EXERCISE HYPERVENTILATION, DYSPNEA SENSATION AND ERGOREFLEX ACTIVATION IN LONE ATRIAL FIBRILLATION

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ABSTRACT

Lone atrial fibrillation may be associated with daily-life disability and exercise limitation. The extracardiac pathophysiology of these effects is poorly explored. In 35 subjects with lone atrial fibrillation (mean age 67±7 years) we investigated pulmonary function, symptom-limited cardiopulmonary exercise performance, muscle ergoreflex (handgrip exercise) contribution to ventilation and brachial artery flow-mediated dilation (as a measure of endothelial function) before and after (average interval 20±5 days) restoring sinus rhythm with external cardioversion. Respiratory volumes and lung diffusing capacity at rest were within normal limits during both atrial fibrillation and after restoring sinus rhythm. Cardioversion was associated with the following changes: a decrease of the slope of exercise ventilation vs carbon dioxide (CO₂) production (from 35±5 to 29±3; p<0.01) and of dyspnea sensation (Borg scale from 4 to 2) and an increase of peak oxygen uptake (VO₂) (from 16±4 to 20±5 ml.min⁻¹.kg⁻¹; p<0.01), VO₂ at anaerobic threshold (from 11±2 to 13±2 ml.min⁻¹.kg⁻¹; p<0.05) and O₂ pulse (from 8±3 to 11±3 ml.beat⁻¹; p<0.01). After cardioversion, the observed improvement in ventilatory efficiency was accompanied by a significant peak end-tidal CO₂ increase (from 33±2 to 37±2 mmHg; p<0.01) and no changes in dead space to tidal volume ratio (from 0.23±0.03 to 0.23±0.02; p=ns). In addition, the ergoreflex contribution to ventilation was remarkably attenuated, and the brachial artery flow-mediated dilatation significantly augmented (from 0.32±0.07 to 0.42±0.08 mm; p<0.01). Ten patients had atrial fibrillation relapse, and, compared to values after restoration of regular sinus rhythm, invariably showed worsening of endothelial function, exercise ventilatory efficiency and muscle ergoreflex contribution to ventilation.

In subjects with lone atrial fibrillation, an impairment in ventilatory efficiency appears to be involved in the pathophysiology of exercise limitation, and to be primarily related with a demodulated peripheral control of ventilation.

Key words: Lone Atrial Fibrillation, Exercise, Ventilation, Dyspnea
INTRODUCTION

Lone atrial fibrillation is the most common sustained arrhythmia encountered in clinical practice (11,39). A reduced maximal exercise oxygen uptake (VO\textsubscript{2}) (12,21,22) is a frequent finding, and exercise intolerance is a not uncommon daily-life disability factor (19,23). As to the pathophysiological bases of physical limitation, previous studies have extensively investigated the putative role of hemodynamic abnormalities associated with atrial fibrillation (3,8,10,36). Exercise performance, however, not only depends on the cardiovascular system function but on any organ system involved in O\textsubscript{2} transport, including the respiratory system, skeletal muscles, hormonal and neural feed-back control system for breathing, cardiac output, blood pressure and blood volume. A contribution of peripheral changes resulting from this arrhythmia to the pathogenesis of exercise intolerance is undefined, although there are good reasons to believe that this is a possibility. In fact, the intermittent peripheral blood flow dynamics might affect the shear stress flow-mediated vascular control, impair the blood flow redistribution to exercising muscles (13,35) and sustain changes in muscle myofibrillar energetics (25). An irregular ventricular activity as induced by atrial fibrillation leads to a significant increase of the sympathetic outflow, which is responsible for an abnormal reflexogenic cardiovascular control and neural imbalance (37). Both an inadequate muscle perfusion (stimulation of group IV afferents sensitive to metabolic by-products) and an increased sympathetic activity (hyperkinetic cardiovascular response to exercise that limits tolerance to physical activity) may affect the ventilatory response to exercise. In addition, the lack of the atrial contribution to ventricular filling may in cases of diastolic dysfunction facilitate subclinical interstitial lung edema.

Cardiopulmonary exercise testing (CPET) has the potential of grading the severity of exercise limitation and detecting the organ system involved in the reduced exercise performance (1,15). An analysis of the effects that an irregular ventricular activity produces on the cardiopulmonary performance may expand our knowledge concerning the etiology of exercise intolerance in atrial fibrillation.

We hypothesized that peripheral extracardiac factors may be relevant to the overall exercise performance. To this end, resting pulmonary function, CPET, brachial artery flow-mediated dilation (as an index of the conduit arteries endothelial function) tests, and the ergoreflex test (for exploring the influence of reflexes of muscular origin on the ventilatory control) were performed before and after conversion to sinus rhythm in patients with lone atrial fibrillation. Those who had arrhythmia relapse after cardioversion served as controls.

METHODS

Study Population. 35 patients (30 men and 5 women) with known lone atrial fibrillation for 10 to 12 months were prospectively investigated. Lone atrial fibrillation was defined as ECG evidence of atrial fibrillation in the least two consecutive follow-up visits separated by an interval of 3 months.
Exclusion criteria were the following: 1) history of high blood pressure; 2) significant valvular heart diseases; 3) previous myocardial infarction; 4) New York Heart Association class III to IV heart failure; 5) angina, chronic obstructive lung disease, claudication or any other abnormality potentially interfering with maximal exercise testing performance; 6) thyroid dysfunction; 7) abnormal lung function. In all patients anticoagulant therapy was such as to maintain prothrombin time within a target range of 1.5-2.0 x control for at least 4 weeks before external cardioversion. 50% of patients were taking digoxin and 34% were taking verapamil. None was receiving beta-blockers. Treatment with cardioactive agents was withheld for at least five-half lives before CPET. Before entering the study, all subjects gave informed written consent. The study was approved by the local Ethical Committee.

Study Design. From 8 to 10 days before cardioversion, patients underwent pulmonary function tests and a maximal CPET for familiarization with the procedure. CPET was then repeated 5 days before cardioversion and was taken as representative of patients’ maximal exercise capacity. Three days before restoration of synus rhythm, a handgrip exercise test was performed for evaluating ergoreflex. After an interval of 18±5 days following external cardioversion, patients repeated CPET and, in the next 48 hours, an ergoreflex test. Investigators who read the exercise results were blind to the study design and purpose.

Echocardiography. Two-dimensional and Doppler cardiac ultrasounds were performed by current methods. Pulmonary artery systolic pressure, left atrial dimensions, left ventricular end-systolic and end-diastolic chamber dimensions and left ventricular volumes, by the area-length method (to measure ejection fraction), were quantitated by standard techniques.

Pulmonary Function Tests. Spirometry was performed with equipment that met the American Thoracic Society performance criteria (2). To adjust for height, age, and sex we used published prediction equations for forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) (17). Diffusing lung capacity for carbon monoxide (DLco) was determined twice with washout intervals of at least 4 minutes (the average was taken as the final result) with a standard single breath technique. DLco subcomponents, i.e., the alveolar-capillary membrane diffusion capacity (Dm) and the capillary pulmonary blood volume available for gas exchange (Vc), were determined according to the method of Roughton and Forster (30). This method partitions diffusing capacity into its component resistances: the diffusive resistance of the alveolar-capillary membrane (1/Dm) and the reactive resistance due to capillary blood (1/θVc, where θ = the rate of reaction of CO with haemoglobin) according to the following equation, which assumes that the red blood cell membrane has a negligible resistance to gas exchange:

\[
\frac{1}{\theta} = 14.6/Hb \times [(0.001 \times PAO_2) + 0.0314]
\]

where Hb is the subject’s hemoglobin concentration (g.dl⁻¹) and PAO₂ is the alveolar O₂ partial pressure. Measuring DLco at different FiO₂ (20%, 40%, 60%), a plot of 1/DLco against 1/θ will yield a straight line with a Y-intercept of 1/Dm and a gradient of 1/Vc.
**CPET Measurements.** Each patient performed a supervised, standard, progressively increasing (personalized ramp protocol) work rate (WR) CPET to maximum tolerance on an electromagnetically braked cycle ergometer. Gas exchange measurements (*Cardiopulmonary Metabolic Cart, Sensormedics Vmax Spectra*) were obtained at rest (3 min), during 2 minutes of unloaded cycling at 60 rpm followed by a progressively increasing WR exercise and 3 minutes of recovery. Heart rate (HR), 12-lead ECG, and cuff blood pressure were monitored and recorded. HR reserve was calculated as the difference between resting and peak exercise HR. Minute ventilation (VE, BTPS), O₂ uptake (VO₂, STPD), CO₂ output (VCO₂, STPD), respiratory exchange ratio (RER), dead space to tidal volume ratio (VD/VT) and other exercise variables were computer-calculated breath by breath, interpolated second by second and averaged 10-second interval (38). The V-slope analysis method was used to measure the anaerobic threshold (4). The ratio of O₂ uptake to WR increase (ΔVO₂/ΔWR) and oxygen pulse (O₂ pulse) were determined as previously described (15). Ventilation efficiency during exercise was expressed as the slope of VE vs VCO₂ over the linear component of VE vs VCO₂ (34). O₂ arterial saturation was monitored with an ear oxymeter (*Sensormedics*). PaCO₂ was estimated from the end-tidal partial pressure of carbon dioxide (PETCO₂) as gauged from the formula of Jones et al (18). Peak exercise O₂ uptake (peak VO₂) was the highest VO₂ achieved during exercise. Age-, gender- and weight-adjusted predicted VO₂ values were also determined (1). Exercise dyspnea sensation was graded by the Borg scale (5). Dyspnea and breathlessness are used interchangeably and refer to an uncomfortable or unpleasant respiratory-related sensation that normally develops during exercise. Symptoms were related to VE by plotting the Borg score against VE and calculating the slope of this relationship for each test (VE vs Borg score slope).

**Vascular studies.** Vascular assessments were performed according to guidelines of the International Brachial Artery Reactivity Task Force (9). Imaging studies of the brachial artery were performed with a high-resolution ultrasound Hewlett-Packard 11 MHz linear-array transducer, based on the technique described by Celermajer et al. (6). Measurements included brachial diameter and flow velocity assessed by pulsed Doppler with the range gate (1.5 mm) in the center of the artery. The system permitted a direct evaluation of the angle between blood stream and the intersecting ultrasound beam, which was then used to calculate blood flow velocity. Ultrasound images were obtained by the same investigator throughout the study. Blood-flow mediated vasodilation was assessed by measurement of the change in diameter of the brachial artery during reactive hyperemia created by release of a cuff inflated (50 mmHg above systolic pressure for 5 minutes) on the forearm. Arterial diameter was measured in millimeters from the artery-blood interface on both the anterior and posterior walls, coincident with the R waves on the ECG, at 2 sites along the artery for 5 cardiac cycles, with these 10 measurements averaged. The image analysis and measurement of the vasodilator response from repeated studies were performed by an individual who was blinded to the sequence.
We calculated blood flow multiplying the velocity-time integral of the Doppler flow signal by the cross sectional area of the vessel and heart rate. The brachial artery flow-mediated dilatation was calculated as absolute maximal increase in diameter compared with baseline. Reactive hyperemia was calculated as absolute maximal change in flow during hyperemia compared with baseline.

**Ergoreflex Evaluation.** A maximal voluntary handgrip test was measured as the greatest of the peak forces produced by three brief maximal handgrip contractions preliminarily performed before the ergoreflex test. Ergoreceptor stimulation consisted of a 3 minute ventilation recording during rest followed by a handgrip session that was performed twice (4 hours interval) in a random order according to the following protocols: 1) a 5-minute session of rhythmic handgrip achieved by squeezing the balloon of a sphygmomanometer (30 squeezes per min) at 50% of the predetermined maximal capacity followed by 3 minute control recovery; and 2) the same protocol followed immediately after cessation of exercise by three minutes of blood-flow stasis on the exercise arm by inflating an upper arm biceps tourniquet to 30 mmHg above systolic pressure at the beginning of recovery (27). The ergoreflex contribution to ventilation was computed as the difference of the changes in ventilation between the mean value at rest and the average of the second and third minute recovery with and without post-handgrip circulatory occlusion (31).

**Statistical Analysis.** Values are expressed as the mean ± SD. CPET differences between pre- and post-cardioversion were analyzed by paired t-test as well as average changes in VE vs VCO₂ slope, VE vs VO₂ slope and VE vs Borg score slope. An ANOVA multiple comparison test was used for testing differences between pre- and post-cardioversion ergoreflex tests and when comparing differences in the group of patients who presented with atrial fibrillation relapse. A p value of < 0.05 was considered to be significant. Statistical analyses were performed by means of Stata 7.0 package.

**RESULTS**

Thyroid hormone levels, plasma electrolytes, left ventricular dimensions, and ejection fraction (average of 5 consecutive beats) were within normal limits in each subject, and some showed significant atrial enlargement. All CPET were completed without adverse events.

Table 1 summarizes the demographic, spirometric, ecocardiographic and CEPT data at study entry.

**Pulmonary Function Test and CEPT.** All patients exhibited normal lung function (Table 2), and no changes occurred following external cardioversion. The finding that all patients exercised above their anaerobic thresholds and the achievement of a high peak RER (1.07±0.4 pre-cardioversion vs 1.14±0.4 post-cardioversion; p= ns) indicate that patients had developed a significant metabolic acidosis and had exercised at a high, if not maximal, work intensity. Before cardioversion, the symptoms reported for stopping exercise were leg fatigue in 30%, breathlessness in 60%, palpitations in 10%. Interestingly, 20% of subjects who while on atrial fibrillation had stopped
exercise because of dyspnea or palpitations, after restoration of sinus rhythm reported leg fatigue as the limiting symptom.

**Exercise Gas Exchange Analysis.** As shown in Table 2 and Figure 1, cardioversion was associated with significant (p<0.01 all) increases in peak VO$_2$, VO$_2$ at the anaerobic threshold, O$_2$ pulse, $\Delta$VO$_2$/$\Delta$WR and PETCO$_2$ and decreases in the VE vs VCO$_2$ slope, VE vs VO$_2$ slope, VE vs Borg score slope and of HR at rest and peak exercise. No changes in O$_2$ saturation, peak VE, peak respiratory exchange ratio and VD/VT were observed. Interestingly, after cardioversion a significant increase in PETCO$_2$ for any matched exercise time post-cardioversion was observed despite no differences in VD/VT (Figure 2).

**Vascular Analysis.** Brachial artery flow-mediated dilatation and reactive hyperemia to distal circulatory arrest, were significantly improved by external cardioversion (Table 2). An example of improvement in hyperemic response is reported in Figure 3.

**Ergoreflex Test.** Figure 4 depicts the ventilatory responses to handgrip preceding and following restoration of sinus rhythm, without and with blood flow stasis by cuff occlusion. A significant difference in ventilation between the recovery with post-handgrip circulatory occlusion and the recovery without, reflects the ergoreflex component to the ventilatory response to exercise.

**Atrial Fibrillation relapse.** 10 subjects had atrial fibrillation relapse after restoration of sinus rhythm. Interestingly, in this group CPET variables, endothelial function and the ergoreflex component to the ventilatory response to handgrip, all reverted to pre-cardioversion levels after fibrillation relapse (Table 3).

**DISCUSSION**

This study provides, for the first time, the evidence that patients with lone atrial fibrillation peculiarly exhibit a high ventilatory activity for CO$_2$ production, and an abnormally increased dyspnea sensation during incremental exercise. Remarkably, restoration of sinus rhythm abolished the ventilatory abnormalities, mitigated the dyspnea sensation and promoted a significant improvement in peak VO$_2$. Activation of muscle ergoreflex and changes in PETCO$_2$ set-point, rather than abnormalities in lung function and ventilation/perfusion matching, account for the observed abnormal ventilatory pattern and are of pathophysiological relevance to the reduced maximal exercise capacity.

How and whether atrial fibrillation and an irregular ventricular contraction may affect exercise physiology has been matter of investigation since several years (2,8,10,12,21,22,36). Physiology-based studies have, however, primarily focused on the hemodynamic bases for exercise intolerance. Exercise gas exchange analysis by means of CPET has been employed in several previous studies, but information available are limited to peak VO$_2$ and to an analysis of cardiac factors involved in its changes (2,8,10,12,21,22,36). We aimed at targeting additional mechanisms that are potentially involved in exercise limitation in patients with lone atrial fibrillation.
**Exercise Performance in Lone Atrial Fibrillation.** An intuitive mechanism for a reduced exercise performance in atrial fibrillation is an inadequate increase of cardiac output limitation. This arrhythmia may affect cardiac output in several ways, including loss of atrial contribution to left ventricular filling, atrio-ventricular valve regurgitation, increased ventricular rate and reduced diastolic time, irregular RR interval. It is controversial whether, at least as concerns atrial fibrillation, a higher HR at rest may limit chronotropic competence by reducing the heart rate reserve. Some reports (3,36) suggest that patients with lone atrial fibrillation, despite a high resting HR, exhibit a maximum attainable HR at peak exercise higher than observed after sinus rhythm conversion, which accounts for the minor differences in peak VO\(_2\) between the two conditions (3,36). Conversely, others studies (12,22) demonstrated that sinus rhythm restoration, compared to simple rate control, translates into a significant improvement in peak VO\(_2\) and submaximal VO\(_2\) kinetics (VO\(_2\) deficit) irrespective of the underlying cardiac disease. In the present study, peak exercise HR was significantly higher during atrial fibrillation, compensating for a higher resting HR. Heart rate reserve pre- and post-cardioversion was similar. Sinus rhythm conversion promoted a 25% rise in peak VO\(_2\), a 37% increase in O\(_2\) pulse and a 30% enhancement of ΔVO\(_2\)/ΔWR, suggesting an improvement in stroke volume, peripheral blood flow distribution and aerobic efficiency. These changes imply that: a) the augmented HR response to exercise during atrial fibrillation may not invariably compensate for the loss of atrial contribution to ventricular filling and/or that b) extracardiac factors may be involved in the overall exercise limitation.

**Exercise Gas Exchange and Ventilation Pre- and Post-Cardioversion.** CPET is the gold standard technique for noninvasively assessing gas exchange and ventilatory response during exercise (37,1). Under this respect, the major finding of the study is that patients while having lone atrial fibrillation exhibited an impaired ventilatory efficiency, as revealed by steeper VE vs VO\(_2\) and VE vs VCO\(_2\) slopes, along with a lower PETCO\(_2\) for any matched exercise time, compared with sinus rhythm. Two isolated studies by Lundstrom et al. (24) and by Schimpf et al. (33) reported an improved ventilatory response to maximal and submaximal exercise, respectively, after conversion of chronic atrial fibrillation to sinus rhythm. However, most patients presented with an underlying heart disease and no mechanistic implications were reported.

There is a growing interest in the pathophysiological relevance attributable to VE vs VCO\(_2\) slope in a variety of cardiac disorders, because this variable is a powerful indicator of clinical course and prognosis in patients with left ventricular dysfunction (7,14,28,29). Traditionally, a steep exercise VE vs VCO\(_2\) slope has been considered to be a distinctive feature of severe heart failure (7,28); current evidence, however, suggests that VE vs VCO\(_2\) slope may be increased even in normal subjects or in patients with preserved left ventricular function (14,28). Although this makes more acceptable the novel concept that lone atrial fibrillation is associated with an abnormal exercise ventilatory efficiency, the basic question concerning the pathophysiological substrate remains to be answered. Different factors may account for an excessive ventilatory response to exercise.
Mathematically, the VE vs VCO₂ slope is determined by three variables: the amount of CO₂ produced, the physiological dead space-tidal volume ratio (VD/VT) and the arterial CO₂ partial pressure. Thus, for a given VCO₂, an increased VE vs VCO₂ slope may be due to either an abnormally high dead space fraction (increased VD/VT), or to a low PaCO₂, or both. A low PaCO₂ derives from an augmented central or peripheral command to ventilation which drives the PaCO₂ below the physiological range, and/or from the occurrence of early metabolic acidosis which demands ventilatory compensation. It follows that measurement of PaCO₂ and calculation of VD/VT are required to quantify ventilatory efficiency. The loss of atrial contraction may, especially in the presence of ventricular diastolic dysfunction, produce an increase in pulmonary venous pressure leading to clinical or subclinical interstitial pulmonary edema and subsequent impairment of the alveolar-capillary diffusing capacity, and/or to ventilation/perfusion mismatching. These possibilities, however, are ruled out in our patients by the fact that alveolar-capillary membrane diffusing capacity and exercise VD/VT were within normal limits and were unchanged after external cardioversion. Conversely, the finding that PETCO₂ was significantly reduced over the entire duration of exercise and increased to normal following restoration of sinus rhythm, is in favor of a primary involvement of extra-pulmonary factors.

**Dyspnea Sensation and Ergoreflex Activation.** Interestingly, lone atrial fibrillation was associated with an increase in breathlessness at any matched level of ventilation, that is not attributable to an augmented dead space ventilation and ventilation/perfusion mismatching on exertion. Lack of variations in arterial oxygen saturation with cardioversion does not support a role for uneven pulmonary capillary recruitment and consequent hypoxemia in the presence of atrial fibrillation, and does not explain the higher dyspnea sensation. In chronic heart failure, group IV afferents, that are primarily sensitive to metabolic by-products (26,31) have been hypothesized to play a key role in the genesis of symptoms and in the progress of the disease (27,28,31). The present study documents a significant activation of the metaboreflex contribution to ventilation in the presence of atrial fibrillation and not while on sinus rhythm. This pattern is paralleled by a blunted conduit artery flow-mediated vasodilatation which is considerably improved with restoration of regular sinus rhythm. What suggests that peripheral blood flow fluctuations in atrial fibrillation may induce exercise muscle underperfusion, impair the endothelial responsiveness to vascular shear stress and contribute to a peripheral reflex increase in ventilation.

Furthermore, during atrial fibrillation anaerobic threshold occurred at a VO₂ significantly lower (-18%) than after cardioversion along with an increased VCO₂. Both VCO₂ and H⁺ are two powerful stimuli to ventilation (38) and well explain hyperventilation and breathlessness sensation for any matched workload. It is also remarkable that in the ergoreflex activation a primary role of high H⁺ concentration in cases of premature anaerobiosis and lactic acid production, has recently been demonstrated (32). All these considerations are in favor of the occurrence of premature WR lactic acidosis or an increase in the sensitivity to the same levels of metabolites.
**Study Limitations.** Lack of a direct measure of changes in PaCO₂ during incremental exercise may represent a limitation to this study. However, in view of a normal DLco (98% of predicted normal value) with a normal alveolar-capillary membrane component, making the estimation of PaCO₂ by PETCO₂ highly reliable, we decided to avoid repeated invasive measures. The same reasoning applies to VD/VT calculation. Further investigation to assess lactic acidosis and chemoreflex responsiveness is warranted. The average age of our patient population was somewhat higher than that reported in previous similar studies. However, age as a cause of a steeper VE vs VCO₂ slope is contradicted by the evidence that atrial fibrillation reoccurrence led to a new onset significant impairment in ventilatory efficiency and a parallel reduction in exercise performance.

**Conclusions.** Our findings provide additional insights into the origin of exercise limitation in patients with lone atrial fibrillation and prospect the possibility that extracardiac factors may be at work. An impaired ventilatory efficiency seems to play a significant pathophysiological role and to be related with a disordered reflexogenic control of ventilation by changes in skeletal muscle perfusion and metabolism.
ACKNOWLEDGMENTS

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REFERENCES


**LEGEND FOR FIGURES**

Figure 1. Average mean values of VE vs VCO₂ slope, VE vs VO₂ slope and dyspnea sensation (VE vs Borg score slope) plotted over each minute of ramp incremental exercise.

Figure 2. Average mean values of VD/VT and PETCO₂ plotted at 2-minute intervals at rest (3 min) during unloaded cycling (2 min), during ramp incremental exercise to peak exercise (broken lines before peak exercise indicate different exercise duration pre- and post-cardioversion) and recovery (3 min). *: p<0.05 vs pre-cardioversion; **: p<0.01 vs pre-cardioversion.

Figure 3. Example of brachial artery Doppler flow in a patient before and after cardioversion in the control state and during reactive hyperemia pre- and post-cardioversion.

Figure 4. Mean values of ventilation at rest (2 min), on exercise (5 min) and in the recovery period (3 min) of ergoreflex test pre- and post-cardioversion. *: p<0.01 vs no occlusion.
Table 1. Demographic and echocardiographic data

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<th>Age, y</th>
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<td>Gender, man/women</td>
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<td>Weight, kg</td>
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<td>Body mass index, kg/m²</td>
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<td>NYHA functional class I-II</td>
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</table>

**Echocardiography**

| Left ventricular end-diastolic dimension, mm | 48±5  |
| Left ventricular end-systolic dimension, mm | 30±5  |
| Left ventricular ejection fraction, %       | 60±5  |
| Left atrial diameter, mm                    | 41±6  |
| Systolic pulmonary pressure, mmHg           | 16±4  |

Abbreviations: NYHA= New York Heart Association
Table 2. Pulmonary function tests, CPET data and results of vascular studies pre- and post-cardioversion.

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<th>Pre-cardioversion</th>
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<td><strong>Pulmonary Function Tests</strong></td>
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<td>% predicted normal value</td>
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<td>1.12±0.1 *</td>
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* = p < 0.05 vs pre-cardioversion; # = p < 0.01 vs pre-cardioversion

Abbreviations: DLco= diffusing lung capacity for carbon monoxide; Dm= alveolar-capillary membrane conductance; Vc= capillary blood volume; HR= heart rate; AT= anaerobic threshold; VO₂= oxygen consumption; WR= work rate; VCO₂= carbon dioxide production; VE= ventilation; RER= respiratory exchange ratio; PETCO₂= end-tidal CO₂; VD/VT= dead space to tidal volume ratio.
Table 3. CPET data, results of vascular studies and ergoreflex activity in 10 patients who presented an atrial fibrillation relapse after successful cardioversion

<table>
<thead>
<tr>
<th></th>
<th>Pre-Cardioversion</th>
<th>Post-Cardioversion</th>
<th>LAF relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR, b . min⁻¹</td>
<td>92±10</td>
<td>65±10 * §</td>
<td>89±10</td>
</tr>
<tr>
<td>Peak HR, b . min⁻¹</td>
<td>137±9</td>
<td>112±11 * §</td>
<td>135±10</td>
</tr>
<tr>
<td>HR reserve, beats</td>
<td>45±10</td>
<td>47±9</td>
<td>46±10</td>
</tr>
<tr>
<td>Peak systolic blood pressure, mmHg</td>
<td>163±19</td>
<td>166±20</td>
<td>161±18</td>
</tr>
<tr>
<td>Peak workload, watts</td>
<td>110±15</td>
<td>126±14 @</td>
<td>110±15</td>
</tr>
<tr>
<td>Peak VO₂, ml . kg⁻¹ . min⁻¹</td>
<td>16.5±4.1</td>
<td>19.8±5.0 @</td>
<td>16.3±4.0</td>
</tr>
<tr>
<td>Peak VO₂, % predicted</td>
<td>62±10</td>
<td>74±12 @</td>
<td>61±10</td>
</tr>
<tr>
<td>VO₂ AT, ml . kg⁻¹ . min⁻¹</td>
<td>11.2±2.0</td>
<td>13.3±2.0 *</td>
<td>11.4±2.0</td>
</tr>
<tr>
<td>O₂ pulse, ml . beat⁻¹</td>
<td>8.2±3.0</td>
<td>12.0±2.0 @</td>
<td>8.5±3.0</td>
</tr>
<tr>
<td>ΔVO₂/ΔWR, ml . W⁻¹ . min⁻¹</td>
<td>8.4±1.0</td>
<td>10.1 ±1.0 * §</td>
<td>8.5±1</td>
</tr>
<tr>
<td>O₂ saturation, %</td>
<td>97±4</td>
<td>96±4</td>
<td>96±3</td>
</tr>
<tr>
<td>Peak VE, l . min⁻¹</td>
<td>59±20</td>
<td>60±21</td>
<td>58±20</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.08±0.2</td>
<td>1.13±0.3</td>
<td>1.10±0.2</td>
</tr>
<tr>
<td>VE vs VCO₂ slope</td>
<td>36±5</td>
<td>30±3 @</td>
<td>35±5</td>
</tr>
<tr>
<td>PETCO₂, mmHg</td>
<td>33±3</td>
<td>37±3 @</td>
<td>34±2</td>
</tr>
<tr>
<td>VD/VT</td>
<td>0.23±0.03</td>
<td>0.22±0.03</td>
<td>0.24±0.03</td>
</tr>
</tbody>
</table>

**Vascular Studies**

Changes in brachial artery flow-mediated dilatation, mm 0.30±0.06 0.41±0.08 @ § 0.33±0.07
Reactive hyperemia, ml⁻¹ . min⁻¹ 310±165 368±191 @ § 310±165
△ brachial artery diameter/△ flow, mm . ml⁻¹ . min⁻¹ x1000 1.03±0.09 1.12±0.1 * 1.04±0.08

**Ergoreflex Activity**

VE, l . min⁻¹ 5.3±2.3 1.2±1.6 @ 5.9±2.2

* = p < 0.05 vs pre-cardioversion; # = p < 0.01 vs pre-cardioversion. §: p<0.05 vs atrial fibrillation relapse; @= p<0.01 vs atrial fibrillation relapse

Abbreviations as in Table 2.
\[ y = 8.0473x + 11.311 \]
\[ y = 6.1298x + 8.5417 \]

\[ y = 0.0261x - 1.62 \]
\[ y = 0.0321x - 0.3661 \]

\[ y = 0.0298x + 5.1045 \]
\[ y = 0.0353x + 4.9222 \]

**VE (l.min\(^{-1}\))**

- Pre-cardioversion
- Post-cardioversion

**Borg score**

**VCO\(_2\) (ml)**

**VO\(_2\) (ml)**

VE

\[ y = 0.0353x + 4.9222 \]
\[ y = 0.0261x - 1.62 \]

\[ y = 0.0321x - 0.3661 \]
\[ y = 0.0298x + 5.1045 \]

\[ y = 0.0353x + 4.9222 \]
\[ y = 0.0261x - 1.62 \]

\[ y = 0.0321x - 0.3661 \]
\[ y = 0.0298x + 5.1045 \]

\[ y = 6.1298x + 8.5417 \]
\[ y = 8.0473x + 11.311 \]

\[ y = 0.0261x - 1.62 \]
\[ y = 0.0321x - 0.3661 \]

\[ y = 0.0298x + 5.1045 \]
\[ y = 0.0353x + 4.9222 \]
**Pre-cardioversion**

- Ventilation (l. min⁻¹)
- Time (min)
- No-occlusion
- Occlusion

**Post-cardioversion**

- Ventilation (l. min⁻¹)
- Time (min)
- No-occlusion
- Occlusion

* denotes statistical significance.