.

Authors’ affiliations

P G Agostoni, M Bussotti, P Palermo, M Guazzi, Centro Cardiologico Monzino, IRCCS, Institute of Cardiology, University of Milan, Milan, Italy

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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.

M B Yilmaz
E Akarca
U Güray
cardiocceptor@tinet.net.tr

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P G Agostoni, M Bussotti, P Palermo and M Guazzi

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