Amplification of Flecainide-Induced Ventricular Conduction Slowing by Exercise
A Potentially Significant Clinical Consequence of Use-Dependent Sodium Channel Blockade

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Proarrhythmic effects of flecainide acetate have been reported during exercise, but the mechanism for the arrhythmogenic interaction between flecainide and exercise is unknown. We hypothesized that the sinus tachycardia of exercise may enhance flecainide-induced conduction slowing by increasing use-dependent sodium channel blockade, thereby facilitating the occurrence of ventricular reentry. To evaluate the modulation of flecainide’s effects by exercise, we studied 19 patients who were receiving therapeutic doses of flecainide for the treatment of cardiac arrhythmias. Sixteen patients underwent treadmill exercise testing by a modified Bruce protocol. During exercise, QRS duration increased progressively from 94±22 msec (mean±SD) at rest to 116±25 msec (p<0.001) at a mean heart rate increase of 84±32 beats/min. The patient with the greatest QRS increase developed a monomorphic ventricular tachycardia at peak exercise. At rest, the QRS duration after treatment with flecainide increased 12.1±10.0% compared with the pretreatment value, and with exercise, the QRS duration increased by a further 28.1±17.0% compared with the predrug value. We found that the best predictor of further exercise-induced QRS slowing was the change in QRS duration produced by flecainide at rest (r=0.76, p=0.001). In an age- and disease-matched control group, the QRS duration did not change during exercise that caused a similar heart rate increase. Abrupt increases in heart rate by ventricular pacing during electrophysiologic study in seven patients prolonged their QRS duration as an exponential function of beat number, with an onset rate constant (0.033±0.006/beat) that is comparable to flecainide’s rate constant for use-dependent changes in \( V_{\text{max}} \) in vitro. The QRS increases were similar when compared for corresponding heart rate changes produced by ventricular pacing (13.9±3.1%) and by exercise (12.6±6.7%) in four patients undergoing both. We conclude that exercise causes a rate-dependent augmentation of flecainide’s effects on ventricular conduction by enhancing state-dependent sodium channel blockade, potentially causing ventricular arrhythmogenesis in predisposed patients. (Circulation 1989;79:1000–1006)

Class I antiarrhythmic drugs have frequency-dependent effects on cardiac sodium channels, leading to greater reductions in \( V_{\text{max}} \) of ventricular tissue at faster stimulation rates.

These effects have been incorporated into recent molecular models of antiarrhythmic drug action.1–4 The first model1–2 is based on the interaction between drugs and sodium channels on different affinities of various drugs for different sodium channel states. The second model3,4 is based on drug binding to a constant affinity channel receptor, with receptor access determined by channel gating. These models have important potential clinical implications2 related to the mechanisms of antiarrhythmic drug action in vivo. Electrophysiologic studies with programmed electrical stimulation have shown qualitative frequency-dependent sodium channel blockade for antiarrhythmic drugs in humans.5,6 In addition, quantitative studies have shown kinetics of action of sodium channel blockers in vivo animal models7–9 paralleling their kinetic effects in vitro.7,10,11
TABLE 1. Characteristics of the Patient Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients receiving flecainide</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise study</td>
<td>Electrophysiologic study</td>
</tr>
<tr>
<td></td>
<td>16*</td>
<td>7*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54.4±15.2</td>
<td>58.6±10.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other†</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Flecainide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma concentration (μmol/l)</td>
<td>1.5±0.6</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Dosage (mg/day)</td>
<td>250±52</td>
<td>271±49</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis (n/total)</td>
<td>4/16</td>
<td>4/7</td>
</tr>
<tr>
<td>β-Blockers (n/total)</td>
<td>3/16</td>
<td>1/7</td>
</tr>
</tbody>
</table>

*Four patients underwent both the exercise and the electrophysiologic studies.
†Consists in the exercise group of five patients with cardiac arrhythmias (paroxysmal atrial fibrillation, 2; nonsustained ventricular tachycardia, 1; isolated premature ventricular contractions, 1; and paroxysmal atrial tachycardia, 1) and no known heart disease. In the electrophysiologic study group, one patient had a cardiomyopathy due to alcoholism. In the control group, one patient had isolated premature ventricular contractions and no structural heart disease.

is, therefore, good evidence to suggest that the predictions of basic molecular models of antiarrhythmic drug action1–4 apply to the effects of these agents on conduction in vivo.

Flecainide acetate is a class IC antiarrhythmic agent according to the modified Vaughan-Williams classification12 and is effective in treating a variety of cardiac arrhythmias.13 Flecainide has caused occasional proarrhythmic reactions, including the de novo occurrence of sustained ventricular tachyarrhythmias or an increase in the severity of preexisting ventricular arrhythmias.14,15 A recent study suggests that flecainide-induced ventricular tachyarrhythmias have a propensity to occur during exercise.16 The mechanisms underlying exercise-induced arrhythmogenesis in the presence of flecainide have not been previously examined.

The conduction slowing typically produced by flecainide is probably due to sodium channel blockade, as reflected by the depression of V_max that it produces in vitro.17,18 Like other class I drugs, flecainide reduces V_max slightly in the absence of stimulation, but with stimulation, a substantial decline in V_max to a new steady state occurs.17 A similar rate-dependent change in block occurs with an abrupt change in stimulation frequency.17,18 Flecainide-induced reductions in V_max are substantially augmented by increases in stimulation frequency throughout the physiologic range of heart rates.17,18

We reasoned that the sinus tachycardia of exercise may amplify the sodium channel blockade produced by flecainide acetate through rate-dependent mechanisms. This amplification would result in an increase in drug-induced conduction slowing and possibly lead to ventricular arrhythmogenesis in predisposed patients. The purpose of this study was to determine whether flecainide-induced ventricular conduction slowing is increased by exercise and to determine the mechanism responsible for this phenomenon.

Methods

Patient Population

The study group consisted of 19 patients receiving flecainide acetate for the treatment of cardiac arrhythmias. Six patients not treated with flecainide served as the control group. The characteristics of both groups are summarized in Table 1. Groups did not differ significantly in age, sex, or cardiac diagnosis.

Exercise Testing

Treadmill exercise testing was conducted according to a modified Bruce protocol.19 A 12-lead electrocardiogram (ECG) was obtained before exercise. ECG leads CC5, CM5, and CL were used for monitoring during exercise. Recordings were obtained at a paper speed of 100 mm/sec before the exercise test and at frequent intervals during the test.

Electrophysiologic Study

Electrophysiologic testing was performed in seven patients in the fasting, nonseated state as part of the clinical evaluation of drug efficacy in treating ventricular tachycardia. Four of these patients also underwent exercise testing while receiving oral flecainide. A quadripolar electrode catheter was positioned in the right ventricular apex by way of
the right femoral vein. Stimulation was performed with 1.5-msec square wave pulses with twice late diastolic threshold current controlled by a programmable stimulator (Bloom Associates, Flying Hills, Pennsylvania). Electrocardiographic leads I, aVF, and V1 and a right ventricular elecrogram were recorded simultaneously at 100 mm/sec with a paper recorder (Mingograf T16, Siemens-Elema, Stockholm, Sweden). The kinetics of flecainide-induced conduction slowing were assessed by 30–60-second trains of ventricular stimulation at rates of 100, 120, and 150 beats/min. No stimulation was performed for a minimum of 60 seconds between trains of ventricular stimuli. All runs of test stimuli were begun abruptly during sinus rhythm, and stimulation was continued in all cases until changes in QRS duration had stabilized. The study protocol lasted approximately 10 minutes and was performed before the routine clinical study in each case.

Drug Dosage and Assay

All patients had been receiving flecainide at the same dose for at least 3 days at the time of either exercise or electrophysiologic study. The attending physician selected the flecainide dose based on clinical criteria. Blood samples for subsequent flecainide assay were drawn at the time of the exercise test or electrophysiologic study. Plasma flecainide concentrations were measured with a commercially available fluorescence polarization immunoassay technique (Abbott Laboratories, Mississauga, Ontario, Canada).

Data Analysis

Exercise-induced QRS changes. Only ECG tracings showing normal sinus rhythm were used for analysis. QRS duration was measured indepen-

dently by two observers who were unaware of the identity and treatment status of each patient. The electrocardiographic lead that best allowed identification of the onset and offset of QRS complexes was used for all QRS measurements in a given patient. Each observer measured the average duration of three consecutive QRS complexes at each heart rate. The average result of the two observers was used for analysis of the relation between heart rate and QRS duration.

Changes in QRS duration resulting from ventricular pacing. QRS duration was measured as a function of beat number after the onset of ventricular pacing. A steady state was always achieved within 90 complexes after the onset of stimulation. The mean QRS duration of three complexes at steady state was considered representative of the QRS duration at that frequency. Only QRS complexes of consistent configuration were used for analysis. Capture or fusion complexes occasionally occurred and were excluded from consideration. Rate-related changes were evaluated by comparing steady-state QRS duration at a more rapid ventricular pacing rate with the steady-state duration of QRS complexes of the same configuration at a slower rate. The kinetics of the onset of rate-dependent block were analyzed by previously described methods.11,12,20

Statistical Analysis. Group data are presented as the mean±SD. Comparisons between two groups of experimental data were made with unpaired Student’s t tests. We used multilinear regression analysis to relate drug-induced QRS prolongation during exercise to possible determining factors (flecainide dose, serum flecainide concentration, percent change in QRS duration at rest resulting from flecainide, and percent change in heart rate

FIGURE 1. Plots of changes in QRS duration relative to increases in heart rate in patients treated with flecainide (top panel) and in the control group (bottom panel). All changes are expressed as a percent increase from the values measured at rest immediately before exercise. Top Panel: In all patients receiving flecainide, QRS duration increased progressively during exercise. QRS increases at peak heart rate varied from 6.7 to 55.9% (mean, 24±12.7%) among patients. The patient who had the greatest exercise-induced change in QRS duration (*) had a ventricular tachycardia (Figure 2) at peak heart rate during exercise. Bottom Panel: In control patients, the percent change in QRS duration did not deviate significantly from the zero line; values vary from −5.6 to 3.8%.
The significance of regression was determined by an analysis of covariance. Two-tailed tests were used for all statistical comparisons, and $p<0.05$ was considered to be significant.

Results

Exercise

In all patients receiving flecainide, QRS duration increased progressively during exercise from $94\pm22$ to $116\pm25$ msec ($p<0.001$) at a mean heart rate increase of $84\pm32$ beats/min (Figure 1, top). In the control group, the QRS duration was $79\pm10$ msec before and $80\pm11$ msec (NS) after exercise, which caused a heart rate increase of $84\pm29$ beats/min (Figure 1, bottom). The patient receiving flecainide who had the greatest QRS increase during exercise developed a ventricular tachycardia at peak heart rate. His ventricular tachycardia (Figure 2, bottom) was monomorphic and was sustained for 30 seconds, after which it terminated spontaneously. This patient had had a previous exercise test while not receiving flecainide and had shown neither arrhythmia nor QRS prolongation at a similar work load.

The QRS durations of patients before treatment were compared with those of patients at rest and at peak exercise during treatment with flecainide. The QRS duration of patients at rest after treatment with flecainide increased by $12.1\pm10.0\%$ compared with the pretreatment value. During exercise, the QRS increased a further $28.1\pm17.0\%$ compared with the predrug value. Stepwise multilinear regression analysis showed that the only variable that significantly correlated with the extent of exercise-induced QRS increase was the percent increase in QRS duration on the resting ECG produced by flecainide compared with pretreatment values ($r=0.76$, $p=0.001$). The only other variable that improved the multilinear correlation coefficient was the percent heart rate increase resulting from exercise, which improved the $r$ value to $0.84$ ($p<0.001$) when included in the analysis. Neither flecainide dose nor serum flecainide concentration were independent predictors of the degree of exercise-induced QRS prolongation.

Electrophysiologic Study

Seven patients who received flecainide were studied during electrophysiologic testing. In all seven, abrupt changes in heart rate by ventricular pacing increased QRS duration. Changes in QRS duration after the onset of ventricular pacing followed an exponential relation with beat number (Figure 3). The mean rate constant for QRS prolongation in the seven patients studied was $0.033\pm0.006/beat$. Four patients underwent both electrophysiologic study and exercise testing. In these four patients, the QRS increase resulting from exercise ($12.6\pm6.7\%$) was very similar to the QRS...
increase produced by ventricular pacing (13.9±3.1%, p=NS) when values were compared for a corresponding increase in heart rate (Figure 4).

Discussion

We have shown that flecainide-induced QRS prolongation is increased by exercise. The degree of additional change in QRS duration produced by exercise was similar to that produced by ventricular pacing throughout a corresponding range of heart rates. A comparable degree of exercise did not alter QRS duration in a set of disease-matched control patients. These observations suggest that the tachycardia associated with exercise is the major factor responsible for the additional conduction slowing resulting from exercise in patients treated with flecainide. Although other factors such as autonomic changes and myocardial ischemia may have had a modulating role, the occurrence of exercise-induced QRS prolongation in patients treated with flecainide while on β-blocker therapy, as well as in several patients without coronary artery disease, suggests that these other factors were not of primary importance. Furthermore, the changes in QRS duration produced by ventricular pacing displayed an exponential onset that had a rate constant of 0.033±0.006/beat. This onset rate constant is very similar to that determined for flecainide effects on Vmax (an index of inward sodium current) in vitro, 0.029±0.006/beat.17 Therefore, our results provide strong evidence that exercise enhances flecainide’s effects on ventricular conduction by increasing the drug’s rate-dependent interaction with cardiac sodium channels.

Our results provide further insights into the underlying mechanisms of the interaction between exercise and flecainide. In a recent study, Cascio et al22 showed that exercise accentuated the QRS prolongation produced by amiodarone, which also has use-dependent class I properties.23,24 Our study differs from theirs in that we have both evaluated the specific role of heart rate by comparing QRS changes during exercise with those resulting from tachycardia produced by ventricular pacing and studied the onset time course of conduction changes during pacing at a constant frequency. We found that, in patients receiving flecainide, the increase in QRS duration at rest was the most important determinant of the degree of further QRS prolongation resulting from exercise. Similarly, Cascio et al22 found that the degree of amiodarone-induced QRS prolongation at rest is an important predictor of further QRS prolongation produced by exercise. These results are not surprising because the degree of QRS prolongation on the resting ECG is a direct indicator of the drug’s pharmacodynamic action of interest.

Antiarrhythmic drugs could have arrhythmogenic actions by a variety of mechanisms, including abnormal impulse formation (afterdepolarizations and abnormal automaticity) and abnormal impulse propagation resulting in reentry.25,26 Class IC drugs do not result in cellular calcium overload or action potential prolongation.12 Therefore, they would be unlikely to produce delayed or early afterdepolarizations.27-29 The most characteristic property of class IC agents is their potent sodium channel
blocking and conduction-slowing action,12 which is most readily related to their arrhythmogenic potential in the context of a reentrant arrhythmia mechanism. The ability to sustain reentry depends on a critical balance between conduction velocity and refractoriness in the reentrant circuit.26,30 A potential reentrant circuit could exist, particularly in the presence of heart disease, but if refractoriness exceeded circuit time, no manifest reentry would occur. If a drug slowed conduction in this circuit to the point at which conduction time exceeded refractory period, sustained reentry would then become possible.

The occurrence of this type of arrhythmogenic mechanism should depend on the presence of a preexisting substrate that can support reentry and on the magnitude of drug-induced conduction slowing. Consistent with this mechanism is the observation that flecainide is much more likely to produce proarrhythmic effects in patients with a history of structural heart disease or ventricular tachyarrhythmias or both than in patients without such a history.31 Similarly, flecainide, even at toxic doses, does not induce ventricular arrhythmias in normal dogs,32 but it does cause dose-related arrhythmogenicity in dogs with prior myocardial infarctions.33 In patients predisposed to develop reentrant ventricular arrhythmias, the enhancement of flecainide-induced conduction slowing by exercise may be sufficient to allow manifest reentry to occur. This may account for the occurrence of ventricular tachycardia in our patient with the greatest exercise-induced conduction slowing and for the occurrence of proarrhythmia described by Anastasiou-Nana et al.16

Routine exercise testing has been advocated as a means to detect potential proarrhythmic responses to flecainide.16 Our results indicate that the degree of flecainide-induced QRS prolongation in the resting ECG is a good predictor of further conduction slowing during exercise, and they suggest that changes in the resting ECG could be used to select patients at increased risk of proarrhythmia during exercise. The value of exercise testing for the prediction of proarrhythmia due to flecainide, either routinely or in selected subgroups, needs to be tested prospectively.

We used QRS duration as an indicator of flecainide’s effects on ventricular conduction. Recent work with epicardial mapping shows that QRS duration changes accurately reflect antiarrhythmic drug effects on ventricular conduction, provided that the QRS configuration remains constant.34 The similarity between the onset kinetics that we observed for flecainide’s effects on conduction in humans and the values reported for changes in V max in vitro17 indicates the relevance of basic models of antiarrhythmic drug action1–4 to achieve an understanding of the clinical properties of these compounds. Moreover, we have shown that the use-dependent actions described by these models account for exercise-induced ventricular conduction slowing in patients treated with flecainide. The latter phenomenon may have an important role in producing ventricular proarrhythmic actions in predisposed patients, indicating the potential clinical importance of the rate-dependent actions of antiarrhythmic drugs.

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