Clinical, adrenergic and heart endocrine measures in chronic atrial fibrillation as predictors of conversion and maintenance of sinus rhythm after direct current cardioversion

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The aim of this study was to evaluate clinical, adrenergic and endocrine factors that could predict sinus rhythm maintenance after direct current cardioversion in chronic atrial fibrillation.

Nineteen patients with chronic non-rheumatic atrial fibrillation (mean duration 6 ± 5 months) were studied. They were exercised 24 h before cardioversion at maximum effort with the Naughton protocol. Heart rate and blood pressure at rest and exercise were recorded and blood samples were taken for the assessment of adrenergic activity, by measuring cyclic adenosine monophosphate, heart endocrine function, atrial natriuretic peptide and its second messenger, cyclic guanosine monophosphate. Fifteen of the 19 patients were initially converted to sinus rhythm (eight patients with external and seven patients with internal DC shocks). After 3 months eight patients remained in sinus rhythm and 11 had relapsed, most of them within the first month. On exercise the chronotropic response was lower in the group who remained in sinus rhythm than in the group in atrial fibrillation (peak heart rate 147 ± 11 beats . min⁻¹ vs 165 ± 24 beats . min⁻¹, P=0.02). During exercise, the systolic blood pressure in the sinus group reached higher values than in the group who relapsed (192 ± 17 mmHg vs 176 ± 18 mmHg, P=0.03). Cyclic adenosine monophosphate increased significantly from rest to peak exercise in the sinus rhythm group (from 23 ± 9 pmol . ml⁻¹ to 31 ± 15 mol . ml⁻¹, P=0.02) while it remained unchanged in the atrial fibrillation group (25 ± 10 pmol . ml⁻¹ to 24 ± 8 pmol . ml⁻¹, P=0.02). For all 19 patients the difference in cyclic adenosine monophosphate between rest and exercise was negatively correlated with maximum heart rate (r=0.58, P=0.009). Atrial natriuretic peptide increased from rest to peak exercise in the sinus rhythm group (from 129 ± 58 fmol . ml⁻¹ to 140 ± 66 fmol . ml⁻¹) while it remained unchanged in the group in which atrial fibrillation persisted or recurred (from 112 ± 58 fmol . ml⁻¹ to 111 ± 53 fmol . ml⁻¹, P=0.002). A significant correlation between atrial natriuretic peptide and cyclic guanosine monophosphate levels at exercise before cardioversion was found for the sinus rhythm group only (r=0.76, P=0.02).

In patients with non-rheumatic chronic atrial fibrillation evaluation of clinical parameters such as heart rate and blood pressure changes during maximal exercise can be useful in the choice of suitable therapy. An inadequate increase in plasma cyclic-adenosine monophosphate and atrial natriuretic peptide on exercise could predict patients with more severe underlying disease, where cardioversion should not be recommended.

Key Words: Atrial fibrillation prognosis, atrial natriuretic peptide, cyclic guanosine monophosphate, cyclic adenosine monophosphate.

Introduction

Chronic atrial fibrillation is one of the most common arrhythmias and its management is still under evaluation. Sustained high ventricular rate responses have been implicated as a cause of cardiomyopathy. Therapeutic options that could be offered to these patients are either cardioversion to sinus rhythm, or, when this is not feasible, pharmacological or ablation treatment.

Exercise studies have been used to evaluate the chronotropic response in patients with chronic atrial fibrillation.
fibrillation and have been associated with patient functional capacity or underlying heart disease. An inverse relationship has been observed between functional capacity, measured as a peak oxygen consumption, and heart rate at low levels of exercise.

Adrenergic activity, as expressed by norepinephrine plasma levels, and chronotropic responses during exercise have been evaluated in patients with congestive heart failure in sinus rhythm, but information on such parameters in patients with chronic atrial fibrillation is lacking.

In this study we evaluated patients with chronic non-rheumatic atrial fibrillation to investigate the relationship between their chronotropic response and their neurohormonal profile during exercise. Conversion to sinus rhythm with DC shock was attempted in all patients and we tried to correlate the outcome to clinical or endocrine factors, with a view to discovering which of these factors might discriminate the patients in whom DC cardioversion is likely to be successful.

We measured cyclic adenosine monophosphate (c-AMP) plasma levels at rest and exercise as an indicator of the total $\beta_1$ and $\beta_2$ adrenergic activity. Changes in plasma levels seem to reflect intracellular changes and measurement of such changes seems to be more reliable than immediate assay of catecholamine activity. In parallel, we evaluated the plasma levels of atrial natriuretic peptide and its second messenger, cyclic guanosine monophosphate (cGMP), because atrial natriuretic peptide production seems to be related to the mechanical and electrical situation of the atrial myocardium. Atrial natriuretic peptide has been found to increase during exercise in normal individuals, according to the intensity of the workload.

Study protocol

Patients who were included in the study started anticoagulant therapy with coumadine 15 days before the procedure, in order to increase their prothrombin time to at least double the normal values. Anticoagulant therapy was continued for at least 3 months, regardless of the rhythm. Medical treatment was discontinued 3 days before performing exercise test. Patients underwent a treadmill exercise test 24 h before cardioversion, using the modified Naughton protocol, and exercised until maximum effort was achieved. Only patients who were unable to continue because of fatigue stopped the exercise test; none developed angina during the test. If angina had developed the patients were not to be included in the protocol. Heart rate and systolic blood pressure were monitored at rest and during the exercise test and averages were calculated over at least ten cardiac cycles. Blood samples were drawn from the antecubital vein at rest in the supine position before the test, and within 5 min after peak exercise. All patients underwent M-mode echocardiography before cardioversion with the use of a 2.5 MHz transducer (Advanced Laboratories — Ultramark 9). Left atrial systolic diameter, end-systolic diameter (ESD), end-diastolic diameter (EDD), and thus fractional shortening as the EDD-ESD/EDD ratio of the left ventricle were estimated according to the guidelines of the American Society of Echocardiography. All calculations were the average of at least six cardiac beats for patients in sinus rhythm and 10 cardiac beats for patients with atrial fibrillation. All patients were informed about the study and gave their written consent. They were advised to visit the outpatient clinic if they developed any symptoms, mainly palpitations, otherwise they were regularly examined once a month for a period of 3 months. Clinical examination and a 12 lead ECG were used to evaluate whether they maintained sinus rhythm.
Table 1  Clinical and echocardiographic data of patients who maintained sinus rhythm or in whom atrial fibrillation persisted or recurred

<table>
<thead>
<tr>
<th></th>
<th>Maintained SR</th>
<th>Recurred AF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>7 ± 5</td>
<td>6 ± 4</td>
<td>0.52</td>
</tr>
<tr>
<td>Patients age (years)</td>
<td>66 ± 7</td>
<td>59 ± 4</td>
<td>0.02</td>
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<tr>
<td>Left atrial systolic</td>
<td>41 ± 5</td>
<td>46 ± 5</td>
<td>0.08</td>
</tr>
<tr>
<td>diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>33 ± 10</td>
<td>34 ± 3</td>
<td>0.78</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>51 ± 9</td>
<td>51 ± 4</td>
<td>0.73</td>
</tr>
<tr>
<td>FS (%)</td>
<td>36 ± 9</td>
<td>32 ± 6</td>
<td>0.18</td>
</tr>
</tbody>
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SR=sinus rhythm; AF=atrial fibrillation; ESD=left ventricular end systolic diameter; EDD=left ventricular end diastolic diameter; FS=left ventricular fractional shortening.

Atrial natriuretic peptide, cyclic guanosine monophosphate and cyclic adenosine monophosphate measurements

Blood samples were taken in tubes containing EDTA (7.5 mm) and a protease inhibitor (trasylo, 500 kIU . ml~ '). The plasma was separated by centrifugation and kept at −35°C until estimations. cyclic-AMP, cGMP and ANF were estimated using the 125I radioimmunoassay kits of Amersham, England. The concentrations of the cyclic nucleotides were expressed in pmol . ml~' plasma, and those of atrial natriuretic peptide in fmol . ml~'. The coefficients of variation for all three estimations were below 10%.

Statistical analysis

Values were expressed as mean ± standard deviation. Comparison of values between patients with persistent or recurrent atrial fibrillation and those who remained in sinus rhythm was performed using ANOVA to compare values within groups. Discriminant stepwise analysis was done using as independent variables the changes induced by exercise. Linear regression was used for correlation. (P<0.05 was considered as statistically significant).

Results

Fifteen of the 19 patients were initially converted to sinus rhythm (eight patients with external and seven patients with internal DC shocks). After 3 months, eight patients remained in sinus rhythm and the rest had relapsed during the first month of the follow-up.

The clinical and echocardiographic findings before cardioversion are shown in Table 1. The duration of the atrial fibrillation was not significantly different between the group who maintained sinus rhythm and the group who relapsed (7 ± 5 months vs 6 ± 4 months, respectively). The patients' age was higher in the 'maintained' group than in the 'relapsed' group (66 ± 7 years vs 59 ± 4 years, P=0.02). The age range was 54 ± 73 years in the maintained group and 52–64 in the relapsed group. We consider these differences as random observations with no clinical significance.

The left atrial diameter was smaller in the maintained group than in the group where atrial fibrillation persisted or recurred, but the difference did not reach statistical significance (41 ± 6 mm vs 46 ± 5 mm respectively, P=0.08) (Table 1). The end-systolic and end-diastolic diameters of the left ventricle were not different in the two groups. The fraction shortening of the left ventricle was also not different in the group which remained in sinus rhythm or relapsed (36 ± 9% vs 32 ± 6%, P=0.18) (Table 1).

The heart rate at rest (93 ± 17 beats . min~' vs 97 ± 26 beats . min~', P ns), was not statistically different between the two groups. On exercise, a significant difference was found between the group which remained in sinus rhythm and the group in which fibrillation persisted or recurred (147 ± 11 beats . min~' vs 165 ± 24 beats . min~' at peak exercise, respectively, P=0.02), Fig. 1. The systolic blood pressure at rest was not statistically different (135 ± 15 mmHg vs 136 ± 18 mmHg) for the two groups. During exercise, the systolic blood pressure in the group which maintained sinus rhythm was higher than in the group in which it recurred (192 ± 17 mmHg vs 176 ± 18 mmHg, P=0.03).

Cyclic adenosine monophosphate measurements

During exercise, cyclic AMP increased from rest to peak exercise in the group which remained in sinus rhythm (from 23 ± 9 pmol . ml~' to 31 ± 15 pmol . ml~') while it remained unchanged in the group in which atrial fibrillation persisted or recurred (25 ± 10 pmol . ml~' to 24 ± 8 pmol . ml~'). The difference between the groups was significant (repeated measures ANOVA, P=0.02, Fig. 1). The changes in cyclic AMP plasma levels from rest to exercise were negatively correlated with the maximum heart rate at the pre-cardioversion exercise test, (r=-0.58, P=0.009, Fig. 2). The increases in cyclic AMP from rest to exercise were positively correlated with the fractional shortening of the left ventricle (r=0.46 P=0.04, Fig. 3).

Atrial natriuretic peptide and cyclic guanosine monophosphate measurements

During exercise, plasma atrial natriuretic peptide increased from rest to peak exercise in the group which remained in sinus rhythm (from 129 ± 58 fmol . ml~' to 140 ± 66 fmol . ml~'), while there was no change in the group where atrial fibrillation persisted or recurred (from 112 ± 58 fmol . ml~' to 111 ± 53 fmol . ml~', ANOVA P=0.002, Fig. 1).
Figure 1  The heart rate (HR, beats min⁻¹), blood pressure (SBP, mmHg), atrial natriuretic peptide (ANP, Fmol ml⁻¹), cyclic AMP (cAMP, pmol ml⁻¹) and cGMP (cGMP, pmol ml⁻¹) at rest (1) and exercise (2) are shown. ○ = The maintained sinus rhythm patients; ● = the patients in whom atrial fibrillation recurred or in whom cardioversion failed.

Figure 2  A negative correlation between maximal heart rate on exercise (HRex, beats min⁻¹), and the increase in cyclic AMP from rest to exercise (ΔcAMP, pmol ml⁻¹).

Figure 3  A positive correlation was found between the fractional shortening of the left ventricle (FS, %), and the increase of the cyclic AMP to exercise (ΔcAMP, pmol ml⁻¹).

The cyclic guanosine monophosphate levels at rest were lower in the group which maintained sinus rhythm than in the group in which it recurred or in which atrial fibrillation persisted (8 ± 3 pmol ml⁻¹ vs 14 ± 7 pmol ml⁻¹, P<0.04, Fig. 1). The group which remained in sinus rhythm after 3 months showed a significant correlation between atrial natriuretic peptide and cyclic guanosine monophosphate levels at exercise before cardioversion (r=0.76 P=0.02). This correlation was not found in the group with persisting fibrillation (r=0.086, P=0.80).

**Discriminant analysis**

The possibility that the changes in systolic blood pressure, heart rate, cAMP, cGMP and atrial natriuretic peptide measured during exercise may predict relapse, was examined by entering the data of the patients with successful cardioversion in a discriminant analysis model (forward stepwise, F to enter=2.00). The first group consisted of the 'relapsed to atrial fibrillation' (n=7) and the second of 'the non-relapsed within 3 months' (n=8).
The heart rate response at exercise in patients with atrial fibrillation has been examined by many investigators. Adwood et al.\(^\text{18}\) found that patients with lone atrial fibrillation on exercise have a higher maximal heart rate than patients with known heart diseases. Van den Berg et al.\(^\text{18}\) observed an inverse relationship between heart rate and peak oxygen consumption during the first stage of exercise. In our study, the group of patients who failed conversion or in whom atrial fibrillation recurred had higher heart rates at peak exercise.

The blood pressure response to exercise was higher in the group which remained in sinus rhythm than in the atrial fibrillation group, suggesting that this group of patients had a better haemodynamic condition\(^\text{23}\).

During exercise in normal subjects, there is an increase in norepinephrine release from sympathetic post-ganglionic nerve endings and in epinephrine plasma levels. Both catecholamines stimulate the $\alpha_1$, $\beta_2$, and $\alpha$ receptors. Heart rate and contractility are enhanced, mainly by $\beta_1$ receptors, while the stimulation of $\beta_2$ receptors increases skeletal muscle blood flow. Cyclic AMP levels express $\alpha$ and $\beta_2$ receptors activity, but $\beta_2$ receptors produce ten times more cyclic AMP than do $\beta_1$ receptors\(^\text{24,25}\).

In patients with congestive heart failure and sinus rhythm it is known that norepinephrine plasma levels are increased on minimal exercise, and the increase to maximal exertion is attenuated, or there is a reduced reflex response to end-organ refractoriness\(^\text{26,26}\). To our knowledge, there has been no study which has examined the adrenergic activity expressed by cyclic AMP plasma levels during exercise in patients with atrial fibrillation. Our findings suggest that there is a correlation between the systolic function of the left ventricle and cyclic AMP levels. The lower or attenuated cyclic AMP production during exercise in patients with lower systolic function could be interpreted as the result of reduced responsivity of the $\beta$-receptors, mainly the $\beta_2$ type. Thus, $\beta$ adrenergic activity, expressed by plasma cyclic AMP response to exercise, seems to be related to the severity of the underlying heart disease, while the possibility of conversion to sinus rhythm in patients with no increase in cyclic AMP is rather diminished. The inverse relationship between maximum systolic heart rate and the increase in the cyclic-AMP from baseline to exercise.

### Table 2 Results of discriminant analysis (forward stepwise) for the patients with successful cardioversion and relapse (group 1) or no relapse (group 2). Independent variables and the changes during exercise before cardioversion are shown.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wilks' Lambda</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$AMP</td>
<td>0.6933</td>
<td>11.54</td>
<td>0.0068</td>
</tr>
<tr>
<td>$\Delta$SBP</td>
<td>0.5011</td>
<td>5.57</td>
<td>0.04</td>
</tr>
<tr>
<td>$\Delta$ANF</td>
<td>0.4693</td>
<td>4.58</td>
<td>0.038</td>
</tr>
<tr>
<td>$\Delta$cGMP</td>
<td>0.3983</td>
<td>2.37</td>
<td>0.15</td>
</tr>
<tr>
<td>Variable not in the model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$HR</td>
<td>0.2898</td>
<td>0.99</td>
<td>0.34</td>
</tr>
</tbody>
</table>

A significant function was found (Wilks' Lambda=0.3219, F (4,10)=5.27, $P=0.0015$) that included the changes in cyclic AMP, systolic blood pressure and atrial atrinuretic peptide and cyclic GMP (Table 2), with an overall correct classification score of 93.3%.

Using this model, three of the four patients with unsuccessful cardioversion were classified in the first (relapse) group (75% correct) and this justifies the categorization of these patients to the patients with relapse.

### Discussion

The principal findings of our study are that some clinical parameters, such as adrenergic and heart endocrine activity on exercise, may help select patients with non-rheumatic atrial fibrillation who are suitable for direct current cardioversion. Patients with higher heart rates and less blood pressure response from rest to exercise seem to be unlikely to convert to sinus rhythm or to remain in sinus rhythm for longer periods than 3 months. Another interesting observation was that the fractional shortening of the left ventricle was positive in the first (relapse) group (75% correct) and this justifies the categorization of these patients to the patients with relapse.

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The heart rate response at exercise in patients with atrial fibrillation has been examined by many investigators. Aberg et al.\(^\text{22}\) observed a non-linear relationship between functional capacity and heart rate. Adwood et al.\(^\text{18}\) found that patients with lone atrial fibrillation on exercise have a higher maximal heart rate than patients with known heart diseases. Van den Berg et al.\(^\text{18}\) observed an inverse relationship between heart rate and peak oxygen consumption during the first stage of exercise. In our study, the group of patients who failed conversion or in whom atrial fibrillation recurred had higher heart rates at peak exercise.

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seems to be associated with the patients' functional capacity. It has been found that heart rate during exercise in patients with atrial fibrillation and peak oxygen uptake is less than 20 ml mm$^{-1}$ kg$^{-1}$, the systolic heart rate is negatively correlated$^{[9]}$.

Concerning the atrial natriuretic peptide levels, our findings show that patients who have an increase in atrial natriuretic peptide from rest to peak exercise before defibrillation have a better outcome. The poor prognosis of patients producing lower atrial natriuretic peptide can be attributed to the atrophy and degeneration of atrial myocytes with interstitial fibrosis and monocyte infiltration. There is some evidence that, in patients with atrial standstill, the levels of atrial natriuretic peptide are very low and remain unchanged on exercise, probably because of the above mentioned degeneration of atrial myocytes$^{[27]}$. The patients in whom defibrillation fails to restore sinus rhythm, or have early recurrence of fibrillation, probably represent the population of patients with more extensive illness of the atrium, so the production of atrial natriuretic peptide is impaired. The atrial natriuretic peptide on exercise also increases in normal individuals and in other patients with diseases such as hypertension$^{[19,28]}$. This has been linked with increased venous return during exercise and elevation of systolic blood pressure, which consequently increases atrial pressure. This increase in pressure induces atrial stretch and an increased frequency of atrial depolarization for secretion of atrial natriuretic peptide$^{[29]}$. Patients with atrial fibrillation have high atrial natriuretic peptide levels at rest. The ability of the atrial myocardium to produce more atrial natriuretic peptide on exercise probably shows an adequate secretory reserve of atrial myocytes$^{[30]}$.

Cyclic GMP is a second messenger of atrial natriuretic peptide and it was measured simultaneously with atrial natriuretic peptide in all samples. The finding of high cyclic GMP levels at rest in the group who did not maintain sinus rhythm is of interest. This might be explained by the possibility of subclinical heart failure in this category of patients$^{[30,31]}$. Patients who remained in sinus rhythm had a considerable correlation between atrial natriuretic peptide and cyclic GMP plasma levels on exercise. This correlation was absent in the group of patients where conversion failed or fibrillation recurred. This uncoupling has been observed by other investigators in patients with severe heart failure$^{[32,33]}$. It may be due to a sustained high plasma concentration of atrial natriuretic peptide over a long period of time as a consequence of down-regulation of the hormone's receptors. Dussaule et al.$^{[34]}$ examining patients with mitral stenosis undergoing balloon valvulotomy, found that when they were in atrial fibrillation the cyclic GMP plasma levels were independent of atrial natriuretic peptide levels, while this was not the case in patients who were in sinus rhythm. Our results are in agreement with these observations.

In conclusion, our results show that there are definite clinical and laboratory findings in response to exercise which could predict subgroups of patients with non-rheumatic atrial fibrillation who would benefit from direct current cardioversion. Assessment of the changes in cyclic AMP, atrial natriuretic peptide and cyclic GMP during exercise before cardioversion could assist in the choice of the most suitable treatment for these patients.

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References


