Exercise tolerance in patients with mitral stenosis before and after acute percutaneous mitral valvuloplasty

Role of lung diffusing capacity limitation?


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The aim of this study was to specify in patients with tight mitral stenosis whether lung diffusing capacity could play a role in their exercise intolerance. A similar study was recently carried out in patients with moderate chronic heart failure.

Ten patients with tight mitral stenosis were studied before and 6 months after successful percutaneous transvenous balloon valvuloplasty and compared to six control subjects. Measurements of diffusing capacity, evaluated by the lung transfer factor (TLCO) and by the transfer coefficient (TLCO/VA), obtained at rest and during early recovery after cardiopulmonary exercise testing were performed. Cardiac output was determined non-invasively, both at rest and during exercise, using the carbon dioxide exponential rebreathing technique.

Prior to valvuloplasty, TLCO and TLCO/VA were not different at rest between the two groups. During exercise, patients differed from control subjects, with lower oxygen uptake ($P<0.001$) and lower cardiac output at peak exercise ($P<0.001$). These values at peak exercise were significantly correlated ($P=0.02$; $r=0.75$). Moreover, patients differed from control subjects at early recovery after peak exercise with an absence of increase in TLCO ($P<0.05$).

Six months after valvuloplasty, a decrease of both TLCO ($P<0.01$) and TLCO/VA ($P<0.05$) was observed at rest. During exercise, comparison of patients demonstrated a significant increase of both peak exercise oxygen uptake (SLVO$_2$, $P<0.01$) and cardiac output ($P<0.001$). At early recovery after peak exercise there was a significant increase in TLCO ($P<0.05$) and TLCO/VA ($P<0.01$), such that a $\Delta$TLCO and a $\Delta$TLCO/VA appeared ($P<0.05$) identical to that observed in control subjects. Moreover, $\Delta$SLVO$_2$ was significantly correlated in patients with $\Delta Q+\Delta$TLCO/VA ($P=0.02$; $r=0.72$).

In conclusion, this study suggests a role, at least partial, of lung diffusing capacity in exercise intolerance in patients with tight mitral stenosis and in the improvement of their aerobic exercise capacity demonstrated after successful percutaneous balloon valvuloplasty.

Key words: Mitral valve stenosis, percutaneous balloon valvuloplasty, lung diffusing capacity, cardiopulmonary exercise testing, cardiac output.

Introduction

In a previous study, during early recovery after peak exercise we demonstrated an absence of increase in pulmonary diffusing capacity in patients with moderate chronic heart failure, in comparison to control subjects$^{[1]}$. This result suggests that pulmonary diffusing capacity may have a role, at least in part, in limiting aerobic exercise capacity in patients with limitation in effort due to cardiac disease$^{[2]}$. 


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If this hypothesis is correct, the cure for the underlying cardiac disease should restore the 'physiological' increase of pulmonary diffusing capacity in early recovery after peak exercise and should improve aerobic exercise capacity.

Mitral valve stenosis provides an ideal pathophysiological model to verify this hypothesis, since percutaneous valvuloplasty in patients with tight mitral stenosis can provide curative treatment with immediate and long-term positive results. However, before treatment, in patients with tight mitral valve stenosis, studies of exercise pulmonary diffusing capacity demonstrated either no change or an increase — conflicting results. To our knowledge, exercise pulmonary diffusing capacity has never been studied before in patients following treatment.

Thus, the aim of this study was to specify whether lung diffusing capacity could play a role in exercise intolerance in patients with tight mitral stenosis. We therefore compared the measurements of diffusing capacity, evaluated by the lung transfer factor (TLCO) and by the transfer coefficient (TLCO/VA), obtained at rest and during early recovery after exercise. Measurements were taken using muscular exercise testing, in a group of normal subjects and in a group of patients with tight mitral stenosis, prior and 6 months after successful percutaneous mitral valvuloplasty.

Methods

Subjects

Twenty subjects were studied (13 women and seven men), none significantly overweight. Ten consecutive subjects with tight mitral stenosis were selected for percutaneous transvenous balloon mitral valvuloplasty and 10 normal subjects volunteered to serve as controls.

The ten patients with severe symptomatic mitral stenosis comprised seven women and three men, aged 28 to 56 years (mean 44.5 ± 2.9), with class III heart failure (New York Heart Association classification). Eight patients demonstrated normal sinus rhythm and two had atrial fibrillation. All 10 patients were in a clinically stable condition at the time of the test, with no history of worsening heart failure or a change in cardiac medication in the previous 2 months. Tight mitral stenosis was assessed from clinical and radiological examinations and by Doppler echocardiography. Mitral valve area was less than 1 cm² was assessed using the Gorlin formula. Immediately after valvuloplasty, the balloon valvotomy catheters were removed in order to take haemodynamic measurements. Afterwards, cine left ventriculography in the right anterior oblique projection was used to evaluate the severity of mitral regurgitation. Doppler mitral valve gradients were determined using standard echocardiographic techniques before, during and 6 months after valvuloplasty.

Mitral valvuloplasty

Valvuloplasty was performed successfully with the anterograde transseptal technique using an Inoue balloon. Procedures were considered successful if the final mitral valve area was greater than 1.5 cm², or had increased more than 50% from baseline, without a prominent increase in mitral regurgitation. Right and left heart pressures and mitral gradient were measured before and after valvuloplasty. Mitral valve area was calculated by the Gorlin formula. Immediately after valvuloplasty, the balloon valvotomy catheters were removed in order to take haemodynamic measurements. Afterwards, cine left ventriculography in the right anterior oblique projection was used to evaluate the severity of mitral regurgitation. Doppler mitral valve gradients were determined using standard echocardiographic techniques before, during and 6 months after valvuloplasty in all patients. Mitral valve area was calculated 6 months after valvuloplasty by Doppler echocardiography with a baseline mean score of 7.4 ± 0.5, and in the absence of left atrial or auricular thrombus as demonstrated by transoesophageal echocardiography. Severe mitral stenosis was confirmed by haemodynamic measurements obtained during the procedure just before the valvuloplasty.

None of the patients had a history of pulmonary disease, excluding consequences due to severe mitral stenosis, smoking (during the previous 5 years), implanted pacemaker, amiodarone or beta-blocker treatment, or exercise intolerance for any reason other than fatigue or dyspnoea.

The control group consisted of 10 sedentary subjects in normal physical and medical condition according to clinical, radiological, electrocardiographic, echocardiographic and spirometric examinations. None of them was a smoker, on medication or engaged in regular sports. From this control group, six subjects (four women and two men), aged 42 to 66 years (mean 50.6 ± 4.3) were selected in order to be comparable in age, height and body mass with the 10 patients with severe mitral stenosis before their balloon valvuloplasty (anthropometric characteristics are reported in Table 1). Informed consent to participate in this study was obtained from all patients and control subjects.

<table>
<thead>
<tr>
<th>Anthropometric characteristics of patients with mitral stenosis and control subjects</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Subjects</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Body mass (kg)</td>
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</table>

ns = not significant; values are reported as mean ± SEM.
the pressure half-time formula. Pulmonary arterial pressure was measured during catheterization before and immediately after valvuloplasty. It was also indirectly evaluated 6 months after valvuloplasty from the Doppler tricuspid insufficiency systolic peak gradient when tricuspid insufficiency persisted (seven out of 10 patients). Pulmonary and cardiac haemodynamic measurements before and after successful mitral valvuloplasty are summarized in Table 2.

**Baseline spirometry flow volume and arterial blood gases analysis**

Lung function studies included forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁). Tiffeneau's ratio (FEV₁/FVC) was then calculated. Measurements were taken using a whole body plethysmograph (Transmural Bodybox 2800, Sensormedics, California, U.S.A.). The theoretical values established by Quanjer were used. Arterialized blood samples for partial pressure of oxygen (PaO₂) and partial pressure of carbon dioxide (PaCO₂) were obtained at rest from the ear lobe by a micromethod (IL 1306, Milan, Italy); the oxygen saturation (O₂ Sat) was then deduced.

**Diffusing capacity measurement (TLCO)**

Single-breath TLCO was performed using the method reported previously. A P.K. Morgan transfer test (Chatham, Kent, U.K.) was used to measure TLCO with the modified technique described by Ogilvie et al. and according to the recommendations of the European Respiratory Society. Subjects wore noseclips and were studied in the sitting position. After the subject had adapted to the mouthpiece, the tidal volume was recorded at least four to six times to determine a regular end-expiratory baseline; the subject exhaled to residual volume and then rapidly inspired the gas mixture to total lung capacity (TLC). The inhaled gas mixture was: He=10%, N₂=21%, carbon monoxide=2800 ppm, and balance N₂. Breath-holding at TLC was maintained by asking the subject to relax against the closed valve. After 10 s of breath-holding, the subject rapidly exhaled to residual volume. The first 750 ml were set as the wash-out volume; the next 600 ml were used as the sample volume. The breath-holding time was computed according to the Jones-Meade timing technique. Repeat tests were separated by a washout period of at least 4 min. Maneouvres with breath-holding time above 11 s or less than 9 s were rejected. Unless the inspiratory volume was greater than 90% of the subject's vital capacity, and unless there were at least two technically acceptable tests with TLCO that differed by less than 5%, the test was repeated or rejected. Results are expressed as the mean values of the two closest measurements. The single-breath alveolar volume (VA) was derived by helium dilution and expressed in litres (STPD), carbon monoxide concentration in ml carbon monoxide/min/mmHg (STPD) and the carbon dioxide exponential rebreathing technique through a previously reported method.Expired CO₂ was continuously sampled at the mouth for analysis of CO₂, using a rapid response infrared analyser (Rubis 3000, Cosma, France). The end-tidal carbon dioxide tension (PETCO₂, mmHg) was calculated from the average of

<table>
<thead>
<tr>
<th>Table 2 Haemodynamic measurements in patients with mitral stenosis before and after valvuloplasty (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before valvuloplasty</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
</tr>
<tr>
<td>Mean PcwP (mmHg)</td>
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<tr>
<td>Mean LAP (mmHg)</td>
</tr>
<tr>
<td>Max MVG (mmHg)</td>
</tr>
<tr>
<td>Mean MVG (mmHg)</td>
</tr>
<tr>
<td>MVA (cm²)</td>
</tr>
</tbody>
</table>

LAP=left atrial pressure (mmHg); MVA=mitral valve area (cm²); MVG=mitral valve gradient (mmHg); PAP=pulmonary arterial pressure (mmHg); PcwP=pulmonary capillary wedge pressure (mmHg); values are reported as mean ± SEM. †=by catheter measurements; ‡=echo Doppler measurements; §=Doppler measurements obtained in 7 of the 10 patients. **P<0.01; ***P<0.001: measurements compared immediately and 6 months after valvuloplasty.

**Cardiac output measurement (Q)**

Cardiac output (Q) was determined non-invasively, both at rest and during exercise, using the carbon dioxide exponential rebreathing technique through a previously reported method. Expired CO₂ was continuously sampled at the mouth for analysis of CO₂, using a rapid response infrared analyser (Rubis 3000, Cosma, France). The end-tidal carbon dioxide tension (PETCO₂, mmHg) was calculated from the average of
the last 10 breath cycles prior to the rebreathing manoeuvre. Immediately following this procedure, subjects performed a 10–12 s CO₂ rebreathing manoeuvre, as described by Jones et al.²⁰ and modified by MacKelvie et al.¹⁷ (exponential technique), with a 7% CO₂ in O₂ gas mixture, in order to compute a bag equilibrium carbon dioxide tension (PbCO₂, mmHg). PaCO₂ (mmHg) was estimated from the corrected endtidal concentration²⁰: [PaCO₂ = 5.5 + 0.9 PETCO₂ – 0.0021 VT (ml BTPS)]. Mixed venous carbon dioxide tension (PvCO₂, mmHg) was estimated from the rebreathing equilibrium plateau, with a downstream correction²⁰: [PvCO₂ = PbCO₂ – (0.24 PbCO₂ – 11)]. The partial pressures were converted into concentrations (C), [CCO₂ (ml. dl⁻¹) = 11.02 PCO₂ ³⁷⁶⁰²], and cardiac output (Q) was then calculated according to the Fick formula: [Q (l. min⁻¹) = VCO₂ (l. min⁻¹)/C(v-a) CO₂ (ml. dl⁻¹)] where C(v-a) CO₂ is the venous-arterial content difference for CO₂.

**Exercise testing**

The exercise test was conducted on a cycle ergometer (Monark 864) and ventilatory gas exchanges were measured with a breath-by-breath automated exercise metabolic system (CPX, Medical Graphics, Saint Paul, Minnesota, U.S.A.). Subjects breathed through a low resistance valve. Expiratory airflow was measured with a pneumotachograph connected to a pressure transducer. Expired gases were analysed for O₂ with a zirconia solid electrolyte O₂ analyser and for CO₂ with an infrared analyser. Before each test, the volume was calibrated by five inspiratory strokes with a 3-l pump and the gas analysers with two gas mixtures of known O₂ and CO₂ concentrations. The incremental exercise test consisted of 3 min unloaded pedalling at 50 rpm and of 30 W increments every 3 min thereafter, until the subject's maximal exercise tolerance was reached. The minute ventilation (VE/minBTPS), oxygen uptake (VO₂/minBTPS), carbon dioxide production (VCO₂), ventilatory equivalent for O₂ (VE/VO₂) and CO₂ (VE/VCO₂), respiratory ratio (R) and the oxygen pulse (O₂ pulse) were determined each minute during the last 20 s of each stage on an integral number of respiratory cycles.

The ventilatory reserve (VR) was calculated from the maximal values of measured (VE max) and estimated ventilation (VE max estimated = FEV₁ × 35) as follows: VR (%) = 100 – (100 × VE max/VE max estimated). Oxygen saturation (O₂ Sat) was measured non invasively during both exercise and recovery using a finger oximeter (Spacelabs 90501). A 3-lead electrocardiogram (D₂, V₂, V₅) was continuously monitored with a cardioscope (Q 3000, Quinton instrument company, Seattle, U.S.A.).

We used the predicted values of Jones²⁰ for VO₂ max and those of Lange-Anderson for the HR max (predicted HR max in beats/min = 210 – 0.65 × age in years), HR reserve (predicted HR max – HR max) and HR response [HRR = (HR max – HR rest)/VO₂ max – VO₂ rest)], where HR max was the heart rate at maximal exercise and HR rest was the heart rate at rest, were calculated²².

### Protocol

The evaluation included clinical, radiological and transthoracic echocardiographic examinations, spirometric values at rest and exercise testing with cardiac output determination and diffusing capacity measurements. Controls were evaluated once and patients with tight mitral valve stenosis were studied before and 6 months after successful valvuloplasty.

The subjects were first submitted to resting spirometry, as well as to a TLCO and blood gas analysis. TLCO measurement was carried out at least twice at rest for 4 min intervals, after explaining the test procedure to the subjects. Before exercise testing, subjects received standardized instructions about the procedure. Resting ventilatory variables were measured for a 2 min period in order to acquaint the subject with the respiratory procedure. Each subject then performed an incremental symptom-limited exercise test in a seated position. Cardiac output was determined at rest, at each stage of effort and during recovery. Immediately after peak exercise, and thus during early recovery, within the first 5 min after the completion of the exercise, the subjects underwent a second TLCO measurement.

All the tests were performed between 0900 h and 1100 h.

### Statistics

The data are expressed as mean ± standard error of the mean (m ± SEM). Both groups were studied at maximal exercise and at the same work load. Group differences were evaluated using a two way analysis of variance (group x work load) and using a Student’s t-test for independent samples to compare controls and patients before mitral valvuloplasty and for dependent samples to compare patients before and after valvuloplasty. Multiple regression analysis of percentage of change in VO₂ between rest and maximal effort was performed with changes in cardiac output (ΔQ) and in ΔTLCO or ΔTLCO/VA added to ΔQ. A P value <0.05 was considered statistically significant.

### Results

**Before valvuloplasty**

A clear exercise limitation was found in the mitral stenosis group with a VO₂ of 14.60 ± 1.75 instead of 27.48 ± 1.92 ml. min⁻¹. kg⁻¹ obtained in the control group (P <0.001). This limitation was, at least in part, due to the low maximal of cardiac output, in comparison with the control group (P <0.001; see Table 3). There
was a significant correlation between variations in VO₂ and in cardiac output between rest and maximal effort (P=0.02; r=0.75).

At rest, there was no significant difference in the diffusing capacity and transfer coefficient between the two groups. During exercise, on the other hand, no increase in diffusing capacity was observed in patients with tight mitral stenosis, such that there was no difference in TLCO between rest and early recovery after peak exercise (ΔTLCO), as opposed to the control group (+9.50 ± 3.34% for control patients 6 months after valvuloplasty vs +9-90 ± 3.47% for TLCO/VA). Therefore, ΔTLCO and ΔTLCO/VA, before and 6 months after valvuloplasty, were significantly different in patients (P<0.05). Their ΔTLCO obtained 6 months after valvuloplasty was identical to that observed in control subjects (+9.60 ± 3.49% for patients 6 months after valvuloplasty vs +9-50 ± 3.34% for the control group) and their ΔTLCO/VA was higher, but not significantly, when compared with the control group (P=0.19; see Table 5).

### Six months after valvuloplasty

**Clinical, spirometric and blood gas results**

Clinically, symptomatic improvement was seen in all 10 patients, nine of them with NYHA grade II dyspnoea and one with grade I dyspnoea, whereas before valvuloplasty, all patients had grade III dyspnoea; the same was true haemodynamically with stable Doppler indices and no significant difference observed 6 months after valvuloplasty between these indices compared with measurements obtained immediately after valvuloplasty (Table 2).

Comparison of spirometric values at rest in patients with mitral stenosis before and 6 months after valvuloplasty demonstrated a trend towards an increase in their FEV₁ (measured, P=0.13 and measured/predicted, P=0.11), no change in their FVC and a significant increase in their Diffuenteau’s ratio (FEV₁/FVC; P<0.05). These results indicated a decrease in airway resistances in these patients. Arterial blood gas levels were not significantly different (see Table 4).

### Lung diffusing capacity at rest and during exercise

Six months after valvuloplasty, paradoxically, a significant decrease of both the TLCO (P<0.001) and the TLCO/VA (P<0.05) was observed at rest. During exercise, a significant increase in the TLCO (P<0.05) as well as in the TLCO/VA (P<0.01) was found, such that a ΔTLCO and a ΔTLCO/VA appeared (+9.60 ± 3.49% for TLCO and +12-90 ± 3.47% for TLCO/VA). Therefore, ΔTLCO and ΔTLCO/VA, before and 6 months after valvuloplasty, were significantly different in patients (P<0.05). Their ΔTLCO obtained 6 months after valvuloplasty was identical to that observed in control subjects (+9-60 ± 3.49% for patients 6 months after valvuloplasty vs +9-50 ± 3.34% for the control group) and their ΔTLCO/VA was higher, but not significantly, when compared with the control group (P=0.19; see Table 5).

![Image of Table 3](https://academic.oup.com/eurheartj/article-abstract/17/4/595/539762)

**Table 3** Diffusing and cardiac output measurements at rest and during exercise in patients with mitral stenosis before valvuloplasty and in control subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mitral stenosis before valvuloplasty</th>
<th>Control n=6</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂</td>
<td>14.60 ± 1.75</td>
<td>27.48 ± 1.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q at rest</td>
<td>3.7 ± 0.2</td>
<td>4.8 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Q at 30 W</td>
<td>7.4 ± 0.3</td>
<td>7.0 ± 0.4</td>
<td>ns</td>
</tr>
<tr>
<td>Q at max exercise</td>
<td>10.4 ± 1.0</td>
<td>28.3 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLCO at rest</td>
<td>98.9 ± 5.2</td>
<td>108.5 ± 6.3</td>
<td>ns</td>
</tr>
<tr>
<td>TLCO early recovery</td>
<td>97.3 ± 6.0</td>
<td>118.0 ± 5.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ΔTLCO rest-recovery</td>
<td>-1.60 ± 2.97</td>
<td>+9.50 ± 3.34</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TLCO/VA at rest</td>
<td>86.1 ± 4.9</td>
<td>93.3 ± 5.5</td>
<td>ns</td>
</tr>
<tr>
<td>TLCO/VA early recovery</td>
<td>90.0 ± 5.7</td>
<td>99.6 ± 6.6</td>
<td>ns</td>
</tr>
<tr>
<td>ΔTLCO/VA rest-recovery</td>
<td>+3.90 ± 2.50</td>
<td>+6.33 ± 1.69</td>
<td>ns</td>
</tr>
</tbody>
</table>

Q=cardiac output (l. min⁻¹); ns=not significant; VO₂=oxygen uptake (ml. min⁻¹ kg⁻¹); TLCO=diffusing capacity and TLCO/VA=transfer coefficient for carbon monoxide (%); *P<0.05; TLCO or TLCO/VA compared at rest and at early recovery.

![Image of Table 4](https://academic.oup.com/eurheartj/article-abstract/17/4/595/539762)

**Table 4** Changes in resting spirometric values and arterial blood gas levels in patients with mitral stenosis, before and 6 months after valvuloplasty

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before valvuloplasty</th>
<th>6 months after valvuloplasty</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured FEV₁</td>
<td>2.43 ± 0.20</td>
<td>2.72 ± 0.18</td>
<td>ns</td>
</tr>
<tr>
<td>Measured FVC</td>
<td>3.45 ± 0.28</td>
<td>3.50 ± 0.29</td>
<td>ns</td>
</tr>
<tr>
<td>Measured pred/FVC</td>
<td>101-49 ± 2.71</td>
<td>101-82 ± 3.82</td>
<td>ns</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.71 ± 0.03</td>
<td>0.79 ± 0.04</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PaO₂</td>
<td>93.2 ± 2.8</td>
<td>92.2 ± 3.9</td>
<td>ns</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>36.6 ± 0.9</td>
<td>36.8 ± 0.8</td>
<td>ns</td>
</tr>
<tr>
<td>O₂ Sat</td>
<td>97.3 ± 0.3</td>
<td>97.4 ± 0.2</td>
<td>ns</td>
</tr>
</tbody>
</table>

FEV₁=forced expiratory volume in one second (l); FVC=forced vital capacity (l); FEV₁/FVC=Diffuenteau’s ratio (%); ns=not significant; O₂ Sat=arterial oxygen saturation (%); PaCO₂=partial arterial pressure of carbon dioxide (mmHg); PaO₂=partial arterial pressure of oxygen (mmHg).
Table 5 Changes in diffusing capacity and transfer coefficient for carbon monoxide, and in cardiac output in patients with mitral stenosis, before and 6 months after valvuloplasty

<table>
<thead>
<tr>
<th></th>
<th>Before valvuloplasty</th>
<th>6 months after valvuloplasty</th>
<th>P value (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLCO at rest</td>
<td>98.9 ± 5.2</td>
<td>88.5 ± 5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLCO early recovery</td>
<td>97.3 ± 6.0</td>
<td>98.1 ± 7.2</td>
<td>ns</td>
</tr>
<tr>
<td>ΔTLCO at rest-recovery</td>
<td>-1.60 ± 2.97 ns</td>
<td>+9.60 ± 3.49*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TLCO/VA at rest</td>
<td>86.1 ± 4.9</td>
<td>75.6 ± 3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TLCO/VA early recovery</td>
<td>90.4 ± 5.7</td>
<td>88.5 ± 4.2</td>
<td>ns</td>
</tr>
<tr>
<td>ΔTLCO/VA at rest-recovery</td>
<td>+3.90 ± 2.50 ns</td>
<td>+12.90 ± 3.47**</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Q at rest</td>
<td>3.3 ± 0.2</td>
<td>3.9 ± 0.2</td>
<td>ns</td>
</tr>
<tr>
<td>Q at 30 W</td>
<td>7.4 ± 0.3</td>
<td>8.8 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Q at max exercise</td>
<td>10.4 ± 1.0</td>
<td>16.4 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Q=cardiac output (l.min⁻¹); ns=not significant; TLCO=diffusing capacity and TLCO/VA=transfer coefficient for carbon monoxide (%); *P<0.05 and **P<0.01=TLCO or TLCO/VA compared at rest and at early recovery. Values are reported as mean ± SEM.

Table 6A Changes in exercise parameters at maximal exercise in patients with mitral stenosis, before and 6 months after valvuloplasty

<table>
<thead>
<tr>
<th></th>
<th>Before valvuloplasty</th>
<th>6 months after valvuloplasty</th>
<th>P value (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max work load (W)</td>
<td>57 ± 5.39</td>
<td>78 ± 4.90</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SLV0₂ max (ml.min⁻¹)</td>
<td>0.90 ± 0.10</td>
<td>1.23 ± 0.07</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SLV0₂ max (ml.kg⁻¹.min⁻¹)</td>
<td>14.60 ± 1.75</td>
<td>19.98 ± 1.25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Meas/pred VO₂ max (%)</td>
<td>51.20 ± 4.65</td>
<td>70.02 ± 3.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VE max (l.min⁻¹)</td>
<td>36.41 ± 3.57</td>
<td>52.05 ± 2.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ventilatory reserve (%)</td>
<td>63.35 ± 4.09</td>
<td>42.23 ± 3.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R max</td>
<td>1.14 ± 0.02</td>
<td>1.24 ± 0.03</td>
<td>0.05</td>
</tr>
</tbody>
</table>

R=respiratory gas exchange ratio; SLV0₂=symptom-limited oxygen uptake; VE=minute ventilation; VE/VO₂=ventilatory equivalent for CO₂; VE/VO₂=ventilatory equivalent for oxygen. Values are reported as mean ± SEM.

Table 6B Changes in exercise parameters at maximal exercise in patients with mitral stenosis, before and 6 months after the valvuloplasty

<table>
<thead>
<tr>
<th></th>
<th>Before valvuloplasty</th>
<th>6 months after valvuloplasty</th>
<th>P value (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate max (beats.min⁻¹)</td>
<td>120.6 ± 8.52</td>
<td>150.9 ± 6.57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR reserve (beats.min⁻¹)</td>
<td>59.8 ± 8.61</td>
<td>30.0 ± 7.38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR response</td>
<td>65.23 ± 9.90</td>
<td>76.95 ± 5.38</td>
<td>ns</td>
</tr>
<tr>
<td>Meas O₂ pulse max</td>
<td>0.074 ± 0.006</td>
<td>0.083 ± 0.005</td>
<td>ns</td>
</tr>
<tr>
<td>Meas/pred O₂ pulse max</td>
<td>78.83 ± 4.24</td>
<td>84.29 ± 5.28</td>
<td>ns</td>
</tr>
<tr>
<td>O₂ Sat max</td>
<td>97.90 ± 0.23</td>
<td>97.90 ± 0.23</td>
<td>ns</td>
</tr>
</tbody>
</table>

HR=heart rate; ns=not significant; O₂ Pulse=oxygen pulse; O₂ Sat=arterial oxygen saturation. Values are reported as mean ± SEM.

**Aerobic exercise capacity**

Comparison of exercise parameters before and 6 months after valvuloplasty showed a marked improvement in exercise capacity, with a significant increase in the maximal workload reached (P<0.05), and in the symptom-limited oxygen uptake (SLV0₂ max; P<0.01). There was also a significant increase in the VE max (P<0.01), combined with a significant decrease in ventilatory reserve, reflecting greater use of patient respiratory capacity at maximal effort. Maximal effort was confirmed by the significant increase of R (P<0.05; see Table 6A).
Concerning the cardiac parameters, the maximum heart rate reached increased significantly 6 months after the valvuloplasty \((P<0.01)\), with a consequent significant decrease in the HR reserve \((P<0.01)\). However, the HR response, the \(O_2\) Sat max and most notably the \(O_2\) pulse max were not significantly different \((P<0.01)\). The oxygen uptake during exercise demonstrated a significant increase beginning at 30 W \((P<0.01)\) and, most noticeably, at maximal exercise \((P<0.001)\); see Table 5. Between rest and maximal effort, variations in \(V_O_2\) and in cardiac output \((\Delta Q)\) tended to be correlated \((P=0.06; r=0.61)\). That correlation became significant when \(\Delta TLCO/VA\) was added to \(\Delta Q\) \((P=0.02; r=0.72)\).

**Discussion**

This study confirms our hypothesis that lung diffusion limitation has a partial role in exercise intolerance in patients with tight mitral stenosis.

First, we have shown that before treatment there was no increase in pulmonary diffusion capacity early recovery after peak exercise and there was a decrease in aerobic exercise capacity, in patients with tight mitral stenosis, in comparison to control subjects. These results are similar to those which we have previously reported in patients with moderate chronic heart failure\(^1\).

Second, 6 months after successful percutaneous mitral valvuloplasty, and thus after curative treatment, we confirm the reappearance in these patients of a ‘physiological’ increase in pulmonary diffusion capacity early recovery after peak exercise, and an improvement in their aerobic exercise capacity. Moreover, after valvuloplasty, the variation between rest and maximal effort in patients’ oxygen uptake was significantly correlated with the variation in cardiac output added to the variation in transfer coefficient.

**Methodology**

Measurement of TLCO at rest has been reported with good reproducibility in normal subjects\(^2\) and in patients with mitral valve stenosis\(^3\). TLCO has also been found to be dependent upon alveolar oxygen tension, haemoglobin concentrations and the degree of lung inflation at the time of breath-holding\(^4\). In this study, all the subjects had satisfactory lung volumes, normal haemoglobin concentrations, and a relatively short breath-holding time was used. In this study we were also interested in looking at the transfer coefficient of carbon monoxide \((TLCO/VA)\), since this ratio is linked to the carbon monoxide transfer per unit of parenchyma ventilated\(^5\).

Single-breath determination of TLCO and TLCO/VA during exercise is more difficult to measure routinely than at rest. Patients should cycle for 3 min at each workload, continue to cycle and perform the breath-holding test, then pause for 5 min rest before the next level of exercise\(^6\). This methodology was not suitable for this study because maximal exercise capacity and cardiac output during exercise by \(CO_2\) rebreathing method measurements were being examined. Moreover, a breath-holding time of 10 s, which would be needed for single-breath determination of TLCO and TLCO/VA, is impossible to perform at peak exercise for both normal subjects and patients. Similar heart rates would be more adapted for comparison of TLCO and TLCO/VA values between at rest and peak exercise. However, this is not feasible due to tachycardia observed at peak exercise.

Manier et al\(^7\) recently studied pulmonary diffusing capacity during early recovery from a progressive maximal exercise, with the use of the single-breath breath-holding method. By this approach, they reported an approximate 13% increase in pulmonary diffusion capacity at early recovery in well-trained subjects (within 2 min) after peak exercise, in comparison with resting values \((P<0.01)\). We therefore used this methodology to evaluate pulmonary diffusing capacity variations during exercise in a previous study in patients with moderate chronic heart failure\(^8\) and similarly in this present study. In these two studies this approach was found to be sensitive enough to demonstrate an approximate 10% physiological increase in pulmonary diffusing capacity at early recovery (within 5 min) after peak exercise in the two control groups. It also confirmed the reappearance of this approximate 10% physiological increase of early recovery pulmonary diffusing capacity in patients after successful valvuloplasty.

To determine cardiac output, we used the \(CO_2\) rebreathing method with the same methodology we recently reported in patients with chronic heart failure, in comparison to control subjects\(^9\). Studies performed at rest and during exercise confirmed that the exponential \(CO_2\) rebreathing method for measurements during exercise was more accurate and better tolerated than the equilibrium \(CO_2\) rebreathing method\(^10\). The \(CO_2\) rebreathing method has been simultaneously and haemodynamically validated at rest, in normal subjects\(^11\) and in patients with chronic heart failure\(^12\) or high blood pressure\(^13\). All the values observed for cardiac output by the \(CO_2\) rebreathing method in this study were in the range of values usually obtained by the thermodilution technique or the direct Fick method for normal subjects and especially for patients with mitral valve stenosis\(^14\).

Mitrval valvuloplasty was performed with the Inoue balloon with good results, as reported in all other series conducted with this technique\(^15\). In this study, improvement was confirmed at 6 months for all patients, by both clinical and Doppler indices. Performing a percutaneous valvuloplasty avoided pleural and pulmonary drawbacks of surgical intervention, and therefore enabled unaltered comparisons of pulmonary function before and after curative treatment in these patients.
Spirometric and aerobic exercise capacity improvements

Changes in spirometric values observed 6 months after valvuloplasty showed a trend towards improvement in measured FEV₁ (P=0.13), which was confirmed by the measured/predicted FEV₁ (P=0.11) and especially a significant increase in Tiffeneau's ratio (P<0.05) since the FVC remained unchanged in this study (Table 4). Yoshioka et al. noted an increase in both the FEV₁ and the FVC after valvuloplasty which explained the absence of change in the Tiffeneau's ratio in their study.275 Nevertheless, their comparative study was completed only one week after valvuloplasty and thus its results could not be directly compared with ours. The increase in FEV₁ and in Tiffeneau's ratio that we observed after 6 months suggests a reduction in airway obstruction.

In subjects with severe mitral stenosis, before valvuloplasty, a marked limitation in aerobic exercise capacity was observed along with a clear reduction in oxygen uptake at maximal exercise as compared to the control group. Maximal exercise in patients was confirmed by a mean respiratory gas exchange ratio above 1.1 at peak exercise. Although this limitation was expected, it has not always been demonstrated: marked limitation in the recent Marzo et al. study with data comparable to ours, moderate limitation in Blackmon et al. and in Cohen Solal et al. and no change in limitation in one third of the cases in Hugenholtz et al. These discrepancies might be related to differences in illness severity of patients included in these studies. Furthermore, this limitation in exercise did not seem to be directly correlated with mitral valve area evaluated at rest. And to our knowledge, oxygen uptake was not evaluated in these studies in comparison to a control group.

A significant reduction in cardiac output was observed at maximum exercise before valvuloplasty. This reduction in cardiac output has already been reported in similar patients in haemodynamic studies during effort using cardiac catheterization or the echocardiographic method but, as far as we know, has not been reported using methods similar to ours.

Six months after valvuloplasty, the improvement in exercise capacity was clearly demonstrated in this study by the significant increase in maximal work load, especially concerning the measured SLVO₂ max (+53%; P<0.01) as well as the measured/predicted SLVO₂ max (+49%; P<0.01), the minute ventilation and the respiratory gas exchange ratio (Table 6A). An improvement after valvuloplasty was also recently reported at 27.1 ± 11.6 months in max SLVO₂ and at 3 months for all of these parameters. In addition, a significant decrease in ventilatory reserve was observed in our study, which suggests better recruitment of the alveoli, as confirmed by the significant increase in max R' as reported during exercise using the CO₂ rebreathing method to our knowledge.) Cardiac output 6 months after valvuloplasty was significantly increased beginning at the 30 W (P<0.01) stage onwards, and especially at maximum effort (+64%; P<0.001; Table 5). This naturally contributed to the clear improvement in exercise capacity in these patients, as assessed by the nearly significant (P=0.06) correlation between ΔVO₂ and ΔQ during exercise 6 months after valvuloplasty.

The other cardiac parameters changed little 6 months after valvuloplasty, except for a significant increase in heart rate (HR) and a consequent significant decrease in the HR reserve (Table 6B), which was not explained by therapeutic changes (breaks in digitalis or amiodarone treatments). In particular, as the max SLVO₂ and HR increased together, no modification in the max O₂ pulse was observed, unlike the significant increase reported in the Chen et al. study.

Pulmonary diffusing capacity

Physiologically, as we detailed in a previous report and as observed in our control group, the pulmonary diffusing capacity increases with effort. At early recovery, in comparison to resting values, pulmonary diffusing capacity physiologically remains increased (mean +13%), as reported by both Manier et al. and by Rasmussen et al., using the same methodology as ours. Pulmonary diffusing capacity then returns to its resting value at 15 and 30 min after peak exercise. At 2–3 h post exercise, an approximate 15% reduction in pulmonary diffusing capacity takes place, whereas systolic cardiac function is normal and total lung capacity increases. This could reflect a physiological sub-clinical pulmonary interstitial oedema, as suggested by Rasmussen et al. After 20 h following exercise, pulmonary diffusing capacity normalizes.

In our study, prior to valvuloplasty, TLCO and TLCO/VA at rest were not significantly different (P values at 0.26 and 0.36 respectively) between patients with severe mitral stenosis and the control group (Table 3). These results are in agreement with previous studies of similar subjects with mitral stenosis, but in conflict with others. Indeed, significant decreases in TLCO and TLCO/VA at rest were reported but particularly in patients with a longer disease evolution. Anatomical alterations of the membrane have been described in patients with mitral stenosis with intimal changes in small lung vessels, fibrosis or thickening of the alveolar walls and an increase in the thickness of the respiratory membrane and consequently in its resistance. According to these alterations, a decrease in diffusing capacity should be observed at rest. But the increase in pulmonary arterial pressure described at rest in patients with mitral stenosis leads to a confirmed higher recruitment of the pulmonary capillary blood volume and therefore probably counterbalances, at rest, negative effects of the impaired membrane in diffusing capacity.

The early recovery after peak exercise diffusing capacity in these patients did not increase and was
Exercise tolerance in patients with mitral stenosis

Six months after valvuloplasty, if the proposed hypothesis is correct, increase in pulmonary artery pressure during exercise, which occurs even after successful valvuloplasty\[^{[45,47]}\], should result in an improvement in diffusing capacity during exercise after valvuloplasty, or at least in a return to its initial level prior to valvuloplasty. Indeed, a reappearance of a 'physiological' increase in early recovery after peak exercise pulmonary diffusing capacity is observed in patients, with a similar percentage increase to that observed in the control group (mean +9.60% in patients versus +9.50% in controls for TLCO). According to the small number of patients and controls included in our report, these preliminary results have to be confirmed in more extensive studies. Nevertheless, they support the explanation of the paradoxical reduction in diffusion observed at rest after valvuloplasty by the decrease in at-rest pulmonary artery pressure, since exercise testing appears to correct this reduction. Furthermore, the reappearance after curative treatment of a 'physiological' increase in early recovery after peak exercise pulmonary diffusing capacity seems to be in agreement with a possible role of the absence of increase in this capacity in patients' limitation in effort due to cardiac disease, as we suggested above, in addition to other well-known factors such as peripheral muscular abnormalities. Indeed, the weak correlation \(P=0.06\) between \(\Delta V O_2\) and \(\Delta Q\) during exercise 6 months after valvuloplasty was improved when \(\Delta TLCO/VA\) was added to \(\Delta Q\) and became significant \(P=0.02\). Although correlations between exercise parameters and exercise performance do not necessarily indicate cause, this higher correlation suggests a role, at least partial, of the improvement in pulmonary diffusion capacity in the improvement of maximal oxygen uptake in these patients.

Which determinants could be speculated to cause this increase in early recovery after peak exercise pulmonary diffusing capacity that occurred after valvuloplasty? This increase does not reflect the ability to generate the same peak pulmonary artery pressure (PAP), nor is it linked to a greater increase in PAP during exercise before and after valvuloplasty, since a smaller increase in PAP after valvuloplasty, as compared to before valvuloplasty, has been demonstrated at peak exercise and at the same submaximal ergometer workload \((42 \pm 12\text{ mmHg} \text{ at 3 months after, vs } 61 \pm 17\text{ mmHg} \text{ before}, P<0.01, n=24)^{[45,47,48]}\). Moreover, this increase is probably not linked to an increase in pulmonary capillary blood volume during exercise, since this volume decreases and normalizes at rest after valvuloplasty\[^{[44]}\], and increases during exercise in proportion to the elevation of pulmonary artery pressure, which is less important after valvuloplasty than before, as reported above. The reappearance after valvuloplasty of this increase in early recovery after peak exercise pulmonary diffusing capacity is also unlikely to be linked to an increase and normalization of the duration of blood-air contact, since before valvuloplasty there was no element suggesting insufficiency in the duration of this contact.

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Six months after valvuloplasty, the mean decrease in pulmonary diffusing capacity at rest was significantly lower than that of the control group (Table 3). These results confirm those that we have previously reported during exercise in patients with moderate chronic heart failure\[^{[11]}\], suggesting a similar time course in pulmonary diffusing capacity during exercise in patients with limitation in effort related to an underlying cardiac disease. Thus, the absence of increase in diffusing capacity during exercise in patients with mitral stenosis could be related, as suggested in patients with moderate chronic heart failure\[^{[41]}\], to an increase in interstitial pulmonary oedema. This is a possible explanation since a worsening in anatomical lesions of the membrane was unlikely in such a short time course. Furthermore, a significant increase in pulmonary artery pressure, which might lead to an increase in pulmonary capillary blood volume and thus diffusing capacity, has been demonstrated during exercise in these patients\[^{[49,45]}\].

Lastly, the shorter exercise time performed by patients in comparison to control subjects seems unlikely to explain the reduction in the exercise-induced improvement in diffusing capacity observed in patients with mitral stenosis, since change from rest to peak exercise in diffusing capacity observed in this study did not significantly correlate with the level of exercise or with the increase in cardiac output. Nevertheless, to definitively test this hypothesis, we have to conduct a new study to compare diffusing capacity registered in patients and controls at the same level of exercise, since its measurement can only be obtained at early recovery after exercise.

Six months after valvuloplasty, pulmonary diffusing capacity at rest was significantly lowered in this study, whether evaluated using the TLCO \(P<0.01\) or the TLCO/VA \(P<0.05\), Table 5). This apparently paradoxical decrease had also been reported in a study completed within a week after valvuloplasty by Yoshioka et al.\[^{[23]}\] in patients similar to ours, with diffusing capacity prior to mitral valvuloplasty not significantly different from that of the control group. However, Ray et al.\[^{[44]}\] recently reported 3 months after valvuloplasty no change in at-rest pulmonary diffusing capacity; but in their study TLCO was already reduced at baseline (mean, 25% of predicted), unlike in the Yoshioka study and in our own. In this study, the decrease in diffusion observed at rest, 6 months after valvuloplasty, is unlikely to be related to a worsening of anatomical abnormalities of the membrane after valvuloplasty or to a decrease in haemoglobin concentrations, which remain unchanged.

We therefore hypothesize that this decrease in diffusion observed at rest is linked to the decrease in mean pulmonary artery pressure, as Groen et al.\[^{[46]}\] have recently reported in the first postoperative year in cardiac transplant recipients, with a mean decrease in DLCO significantly correlated with the change in their pulmonary arterial pressure \(P<0.001\). Indeed, a marked decrease in mean pulmonary artery pressure is recorded at rest immediately and 6 months after valvuloplasty in our study (Table 2), and was confirmed by other reports\[^{[45,47]}\].

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Six months after valvuloplasty, if the proposed hypothesis is correct, increase in pulmonary artery pressure during exercise, which occurs even after successful valvuloplasty\[^{[45,47]}\], should result in an improvement in diffusing capacity during exercise after valvuloplasty, or at least in a return to its initial level prior to valvuloplasty. Indeed, a reappearance of a 'physiological' increase in early recovery after peak exercise pulmonary diffusing capacity is observed in patients, with a similar percentage increase to that observed in the control group (mean +9.60% in patients versus +9.50% in controls for TLCO). According to the small number of patients and controls included in our report, these preliminary results have to be confirmed in more extensive studies. Nevertheless, they support the explanation of the paradoxical reduction in diffusion observed at rest after valvuloplasty by the decrease in at-rest pulmonary artery pressure, since exercise testing appears to correct this reduction. Furthermore, the reappearance after curative treatment of a 'physiological' increase in early recovery after peak exercise pulmonary diffusing capacity seems to be in agreement with a possible role of the absence of increase in this capacity in patients' limitation in effort due to cardiac disease, as we suggested above, in addition to other well-known factors such as peripheral muscular abnormalities. Indeed, the weak correlation \(P=0.06\) between \(\Delta V O_2\) and \(\Delta Q\) during exercise 6 months after valvuloplasty was improved when \(\Delta TLCO/VA\) was added to \(\Delta Q\) and became significant \(P=0.02\). Although correlations between exercise parameters and exercise performance do not necessarily indicate cause, this higher correlation suggests a role, at least partial, of the improvement in pulmonary diffusion capacity in the improvement of maximal oxygen uptake in these patients.

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Hypoxemia, by definition, is a decrease in arterial oxygen tension below a certain threshold (usually 50 mmHg). It can be caused by various factors, such as decreased oxygen delivery to the tissues or increased oxygen consumption by the body. Hypoxemia can lead to a number of symptoms and complications, including fatigue, shortness of breath, and in severe cases, organ damage and failure. The severity of hypoxemia is often assessed using the oxygen saturation level, which typically measures the percentage of hemoglobin molecules that are bound to oxygen. A low oxygen saturation level indicates a decreased oxygen-carrying capacity of the blood, which can worsen the condition of patients with chronic heart failure.
We therefore suggest that the reappearance of this 'physiological' increase could be related to an improvement in membrane permeability at early recovery after peak exercise. This improvement could be due to a time-dependent change in anatomical characteristics of the membrane, with a progressive reconstruction of the alveolocapillary membrane, as suggested by Jahnke et al. who observed at rest a higher diffusion capacity in long-term survivors after heart transplantation than in short-term survivors. But in patients with tight mitral stenosis, Ray et al. reported over a 3-month period after valvuloplasty a normalized pulmonary capillary volume without improvement in the at-rest diffusion capacity, implying enduring structural abnormalities of the alveolar capillary membrane. Long-term studies of diffusion and capillary volume after valvuloplasty are therefore needed to clarify eventual changes in anatomical characteristics of the membrane. The improvement in membrane permeability at early recovery after peak exercise could also be due to functional change, such as a decrease in membrane interstitial oedema. This hypothesis could be related to a better interstitial liquid resorption by the lymphatic system. In severe chronic mitral stenosis at rest, there is no alveolar oedema as a result of increased elimination by the lymphatic system. However, interstitial oedema has been confirmed in patients by high resolution computed tomography, due to limited increase in elimination capacity. During effort and after valvuloplasty, it may be impossible to increase lymphatic resorption to normal levels as it is already at the maximum, leading to an increase of membrane resistance. This increase, possibly related to overworked interstitial liquid resorption by the lymphatic system and which could be called 'humid membrane', was also suggested in our laboratory in 'extreme' athletes. This could explain severe and paradoxical hypoxia at maximum effort. After valvuloplasty, left atrial and pulmonary artery pressures decreased which could explain the disappearance of anomalies in the estimation of pulmonary diffusing capacity or at least a reduction in interstitial oedema making resorption by the lymphatic system easier because it is no longer overworked. During exercise, this would influence a possible improvement in membrane permeability after valvuloplasty.

Conclusion

This study confirms a dramatic improvement in aerobic exercise capacity in patients 6 months after valvuloplasty for severe mitral stenosis. In particular it confirms after valvuloplasty: (1) haemodynamic improvement by a significant increase in cardiac output during exercise as studied for the first time, to our knowledge, by CO\textsubscript{2} rebreathing method; (2) a decrease in alveolar–capillary diffusing capacity observed at rest, most likely linked to a decrease in pulmonary artery pressure and not to a worsening of membrane resistance, and; (3) it suggests the reappearance in these patients of a 'physiological' increase in early recovery after peak exercise pulmonary diffusing capacity.

These data, in agreement with those that we previously reported in patients with chronic heart failure, suggest that diffusing capacity, and therefore pulmonary function, may be involved, in addition to other factors such as peripheral muscular abnormalities, in exercise intolerance in patients with cardiac disease.

References