Rate-Dependent Flecainide Effects on QRS Duration in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is an arrhythmia characterized by highly irregular atrial depolarization. Among various commonly used antiarrhythmic drugs, flecainide is known to decrease conduction velocity in a rate-dependent manner. The aim of this study was to establish a protocol to monitor flecainide's rate-dependent conduction slowing, during physiologic increases in heart rate (HR) in patients with AF. QRS duration at rest and during symptom-limited bicycle exercise stress was measured in 9 patients with persistent AF before and during oral flecainide administration. Flecainide-induced QRS duration prolongation was more pronounced during exercise than at rest. In patients with AF, this characteristic can be monitored and quantified by measuring QRS duration under resting and exercise conditions, helping in determination of antiarrhythmic efficacy and preventing proarrhythmic effects in the individual patient.

1. Introduction

Atrial Fibrillation (AF) results from multiple, rapidly changing and spatially disorganized activation wavelets sweeping across the surface of the atria [1]. It is an arrhythmia characterized by highly irregular atrial depolarisations and irregular ventricular response intervals.

Among various commonly used antiarrhythmic drugs, flecainide, a sodium channel blocker, is known to effect conduction velocity in a rate-dependent manner. It has been found that exercise causes a rate-dependent augmentation of flecainide's effects on ventricular conduction by enhancing state-dependent sodium channel blockade [2]. In addition, the effects of flecainide to increase atrial action potential duration and refractoriness were found to be enhanced by the rapid rates typical of AF in animal settings [3]. A suitable method for evaluating flecainide's effect at different heart rate (HR) in clinical setting could be useful. Therefore, the aim of this study was to establish a protocol to monitor flecainide's rate-dependent conduction slowing, during physiologic increases in HR in patients with persistent AF.

To achieve this goal, a four-phase protocol was introduced: QRS duration was compared before and after flecainide loading during rest condition and exercise, in order to highlight differences of drug effect due to different HR. In addition, the increase in HR was obtained by means of a simple and physiologic test that could be useful to derive information regarding the individual patient's response to flecainide.

2. Methods

2.1. Experimental protocol

Nine patients (6 men/3 women, mean age 54 ± 11 years), referred for cardioversion of AF, were included in this study. A history of AF was present for an interval ranging from some hours to 96 months (mean AF duration 18 ± 32 months). Echocardiographic characteristics were: left atrial diameter 47 ± 4 mm, and left ventricular ejection fraction $61 \pm 6\%$. The pharmacological therapy included digitalis in 4 patients, calcium channel blockers in 3 and beta blockers in 5 (more than one drug is possible for each patient).

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. Exercise testing was repeated after $3 - 5$ days of flecainide loading ($200 - 300$ mg/day). Thus, four clinical experimental conditions were defined: i) rest (R); ii) exercise (E); iii) rest with flecainide (RF); iv) exercise with flecainide (EF).

A continuous 3-lead (X, Y, Z) ECG (Predictor, Dr. Kaiser; 2000 Hz sampling rate) was recorded, but only lead Y was further analyzed. QRS detection was automatically performed and visually checked: missed/misdetected beats were corrected using an interactive software. Premature ventricular contractions or beats with aberrant conduction were identified.

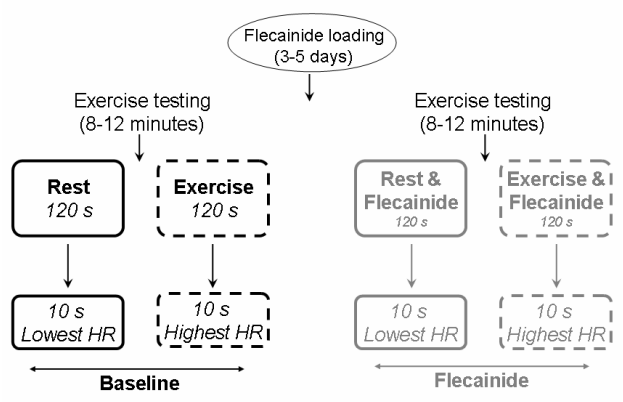

Figure 1. Protocol phases: data were collected in rest and during exercise and acqusitions were repeated after flecainide injection.

2.2. ECG processing

In each phase of the protocol, a 10-second ECG segment was analyzed. In particular, to choose the segment, the mean HR was computed over 10-second windows, sliding every second. At rest the 10-second segment with the lowest HR was selected, whereas the one with the highest HR was chosen in exercise phases in order to enhance different effects of flecainide due to different HR.

For each analyzed segment, a QRST template was computed as the average of all the normal QRST complexes belonging to that segment [4]. An example of aligned QRST complexes and the resulting QRST template is shown in Figure 2, where the absence of P wave replaced by a fibrillatory baseline is clearly observable.

The signal-averaging technique requires that each new beat is aligned against a reference beat, here defined as the first normal beat of the segment. Cross-correlation was used for alignment: a correlation window of 60 ms was considered and located on the most rapidly changing part (upstroke and downstroke) of the QRS complex. A correlation greater than 0.9 was required for acceptance. To reduce baseline wandering effects (mainly occurring during exercise), a high-pass filtering (0.5 Hz) was performed before beats averaging. Finally, onset and offset of the QRS complex were manually detected (D.H.) and then QRS duration was computed. At least 10 QRST complexes were averaged in each segment to obtain the QRST template.

2.3. Statistical analysis

Data are reported as mean $\pm$ one standard deviation. The statistical analysis was carried out using Student's t-test for paired data. A p value of at least 0.05 was considered statistically significant.

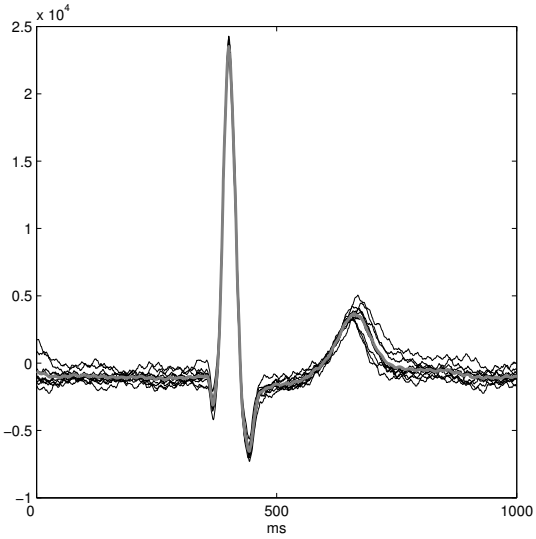

Figure 2. Superimposition of QRST complexes aligned according to cross-correlation (black line) shown with the resulting QRST template (bold grey line).

3. Results

In the following results will be presented and discussed by separating effects due to exercise from those induced by drug infusion.

3.1. Exercise effect

Exercise effect is shown in Figure 3, where rest values (black bars) are compared with exercise ones (white bars). Exercise caused, as expected, an increase on HR and its effect on HR was evident (and with similar behaviour) both before (R vs. E) and during (RF vs. EF) flecainide administration.

However, the effect of exercise on QRS duration was different after drug loading. In fact, at baseline, QRS duration shortened with exercise, whereas after drug loading, exercise was associated with a QRS duration prolongation.

3.2. Flecainide effect

Flecainide did not change HR significantly, even if it tended to decrease it.

On the other hand, flecainide increased QRS duration both at rest and during exercise. Its property of decreasing conduction velocity, thus increasing QRS duration, is much more evident during exercise.

An example of this effect on QRS prolongation for a patient is shown in Figure 4. The QRST template before flecainide loading is shown superimposed to the one af-

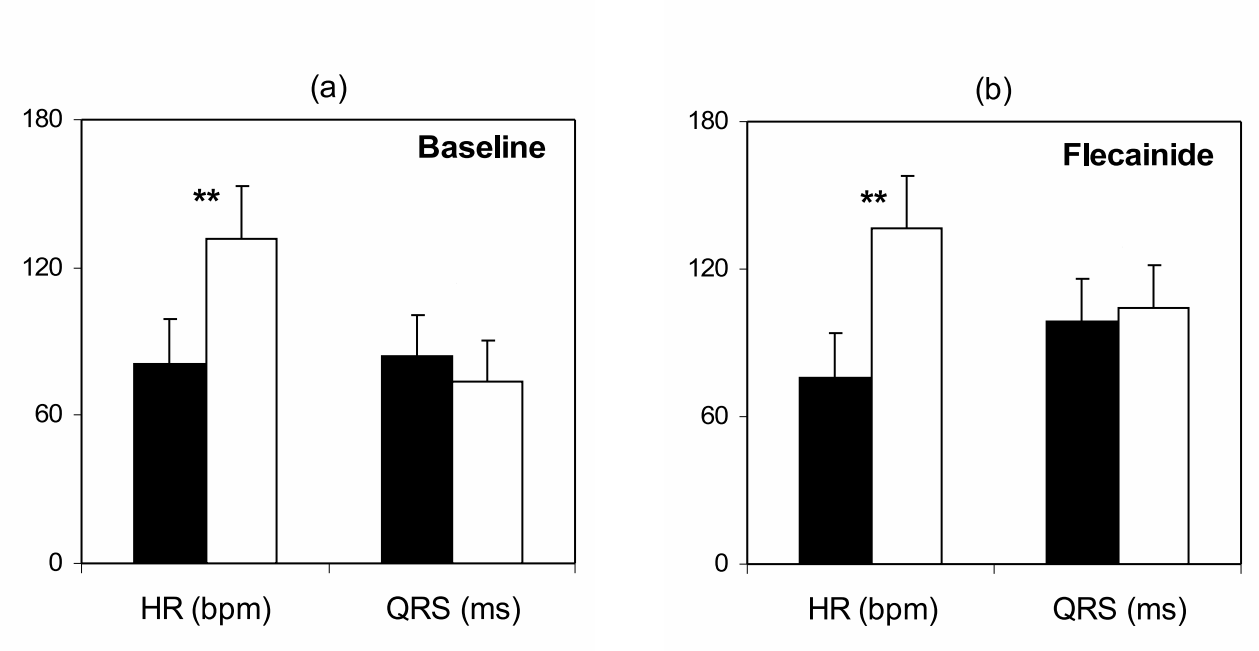

Figure 3. Exercise effect during baseline and after flecainide loading. Rest values (black bars) are compared with exercise ones (white bars), for HR and QRS duration. Significant differences are found between rest and exercise phases. It is worth noting the inverse behaviour of exercise stress after flecainide loading on QRS duration. * $p < 0.05$, ** $p < 0.001$.

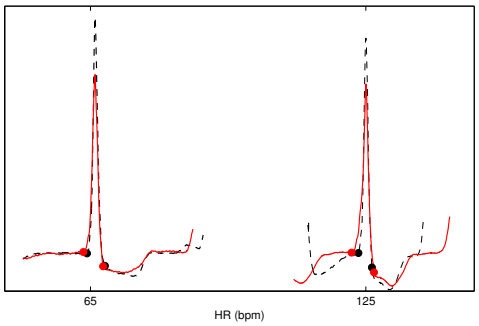

Figure 4. Example of flecainide's effect on QRS duration for a patient. The QRST template before flecainide loading (dotted grey line) is shown superimposed to the one after drug administration (black line) at the lowest and highest heart rate (about 65 and 125 bpm, respectively). QRS beginning and end are represented as well. The major prolongation of QRS duration at higher HR is observable.

ter drug administration at the lowest and highest heart rate (about 65 and 125 bpm, respectively).

Results regarding flecainide effect at different HR for the whole population are shown in Figure 5, where box plots of delta QRS duration (i.e., the difference between values after flecainide loading and values before drug loading), at rest and during exercise are presented. It can be noted a significant higher increase in QRS duration in exercise phase, obviously corresponding to a higher HR.

In all patients but one, an higher increase in QRS duration due to flecainide was observed during exercise, as shown in Figure 6. The only patient not presenting this behaviour was the one having the lowest HR both in rest and in exercise phases.

4. Discussion and conclusions

Among various commonly used antiarrhythmic drugs, flecainide is known to decrease conduction velocity in a

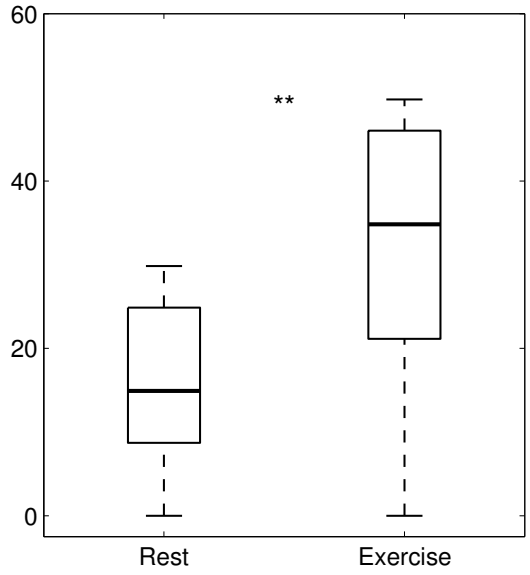

Figure 5. Boxplots of delta QRS duration (i.e., the difference between values after flecainide loading and values before drug loading), at rest and during exercise. Lines at the lower quartile, median, and upper quartile values were plotted. ** $p < 0.001$.

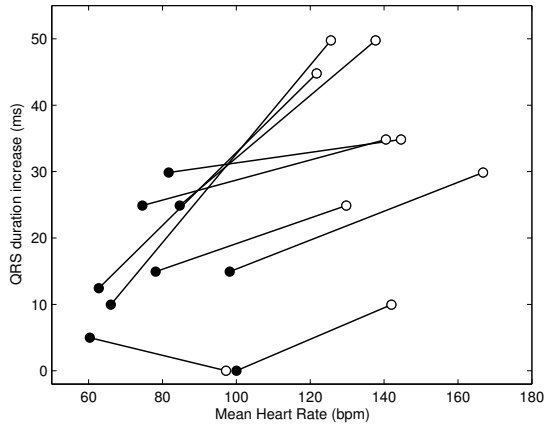

Figure 6. Delta QRS duration (i.e., the difference between values after flecainide loading and values before drug loading), at rest (black circle) and during exercise (white circle).

rate-dependent manner. The aim of this study was to establish a protocol to monitor flecainide's rate-dependent conduction slowing, during physiologic increases in HR in patients with AF. A higher increase in QRS duration was found at higher HR in all patients but one that could be thought to present a too low HR.

In conclusion, in patients with AF, flecainide rate-dependent conduction slowing can be monitored and quantified by the proposed protocol which measures QRS duration under resting and exercise conditions. This protocol may help determining antiarrhythmic efficacy and preventing proarrhythmic effects in the individual patient.

Acknowledgements

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