Exercise Heart Rate Acceleration Patterns during Atrial Fibrillation and Sinus Rhythm

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Background: Patients with atrial fibrillation sustain a significant lower exercise tolerance compared to those in sinus rhythm, even while seemingly in adequate rate-control.

Methods: Exercise testing was performed during atrial fibrillation and after electric cardioversion for 30 patients who were initially treated with AV modifying agents and were considered in adequate rate control. Heart rate parameters were obtained during all exercise stages, and a graphic display of heart rate acceleration was obtained. For those patients who remained in sinus rhythm, an additional exercise test was performed after 1 month.

Results: During atrial fibrillation, heart rate at the completion of Bruce stage 1 and the peak exercise heart rate were significantly higher when compared to sinus rhythm (120 ± 10 bpm vs. 98 ± 11 bpm and 164 ± 16 bpm vs. 129 ± 11 bpm respectively, $p < 0.001$ for both). The time to peak exercise heart rate was significantly shorter during atrial fibrillation (3.5 ± 1 min vs. 6.5 ± 1.5 min, $p < 0.001$), and the total exercise duration was subsequently shorter as well (6 ± 2 min vs. 8.5 ± 2 min, $p < 0.001$). Treatment with beta-blockers prior to exercise did not affect the earlier peaking of the heart rate. After 1 month, similar time to peak heart rate and similar exercise performance were observed among patients, who remained in sinus rhythm, when compared to the post-cardioversion exercise test.

Conclusions: In patients with atrial fibrillation, exercise heart rate acceleration displays a specific pattern of early peaking. Earlier heart rate peaking occurs regardless of ample rate control while at rest or mild physical activity and contributes to overall lower exercise performance.

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A wide variety of symptoms may be present for patients with atrial fibrillation (AF), ranging from a mild sense of palpitation to frank heart failure. Decreased exercise tolerance stands out among these as especially debilitating. AF has been found to reduce exercise capacity in the order of 15–20%,¹ thus causing a true reduction in the quality of life for many and presenting a great treatment challenge for the physicians. It is not uncommon for exercise intolerance to be the presenting symptom of AF^{2,3} and for the strictest rate control at rest and during routine daily activity to fail in adequately control heart rate during moderate exercise.^{4,5} Successful cardioversion and the maintenance of sinus rhythm (SR) thereafter improve exercise ca-

capacity and lower the heart rate during exercise, thus providing one of the several advantages of SR over AF.^{2,6}

Several mechanisms have been linked the low exercise tolerance during AF, including the tachycardia effect on the left ventricular performance,⁷ lower maximal oxygen uptake,² and the effect of the medications. Rapid initial acceleration of the heart rate during exercise while in AF may provide an additional mechanism to the limitation in exercise tolerance. We therefore sought to demonstrate the difference in the heart rate acceleration pattern during exercise and its possible effect on exercise durability, before and after AF cardioversion to SR.

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METHODS

Consecutive patients diagnosed with persistent AF, who were designated by their treating physician to undergo direct-current (DC) cardioversion and had adequate ventricular rate control (see below), were prospectively enrolled to this study. Patients had to be in AF rhythm at the time of enrollment. Patients were not eligible to be enrolled to the study if they had significant heart failure (New York Heart Association [NYHA] III-IV), a permanent pacemaker, inadequate anticoagulation prior to DC (defined as failure to document international normalized ratio levels of 2–3 during the month before DC), history of AV junction conduction abnormalities, inability or contraindications to perform exercise, and inability to provide informed consent. A complete blood count and a thyroid panel were obtained prior to enrollment to the study in order to exclude anemia and hyperthyroidism, respectively, as possible causes for faster AF rate and decreased exercise tolerance.

The study was approved by the Ethical Committee of our hospital.

STUDY PROTOCOL

The study patients continued the use of their rate control medications prescribed by their referring physician until cardioversion was performed. Adequacy of the rate control during AF was conferred by a 24-hour ECG (Holter) recording, at which a mean rate of 100 bpm or less was required⁵ with at least 18 hours of interpretable monitoring. Upon admission, a symptom-limited exercise testing was performed on a standard treadmill device (General Electric T2100, Milwaukee, WI, USA) using the Bruce protocol. The test was terminated upon the occurrence of one the following: chest pain, dyspnea, significant fatigue, ventricular arrhythmias, hypotension, or ST-segment elevation, or >2-mm ST depression. The patient's heart rate was recorded prior to the test, at the time of its initiation, and at every minute thereafter by an intrinsic software. The heart rate achieved at the end of the first stage (3 minutes) was defined as the heart rate representing "moderate" exercise (approximately five metabolic equivalents). Blood pressure and complete electrocardiogram were obtained at the beginning of the test, at the end of every stage, and during recovery. A graphic display of the patient's heart rate during the exercise was obtained by the intrinsic software.

Within 24 hours of the first exercise test, SR was obtained by a DC cardioversion and all rate control medications were discontinued. An identical protocol exercise test was repeated within 1 week, after allowing at least five half-life periods to pass after the discontinuation of the rate-control medications (three half-life periods for Digoxin).^{8,9}

The patients resumed taking their medication used prior to cardioversion following the second exercise test. One month following discharge, the presence of SR was verified by an additional Holter examination and an ECG performed at the time of the medical interview. In case SR was maintained, a third, identical exercise test was performed.

STATISTICAL ANALYSIS

The significance levels were set at 0.05. Data were presented as mean and standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. Comparison between exercise performance over time was performed by Wilcoxon signed-rank test. The box plot present the nonparametric distribution of the exercise performance measurements in each time period. Spearman's correlation analysis was used to determine possible relations between examinees' baseline characteristics (including medication dosages) and heart rates during the different exercise stages and the time to peak heart rate at exercise.

Data were analyzed with SPSS software version 17.0 (SPSS Inc. Chicago, IL, USA).

RESULTS

Patient Characteristics

Thirty consecutive patients were enrolled in this study that was conducted between April 2009 and February 2010. The study participant's baseline clinical and demographic characteristics are summarized in Table 1. All patients had persistent AF of 5 ± 3 (mean $\pm$ SD) months duration prior to enrolment. None of the patients had a history of ischemic or valvular heart disease. Twenty-three of the study patients (76%) were in NYHA functional class 1. ECG tracings obtained during AF and prior to the performance of exercise testing did not demonstrate intraventricular conduction disorder or significant repolarization changes in any of the study patients. Similarly, ECG tracings obtained following cardioversion demonstrated normal

Table 1. Baseline Characteristics of the Study Patients^a

Male, n (%)	21 (70)
Age	57.5 ± 11.5
Hypertension, n (%)	16 (52)
Diabetes, n (%)	12 (40)
Peripheral arterial disease	8 (26)
Hemoglobin (g/dL)	13 ± 10
Thyroid stimulating hormone (milli international units/liter)	2.5 ± 1
Free T4 (picomol/liter)	10 ± 7
Free T3 (picomol/liter)	4.5 ± 3
LVEF	56 ± 12
LVEDV-I (ml/m ²)	34 ± 28
LVESV-I (ml/m ²)	15 ± 13
LAV-I (ml/m ²)	31 ± 19
Duration of AF, months ^b)	5 ± 3
Heart rate during Holter exam	86 ± 8
NYHA functional class, n(%)	
I	23 (76)
II	6 (19)
III	1 (3)
Beta-blocker daily dosage, mg (mean ± SD)	
Atenolol (five patients)	75 ± 25
Bisoprolol (25 patients)	10 ± 5
Digoxin daily dosage ^c , mg	0.125 ± 0

^aPercentages may not total 100 due to rounding (plus-minus values indicate mean ± SD);

^bCounted from first ECG documented arrhythmia;

^cDigoxin was used by 10 (33%) of the study patients.

AF = atrial fibrillation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

atrioventricular conduction. Echocardiographic studies were obtained for all study patients prior to exercise, and were viewed and interpreted by an expert echocardiographer. The left ventricular ejection fraction (LVEF) was within normal limits for all the study patients, excluding three patients who had an estimated LVEF lower than 55% (35% for two patients and 30% for the third patient)—all considered to be secondary to tachycardia-induced cardiomyopathy by the study investigators due to the global, rather than regional, dysfunction profile of the decreased left ventricular function. Clinical and electrocardiographic data suggestive of coronary artery disease were otherwise absent in the entire study population. All patients were treated by beta-blockers as the AV modifying agent (atenolol, five patients, 75 ± 25 mg/day, bisoprolol

25 patients, 10 ± 5 mg/day) and 10 (33%) were treated concomitantly with Digoxin. On the 24-hour Holter examinations that were obtained by all the study patients while at AF and prior to the initial exercise test, the average daily rate was 86 ± 8 bpm, (maximal rate 99 ± 10 and minimal rate 74 ± 11).

Exercise Performance during AF and after Cardioversion

Average resting heart rate prior to exercise during AF was significantly higher when compared to SR (86 ± 8 bpm vs 68 ± 12 bpm respectively, $P < 0.001$). Heart rates at moderate exercise (120 ± 10 bpm vs 98 ± 11 bpm) and peak exercise (164 ± 16 bpm vs 129 ± 11 bpm, $P < 0.001$ for both) displayed similar behaviors. The mean average time to peaking of the heart rate and the mean overall exercise duration were significantly shorter during AF (3.5 ± 1 minutes vs 6.5 ± 1.5 minutes and 6 ± 2 minutes vs 8.5 ± 2 minutes, respectively, $P < 0.001$ for both). The differences in peak exercise heart rates and in total exercise durations are illustrated in Figure 1A and B, respectively. Figure 2 illustrates the individual changes in the time to the peaking of the heart rates. In Figure 3, typical individual examples of heart rate elevation patterns at AF and at SR from one of the study patients are shown. A higher proportion of patients developed shortness of breath leading to exercise discontinuation during AF than during SR (21 [70%] vs 9 [30%] patients, respectively, $P = 0.02$). Other reasons for exercise termination were leg pain (three patients in AF group, two patients in SR groups), hypotension (one patient in each group), and ST segment changes (one patient in SR group).

By using Spearman's correlation analysis, we examined for possible relation between heart rates at rest and at the different exercise stages and the daily dose of beta-blocker used by the patients. Beta-blocker dosage correlated only with the lower resting heart rate ($r = 0.61$, $P = 0.026$) during AF, but not with heart rates during the various exercise stages or with the heart rate acceleration parameter. Additional baseline characteristics were tested for their possible relation with heart rate at rest and during the different exercise stages. These characteristics included the baseline ejection fraction, NYHA functional class, age, duration of AF, and the mean heart rate during a 24-hour Holter

Figure 1. Box plots of various exercise parameters in AF and at SR as achieved immediately after cardioversion and after 1 month. *Top Panel:* Peak exercise heart rates. *Bottom Panel:* Total exercise durations.

examination performed prior to the exercise. Of these, the only significant statistical relation conferred was between younger age and higher peak exercise heart rate ($r = 1.65$, $P = 0.021$, other data are not shown).

**Heart Rate Response during Exercise
1 Month after Cardioversion**

One month after cardioversion, 20 of the 30 originally enrolled (67%) study patients remained in

Figure 2. Plot indicating changes in time to peak exercise heart rate during AF and SR. See Table 2 for statistical significance.

SR. The drug therapy used by the patients was recorded and was found identical to that used at the time of the enrollment to the study in all patients who remained in SR. No significant differences were observed in the various parameters of the first postcardioversion exercise test and the one performed 1 month later (Table 2). Figure 1A and B illustrate peak heart rates and total exercise durations at 1 month after cardioversion, respectively. There was no difference in the occurrence of shortness of breath leading to exercise discontinuation (28% of patients at 1 month after cardioversion vs 42% after cardioversion, $P = \text{NS}$). There was a trend toward higher peak heart rate at the exercise performed 1 month following cardioversion, yet this did not reach statistical significance.

DISCUSSION

In this study, we have shown that patients with AF that were treated by a rate control strategy and had an average heart rate of 86 bpm on a 24-hour Holter monitoring exhibited a unique heart rate acceleration pattern of earlier peaking during the performance of exercise, a pattern that was not evident upon the subsequent return to SR. Earlier heart rate peaking occurred regardless of the rate-control medications used by the patients or of its dosages. Earlier exercise heart rate peaking during AF was accompanied by a significant decrease in exercise tolerance and with more frequent

occurrences of shortness of breath and fatigue as the limiting symptoms during a standard treadmill exercise test. After the establishment and maintenance of SR for 1 month using the same medications that were utilized prior to the cardioversion and repeating the exercise test, we show that, heart rates at the different exercise stages were similar to the ones observed after cardioversion, although a trend toward an increased peak heart rate was observed. The heart rate peaking was similar as well in these two exercise tests. Heart rate peaking occurred significantly later at both exercise tests performed following cardioversion when compared to exercise during AF, without a significant difference that was observed between immediate and 1-month post-cardioversion.

In accordance with these findings, we assume that the earlier peaking of the heart rate during exercise described in our work confers an important effect on exercise duration and on exercise-limiting symptoms for patients in AF rhythm. This observation provides an additional mechanism for the previously established phenomenon of low exercise tolerance described in AF patients.^{2,4–7}

Heart Rate Acceleration Physiology during AF and SR

During the early phases of exercise in SR, elevation in HR is mediated predominantly by the withdrawal of parasympathetic control of the

Figure 3. An example of heart rate elevation patterns as recorded during exercise by the intrinsic software during AF (top) and at SR (bottom) from one of the study patients. Rapid acceleration of the heart rate accompanied by low exercise duration is evident at AF.

sinus node (SN), while in later stages, it is mediated by SN acceleration due to increased sympathetic tone and circulating catecholamines.¹⁰ Conversely, in AF, the ventricular response is governed by the atrio-ventricular node (AVN) and its refractoriness characteristics. As described in earlier studies,^{11–13} acetylcholine possesses significant hyperpolarizing and depressive effects on the AV nodal action potential, which may occasionally even lead to conduction block during regular slow atrial rhythm. It is plausible to assume that part of the earlier peaking of the heart rate during exercise observed in AF rhythm is secondary to the significantly reduced (that could also be considered as practically absent) parasympathetic impact on the AVN. Theoretically, the utilization of beta-blockers may possess an attenuating effect on earlier peaking of the heart rate. Nevertheless, Spearman's analysis performed in our study failed to establish a correlation between heart rates at the different exercise stages and the daily dosages of beta-blockers used by the study patient.

Prior Studies

Hornsten and Bruce were among the first to characterize the exercise heart rate pattern during AF in a study conducted in 1968,¹⁴ noticing that the increased heart rate at rest during AF continued throughout the exercise and into recovery. In a later study, Corbelli et al.¹⁵ described three patterns of heart rate occurring during exercise in a heterogeneous group of patients with AF: tachycardia throughout exercise, bradycardia throughout exercise, and tachycardia early with a plateauing of the heart rate. At this trial, patients were not cardioverted to SR in order to compare their rate response later and the different heart rate response patterns were at least partially attributed to concomitant cardiovascular disease. In a more recent study, Yigit et al. examined the exercise performance and different heart rates during AF and SR after cardioversion.¹⁶ The authors noticed that peak heart rate was significantly higher during AF, and that most of this increase occurred during the first stage of the Bruce protocol. No information was given regarding the medications used by the study patients, as well as the rate control status during daily activity (as patients were not required for a Holter monitoring prior to cardioversion). The mean resting and peak exercise heart rates were higher than those observed in our study (96 bpm vs 86 bpm and 185 bpm vs 161 bpm, respectively), possibly due to different drug regimens or accompanying diseases. No follow-up exercise was performed at a later time for comparison.¹⁶

Initial results from large multicenter clinical trials such as the Atrial Fibrillation follow-up Investigation of Rhythm (AFFIRM) or the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE) studies^{17,18} demonstrated no clear advantage for SR over adequate rate control in terms of cardiovascular outcomes and quality of life, while other large studies such as Pharmacological Intervention in Atrial Fibrillation (PIAF)¹⁹ showed some advantage in terms of exercise performance. Of note, in none of these mentioned studies were the same patients directly compared prior to and after cardioversion to SR. It was only in later subanalyses of these and other multicenter trials that the advantages of SR over AF in terms of survival and quality of life among specific subpopulations were clearly demonstrated.^{20–22} Additional studies conducted in order to examine the contribution of

Table 2. Exercise Performance of Study Patients who Retained SR at 1 Month Postcardioversion^a

	Postcardioversion Exercise	One Month Post Cardioversion Exercise	P- Value
Heart rate prior to exercise, bpm (mean $\pm$ SD)	68 $\pm$ 12	70 $\pm$ 10	0.86
Heart rate at the end of Bruce stage 1 exercise, bpm (mean $\pm$ SD)	96 $\pm$ 11	96 $\pm$ 9	0.16
Peak heart rate during exercise, bpm (mean $\pm$ SD)	129 $\pm$ 11	134 $\pm$ 18	0.20
Time to peaking of the heart rate, minutes (mean $\pm$ SD)	7 $\pm$ 2	7 $\pm$ 2	0.94
Total exercise duration, minutes (mean $\pm$ SD)	9 $\pm$ 2	9 $\pm$ 2	0.22
METs achieved during exercise	12 $\pm$ 7.0	12 $\pm$ 8.0	0.89

^aTwenty-four patients remained in SR after 1 month. Values were obtained automatically by treadmill's intrinsic software and rounded to the nearest complete number (Plus-minus values indicate mean $\pm$ SD). bpm = beats per minute; METs = metabolic equivalents. Other abbreviations are same as in Table 1.

SR to exercise tolerance showed these favorable effects as well,^{1,2,6,16,23–25} leading to the current conception that improvement in exercise tolerance is one of the true advantages of SR over AF with rate control.

In the current era of effective ablation therapy for the treatment of AF, improved exercise tolerance is yet another important advantage SR exerts over AF rhythm. Improved exercise tolerance has been shown to be associated with an improved quality of life and overall prognosis,^{26,27} thus adding an important perspective to the ongoing discussion regarding “rate vs. rhythm control” strategy in the growing population of patients with persistent AF.

Study Limitations

Our study cohort was small and included patients lacking concomitant heart diseases. Studies of larger magnitudes and that will incorporate a wider spectrum of patients with various heart diseases are needed to authenticate our results. Echocardiographic examinations were not performed after cardioversion in order to examine the possibility of ejection fraction or atrial performance improvement immediately after cardioversion. The existence of hemodynamically significant atherosclerotic coronary artery disease was not excluded for the study patients and thus its existence could have potentially influenced exercise performance. Nevertheless, echocardiographic examinations did not show regional wall motion abnormalities, none of the ECG tracings that were obtained was suggestive of the existence of ischemic coronary disease and none of the study pa-

tients described symptoms suggestive of ischemic coronary disease in the medical interviews performed. Maximal oxygen consumption during exercise was not evaluated in this study. Evaluation of oxygen consumption during exercise could have potentially provided additional physiological mechanisms to the differences in the exercise tolerance and to the shortness of breath that occurred in our study patients, both during AF and SR. Beta-blocker therapy was suggested in the past to be associated with a reduction in exercise capacity; it is therefore possible that some of the improvement in exercise duration and shortness of breath during exercise were due to the withdrawal of these drugs. The current recommendations for adequate rate control suggest that patients should be kept at a rate of 60–80 bpm at rest and at 90–115 bpm during moderate exercise. However, a recent study performed by the RACE investigators²⁸ showed that a more lenient approach for rate control is not inferior to strict rate control and is more convenient, because fewer outpatient visits, fewer examinations, lower doses, and less often combination of drugs are needed. We therefore used the criteria of a mean heart rate of 100 bpm suggested originally by the AFFIRM investigators⁵ in order to define adequate rate control. The mean heart rate observed in our study cohort at the end of the first Bruce stage of exercise was 120 bpm, indicating that the patients were reasonably rate controlled. We performed repetitive exercise tests in order to demonstrate improved exercise tolerance after cardioversion to SR. We are not able to exclude a training effect to be in part responsible for the improved exercise performance following cardioversion, yet it would be difficult to expect such an effect to

exist, following one or two exercise tests within 1 month.

CONCLUSIONS

Exercise heart rate during AF is characterized by early peaking and higher heart rates at all stages when compared to SR, thus contributing to lower overall exercise durability. Adequate heart rate control at rest and daily physical activity fails to either predict exercise heart rate or to prevent its early peaking. Slower acceleration of the heart rate during exercise is yet another advantage SR retains over AF rhythm, contributing along with other factors to an improved quality of life.

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