Exercise testing for non-invasive assessment of atrial electrophysiological properties in patients with persistent atrial fibrillation

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Aims Experimental studies suggest that the autonomic nervous system modulates atrial refractoriness and conduction velocity in atrial fibrillation (AF). These modulatory effects are, however, difficult to assess in the clinical setting. This study sought to non-invasively characterize in patients with persistent AF, the influence of autonomic modulation induced by exercise on atrial fibrillatory rate as marker of atrial refractoriness and to identify clinical and electrocardiographic predictors of atrial rate response.

Methods and results In 24 patients (16 males, mean age 60 ± 13 years) with persistent AF (16 ± 25 months), continuous ECGs were recorded during bicycle exercise testing. Fibrillatory rate (in fibrillations per minute, fpm) was assessed at baseline and immediately after termination of exercise with spatiotemporal QRST cancellation and time–frequency analysis. Ventricular response was characterized by time-domain HRV indices. Exercise had no influence on mean fibrillatory rate (409 ± 42 vs. 414 ± 43 fpm, P = NS). Seven patients responded to exercise with an increase in fibrillatory rate (26 ± 10 fpm, P < 0.001) and three with a decrease (-22 ± 8 fpm, P < 0.001), while the remaining 14 patients did not show a response. Responders’ HRV indices changed in response to exercise similarly to that of non-responders. Their baseline fibrillatory rate was, however, lower than that of non-responders (387 ± 18 vs. 425 ± 48 fpm, P = 0.028). No other clinical or echocardiographic variable was associated with fibrillatory rate response. Twelve weeks after cardioversion, responders were more likely to remain in sinus rhythm than non-responders (88 vs. 46 %, P = 0.04).

Conclusions Exercise-induced autonomic activation produces changes in atrial electrophysiological properties that can be detected by time–frequency analysis. Higher baseline fibrillatory rates are associated with an impaired atrial response to exercise that suggests advanced electrical remodelling and reduced sensitivity to autonomic stimuli.

KEYWORDS
Atrial fibrillation; Autonomic nervous system; Exercise testing; ECG

Introduction
The autonomic nervous system has modulating effects on atrial electrophysiological properties in patients with atrial fibrillation (AF) and may influence induction and maintenance but also termination of the arrhythmia. Supporting mechanisms behind AF sustenance are that both vagal and sympathetic stimulation reduce atrial refractory periods and increase atrial heterogeneity thus favouring re-entry.1

Exercise testing is associated with withdrawal of parasympathetic tone and concomitant increase of sympathetic tone2 and is commonly used in clinical practice for evaluation of coronary heart disease and/or diagnosis of exercise-induced arrhythmias.3 Limited information is available on the effects of exercise on atrial electrophysiological properties during AF particularly when they are assessed non-invasively.

Fibrillatory rate has been introduced as a marker for atrial refractoriness and complexity of atrial activation in AF.4 Several studies made use of fibrillatory rate obtained from the surface ECG in order to monitor electrophysiological properties of the fibrillating atria for analysing arrhythmic drug actions or spontaneous diurnal variability.5 Information on atrial response to exercise is still lacking.

Consequently, the purpose of this study was (i) to non-invasively characterize exercise effects on atrial fibrillatory rate in patients with persistent AF and (ii) to identify clinical
and electrocardiographic predictors of fibrillatory rate response.

Methods

Patients

This study included 24 consecutive patients with persistent AF undergoing exercise testing. Clinical characteristics and echocardiographic parameters are presented in Table 1. All patients provided written informed consent before study participation.

All patients underwent symptom-limited bicycle exercise stress testing using a 3-min step-up protocol. Workload increase was chosen according to age- and gender-predicted values, aiming for a test-duration of 8–12 min.

Those 24 patients were the first set of a cardioversion study, whose study protocol has been published previously. In short, after baseline testing, patients received oral flecainide (200-300 mg/day, n = 15) or amiodarone (1200 mg for 7 days, followed by 200 mg/day, n = 9) for 3-5 days and underwent electrical cardioversion if AF persisted. Atrial fibrillation recurrences were determined by ECG and Holter ECG 24 h, 2 and 12 weeks after cardioversion if AF persisted. Atrial fibrillation recurrences were to occur within days to weeks following cardioversion, this atrial refractory periods and their normalization has been found following successful cardioversion. Since fibrillatory rate reflects early AF recurrence was defined as relapse into AF within 2 weeks after cardioversion or when patients’ symptoms suggested AF.

As with previous investigations, for the purpose of this study early AF recurrence was defined as relapse into AF within 2 weeks following successful cardioversion. Since fibrillatory rate reflects atrial refractory periods and their normalization has been found to occur within days to weeks following cardioversion, this follow-up interval was also chosen from a pathophysiological background.

ECG acquisition and analysis

A continuous 3-lead ECG (Predictor, Dr Kaiser; 2000 Hz sampling rate) was recorded with the subject in a supine position before class I or III antiarrhythmic drug initiation. Fibrillatory rate was assessed in 2-min ECG segments at rest and immediately after termination of exercise with spatiotemporal QRST cancellation and time–frequency analysis.

Time–frequency analysis was performed on a bipolar lead whose electrodes were positioned below the left clavicle and at the right sternal border at the sixth intercostal space. In short, QRST complexes were subtracted using spatiotemporal QRST cancellation and the resulting fibrillatory signal was downsampled to 50 Hz and subjected to spectral analysis. The time–frequency distribution of the atrial signal, which was obtained by short-term Fourier transform, was decomposed such that each spectrum could be modelled as a frequency shifted and amplitude-scaled version of the spectral profile. This procedure is based on a spectral profile, dynamically updated from previous spectra, which is matched to each new spectrum using weighted least squares estimation. The frequency shift needed to achieve optimal matching then yields a measure of instantaneous fibrillatory rate of a 2.5-s electrocardiographic segment (overlapping with one segment each second) and is trended as a function of time (Figure 1). Mean fibrillatory frequency was converted to fibrillatory rate (rate = frequency × 60) and expressed in fibrillations per minute (fpm).

It should be noted that the time–frequency analysis includes techniques for rejecting segments with poor signal quality. Thus, the mean fibrillatory rate is computed from segments with reliable rate estimates only, as opposed to conventional power spectral analysis where all segments are included.

An atrial rate response to exercise was considered present if atrial rate changed by >2.5%. This definition is based on previous observations that there is a <2.5% natural variation of fibrillatory rate in 1-min recordings under stationary conditions.

As previously reported for AF analysis, ventricular response was characterized by mean NN (mean of normal-to-normal RR intervals), SDNN (standard deviation of normal-to-normal RR intervals), nMSSD (root-mean-square of successive NN differences), and pNN50 (percentage of NN intervals >50 ms different from preceding interval).

Statistical analysis

Continuous variables are presented as mean ± one standard deviation. Atrial and ventricular rate responses to exercise were assessed using Student’s t-test for paired data. Atrial rate and ventricular response parameters were correlated using Pearson correlation. Responders and non-responders were compared using Student’s t-test for unpaired data for continuous and χ² test for categorical variables. Multivariate analysis was applied to identify independent predictors of fibrillatory rate response including variables with a P-value <0.15 found in univariate analysis. The relation between fibrillatory rate as well as its exercise response and AF recurrences was also analysed using Student’s t-test for unpaired data and χ² test. A P-value <0.05 was considered statistically significant.

Results

Exercise effects on ECG parameters

Exercise resulted in reduction in mean NN, SDNN, rMSSD, and pNN50 (Table 2), but had no influence on mean fibrillatory rate (409 ± 42 vs. 414 ± 43 fpm, P = NS). There was no correlation between fibrillatory rate and ventricular rate parameters at rest or after exercise.

Looking at individual fibrillatory rate responses, 14 patients did not show a rate change >2.5%. However, 10 patients responded to exercise with either an increase in fibrillatory rate (n = 7, 26 ± 10 fpm or 6.8 ± 2.6%, P < 0.001) or a decrease (n = 3, −21 ± 8 fpm or −5.5 ± 2.0%, P < 0.001).

Responders’ clinical and ventricular response variables as well as exercise duration and intensity were comparable with that of non-responders (Table 3). However, responders had a lower baseline fibrillatory rate than their counterparts with no atrial rate response (387 ± 18 vs. 425 ± 48 fpm, P = 0.028) in univariate analysis (β = −0.304, P = 0.04).

As shown in Figure 2, a baseline cut-off rate of 395 fpm predicted a fibrillatory rate response to exercise with a
sensitivity of 70% and a specificity of 79% (AUC = 0.743). None of the patients with a baseline fibrillatory rate >420 fpm responded to exercise with fibrillatory rate changes.

Exercise effects and AF recurrence
During the follow-up period after cardioversion, there were eight AF recurrences (all at 2 weeks), while sinus rhythm was observed in 14 patients. In one patient cardioversion failed, and in one patient atrial flutter developed; both were excluded from this sub-analysis.

Baseline fibrillatory rate was similar in patients still in sinus rhythm compared with patients with AF recurrence (408 ± 41 vs. 422 ± 45 fpm, P = NS). However, exercise responders were more likely to remain in sinus rhythm than non-responders (88 vs. 46%, P = .04). Clinical characteristics and ventricular rate parameters were not associated with AF recurrence.

Discussion
This study shows, for the first time, that exercise-induced adrenergic activation and reduced parasympathetic modulation may produce contrasting effects on atrial electrophysiological properties which resulted in an increase (n = 7) or decrease (n = 3) in fibrillatory rate or no change at all (n = 14). No changes were detectable in patients with higher baseline fibrillatory rates in spite of a preserved exercise-induced ventricular response. Preliminary data suggest that atrial rate response to exercise may be predictive of AF recurrences after sinus rhythm restoration.

The role of the autonomic nervous system in AF
The autonomic nervous system modulates atrial electrophysiological properties in patients with AF. To a greater extent than the ventricles, both parasympathetic and sympathetic nerves richly innervate the atria. Autonomic activation at the atrial level produces complex effects: for

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Table 2  Exercise-induced changes in ventricular response

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Exercise</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean NN (ms)</td>
<td>742 ± 155</td>
<td>567 ± 150</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>180 ± 51</td>
<td>135 ± 43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>260 ± 82</td>
<td>177 ± 63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>79 ± 11</td>
<td>71 ± 11</td>
<td>&lt;0.001</td>
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Figure 1  Time–frequency analysis of AF. Two seconds (out of a 1-min recording) of an ECG signal from a patient with AF (upper panel), and the same interval after spatiotemporal QRST cancellation (middle panel, amplitude scale is magnified five times). This fibrillatory signal is then subjected to spectral analysis techniques. Time–frequency distribution (left box), power frequency spectrum (middle box), and frequency trend (right box).
example, in animal experiments, atrial effective refractory period is shortened favouring re-entry during both sympathetic and vagal stimulation \(^4\) although the changes induced by parasympathetic stimulation are of greater magnitude. \(^5\) Atrial automaticity is instead significantly augmented by adrenergic stimulation. \(^6\) Some recent data in humans suggest that chronic fibrillating atria are more under sympathetic than vagal control \(^7\) and the higher incidence of AF in states characterized by adrenergic activation such as progressing heart failure \(^8\) supports the hypothesis that the sympathetic nervous system plays an important role in the maintenance of this arrhythmia.

Nevertheless, the final effects of autonomic modulation are difficult to assess in the clinical setting taking into account the number of factors that may affect the autonomic profile in each patient and the possibility that atria and ventricles may differently respond to autonomic stimulation.

**Comparison with previous studies**

Since atrial rates obtained from the surface ECG closely reflect intra-atrial rates \(^1\) and are a marker of atrial refractoriness, \(^9\) atrial fibrillatory rate seems to be ideal for monitoring the effects of autonomic tone changes which occur spontaneously during a 24-h period or by specific interventions that may activate the autonomic nervous system. Indeed, the circadian variability of atrial fibrillatory rate has been previously explored, \(^1\) and the response to carotid sinus massage \(^1\) or head-up tilt testing \(^1\) reported. Common findings were an increase in fibrillatory rates in conditions characterized by a sympathetic stimulation/vagal withdrawal as during daytime or with head-up tilting.

Our results are partially in agreement with the earlier findings. Indeed, some of our patients, responded to exercise with a fibrillatory rate increase, while in contrast, a reduction of fibrillatory rate during exercise was observed in others. Considering the latter, it may be worth recalling that contrasting results have also been reported in previous studies on the circadian fibrillatory rate behaviour in patients with persistent AF. \(^1\) It has been found that fibrillatory rate decreased concomitantly with an increase in ventricular rate in the morning hours when sympathetic control mechanisms are prevailing. The existence of this control mechanism is supported by the clinical observation that in some patients AF can also be self-terminated by exercise. \(^2\) In these cases, a fibrillatory rate decrease prior to AF termination may occur, as it has been reported for drug-induced termination. \(^2\)

In all patients of our series, the different responses of fibrillatory rates occurred during a withdrawal of parasympathetic tone and concomitant increase of sympathetic tone as evidenced by changes in NN, SDNN, rMSSD, and pNN50 (despite different cardiac pathologies and medications). \(^2\) It may be speculated that depending on the dominance of one limb of the autonomic nervous system over the other in supporting AF sustenance in the individual patient, fibrillatory rate increased with further sympathetic stimulation if the sympathetic limb is dominant or decreased with vagal withdrawal if the parasympathetic limb is dominant.

To understand why the majority of our patients did, however, not respond to exercise with fibrillatory rate changes, the observation that a high baseline fibrillatory rate was the only predictor for this behaviour is of interest. This could be interpreted as indirect evidence that electrical remodelling indicated by a faster rate, is associated to a decreased sensitivity to autonomic modulation. This possibility is also supported by the results of a previous study.
Exercise effects on atrial electrophysiology

showing that AF patients with a higher fibrillatory rate displayed a lesser degree of circadian atrial rate variability.26 Of special note is also the different behaviour of atrial and ventricular rate responses and the poor correlation between changes in atrial fibrillatory rate and ventricular response. In fact, although there was a rather homogeneous ventricular response, the response of atrial activity was—as discussed in detail before—highly variable thus conforming the different effects of autonomic control mechanisms at the atrial and atrio-ventricular node levels. At this regard, these data also indicate that atrial fibrillatory activity (concealed conduction) is a less important determinant of ventricular rate response during AF than atrio-ventricular conduction properties.28

Although not the main purpose, this study extends previous observations on the relation between electrical remodelling, autonomic activity, and early AF recurrences. This study revealed that subjects who responded to exercise with fibrillatory rate changes had a higher chance to remain in sinus rhythm, while non-responders had a high risk for AF recurrence. On the one hand, a low baseline fibrillatory rate has been suggested as marker of lesser electrical remodelling which was associated with lower risk for AF recurrences.6 On the other hand, an abnormal autonomic control has also been suggested to contribute to electrical remodelling and consequently to a higher risk for AF recurrences.8

Limitations

This study is limited by its sample size including a heterogeneous patient population with different cardiac pathologies and medications. Nevertheless, in agreement with experimental and clinical studies, different types of rate responses to exercise could be identified. Interestingly, they were associated with baseline fibrillatory rate and cardiovascular outcome but not with other clinical variables. Of special note, underlying heart disease, AF duration, or cardioactive medication did not affect fibrillatory rate responses to exercise in univariate and multivariate analysis but the sample size may have prohibited its detection. Although the net effects of exercise on sympathetic stimulation, and/or vagal withdrawal cannot be quantified in the individual patient, importantly, ventricular responses were consistent among all individuals indicating a comparable autonomic stimulus.

Finally, spatio-temporal QRST cancellation and time-frequency analysis were performed at baseline and immediately after exercise termination (not during exercise) due to substantial exercise-induced moving artefact and noise.

Conclusions

Exercise-induced changes in the autonomic nervous system modulate atrial electrophysiological properties, which can be analysed by means of time–frequency analysis. Patients with faster fibrillatory rates at rest and consequently no rate response to exercise are characterized by a higher degree of electrical remodelling which is associated with a reduced sensitivity to autonomic modulation and possibly greater risk for early AF recurrences. Thus, exercise testing may add valuable information on the autonomic and electrophysiological status of the atria in the individual patient with AF.

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Conflict of Interest: none declared.

References