Exercise Testing for Non-Invasive Assessment of Atrial Electrophysiology in Patients with Persistent Atrial Fibrillation

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Abstract

The abstract with its heading should not be more than 75 mm long. This is equivalent to 18 lines of text. Leave 1 line space at the bottom of the abstract before continuing with the next heading. The autonomic nervous system modulates atrial electrophysiology in atrial fibrillation (AF). The purpose of this study was (1) to non-invasively characterize the effects of exercise on atrial fibrillatory rate as marker of atrial refractoriness in patients with persistent AF and (2) to identify clinical and electrocardiographic predictors for rate response.

In 15 patients with persistent AF, mean fibrillatory rate assessed by spatiotemporal QRST cancellation and time-frequency analysis remained unchanged with exercise. There were, however, 6 responders (rate change > 2.5%), with either a rate increase (N=5, 25±9 fpm) or decrease (N=1, -13 fpm). Absolute fibrillatory rate change (%) correlated inversely with baseline fibrillatory rate (r= -0.543, p=.045).

In conclusion, sympathetic activation by exercise modulates atrial electrophysiology in some patients which can be monitored using time-frequency analysis. Higher baseline fibrillatory rates are associated with less autonomic modulation indicating advanced electrical remodeling.

1. Introduction

The autonomic nervous system has modulating effects on atrial electrophysiology in patients with atrial fibrillation (AF) and may support both induction and termination of the arrhythmia [1]. One mechanism behind this is that both vagal as well as sympathetic stimulation reduce atrial refractory periods and increase their heterogeneity.

Sympathetic stimulation using exercise testing is widely used in clinical practice for evaluation of coronary heart disease and/or diagnosis of exercise induced arrhythmias but has not been applied for non-invasive assessment of atrial electrophysiology during AF. Fibrillatory rate obtained from the surface ECG has been introduced as a marker for atrial refractoriness and complexity of AF [2]. Several studies made use of fibrillatory rate in order to monitor electrophysiological properties of the fibrillating atria for analyzing antiarrhythmic drug actions or spontaneous diurnal variability [3] but data on response to exercise are lacking.

Consequently, the purpose of this study was (1) to non-invasively characterize the effects of exercise on atrial fibrillatory rate as marker of atrial refractoriness in patients with persistent AF and (2) to identify clinical and electrocardiographic predictors for rate response.

2. Methods

Study protocol: This observational study included 15 consecutive patients with persistent AF undergoing exercise testing. Clinical and echocardiographic parameters were assessed and all patients provided written informed consent before study participation. The clinical characteristics of the study population are summarized in Table 1.

Gender (male/female)	10/5
Age (years)	55±13
LA diameter (mm)	46±4
LV ejection fraction (%)	60±6
Etiology	
Hypertension	9 (60%)
Valvular heart disease	1 (7%)
Lone AF	5 (30%)
Medication*	
Digitalis	7 (47%)
Calcium channel blocker	6 (40%)
Beta blocker	7 (47%)
AF duration (months)	13±24

* more than one possible

Table 1: Clinical and Echocardiographic Characteristics of the Study Population (n = 15)

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

ECG acquisition and analysis: A continuous 3-lead ECG (Predictor, Dr. Kaiser; 200 Hz sampling rate) was recorded with the subject in relaxed supine position and again after bicycle exercise testing. Fibrillatory rate was assessed in 1-minute ECG segments at baseline and immediately after termination of exercise with spatiotemporal QRST cancellation and time-frequency analysis.

Time–frequency analysis [4] was performed using a bipolar modification of V1 (bipolar lead between below left clavicle to right sternal border at the 6th intercostal space). In short, QRST complexes were subtracted using spatiotemporal QRST cancellation and the resulting fibrillatory signal was downsampled to 50Hz 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 modeled 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 leastsquares estimation. The frequency shift needed to achieve optimal matching then yields a measure of instantaneous fibrillatory rate of a 2.5-second electrocardiographic segment (overlapping with 1 segment each second) and is trended as a function of time (Figure 1). Mean fibrillatory frequency was converted to fibrillatory rate (rate = frequency x 60).

An atrial rate response to exercise was considered present if atrial rate changed by >±2.5 % (supposing ±2.5% as natural variation of fibrillatory rate in one-minute recordings) [5].

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. Responders and non-responders were compared using Student's t-test for unpaired data for continuous and Chi^2-test for categorial variables. Patient characteristics and response to exercise were correlated using Pearson correlation. A p-value <.05 was considered statistically significant.

3. Results

One patient was excluded from further statistical analysis due to an inadequate ventricular rate increase of only 5 bpm (11%) after exercise.

Exercise had no influence on mean fibrillatory rate (410±48 vs. 416±46 fpm, p=NS) while ventricular rate increased from 90±17 to 115±20 bpm (p<.001).

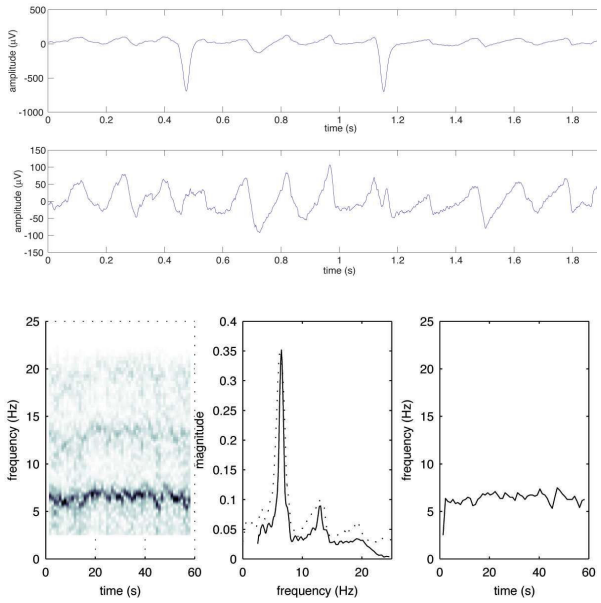

Figure 1: Time-frequency analysis of AF. Two seconds (out of a 1-minute recording) of an ECG signal from a patient with AF (upper panel), and the same interval after spatiotemporal QRST cancellation (middle panel, amplitude scale is magnified five times). This fibrillatory signal is then subjected to spectral analysis techniques. Time-frequency distribution (left box), power frequency spectrum (middle box), and frequency trend (right box).

Six patients responded to exercise with either an increase in fibrillatory rate (N=5, 25±9 fpm) or decrease (N=1, -13 fpm), while the remaining patients (N=8) did not show a response. Responders' ventricular rate increase was similar (27±7 vs 24±9 bpm, p=NS), indicating a comparable adrenergic stimulation during exercise but they had a lower baseline fibrillatory rate than non-responders (385±15 vs. 435±53 fpm, p=.046).

The change of fibrillatory rate (%) correlated inversely with baseline fibrillatory rate (r= -.543, p=.045; Figure 2). No other clinical or echocardiographic variable was associated with fibrillatory rate response.

4. Discussion and conclusions

Main findings: This study, for the first time, has shown that, (1) an increase in sympathetic tone by exercise modulates atrial electrophysiology expressed by an increase or decrease in fibrillatory rate in some patients and (2) a high baseline fibrillatory rate is associated with less autonomic modulation expressed by a lacking rate response.Comparison with previous studies: The autonomic nervous system has complex effects on atrial electrophysiology, namely atrial refractoriness which may support both initiation and sustenance of AF, but also

may terminate it.

Since atrial rates obtained from the surface ECG closely reflect intraatrial rates and consequently atrial refractoriness, atrial fibrillatory rate seems to be ideal for monitoring the effect of autonomic tone changes – either spontaneous (circadian) or by autonomic manoeuvres provoked. Indeed, the circadian variability of atrial fibrillatory rate has been explored, [6;7] and the response to carotid sinus massage [8] or head-up tilt testing [9] analyzed. Common findings were an increase in fibrillatory rates due to adrenergic stimulation as during daytime or with head-up tilting, which is agreement with our observation that the dominant response to exercise was a rate increase. An increase in sympathetic activation may enhance automatism or triggered activity [10] and has also been shown to decrease atrial refractory periods [11].

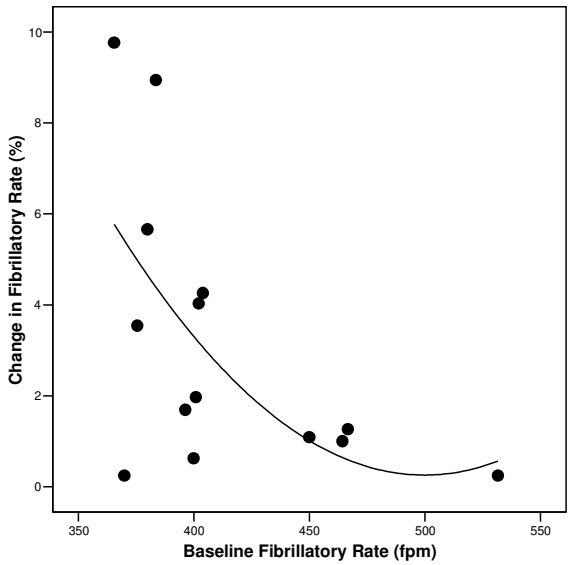

Figure 2: Relation between baseline fibrillatory rate and response to exercise (N=14). r= -.543, p=.045

There was, however, also one patient with a substantial exercise-induced fibrillatory rate decrease. That this response exists is supported by a previous Holter study [7] showing that in a subgroup of patients with persistent AF, fibrillatory rate decreased concomitantly with an increase in ventricular rate in the morning hours when sympthateic activation dominates. Furthermore, clinical observations indicate that AF can be self-terminated by exercise in certain patients [12] which may – as reported for drug-induced termination [3] – be precipitated by a fibrillatory rate decrease.

The majority of our patients did, however, not respond to exercise with fibrillatory rate changes. Interestingly, a high baseline fibrillatory rate was the only predictor for this behavior suggesting a lesser degree of autonomic modulation when electrical remodeling progresses. This finding is in concordance with one previous study showing that AF patients with a higher fibrillatory rate displayed a lesser degree of circadian atrial rate variability [6].

Conclusions: Sympathetic activation by exercise modulates atrial electrophysiology which can be monitored by means of time-frequency analysis. Patients who do not respond to exercise with a fibrillatory rate change may have developed a higher degree of electrical remodeling (“atrial burnout”) which is associated with less autonomic modulation. Consequently, exercise testing may add valuable information on the electrophysiological status of the atria in the individual patient.

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