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The effects of sotalol on ventricular repolarization during exercise

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Abstract: Objective: Although after pacing animal and human studies have demonstrated a rate-dependent effect of sotalol on ventricular repolarization, there is little information on the effects of sotalol on ventricular repolarization during exercise. This study attempted to show the effects of sotalol on ventricular repolarization during physiological exercise. Methods: Thirty-one healthy volunteers (18 males, 13 females) were enrolled in the study. Each performed a maximal treadmill exercise test according to the Bruce protocol after random treatment with sotalol, propranolol and placebo. Results: Sotalol significantly prolonged *QTc* (corrected QT) and *JTc* (corrected JT) intervals at rest compared with propranolol (*QTc* 324.86 ms vs 305.21 ms, $P<0.001$; *JTc* 245.04 ms vs 224.17 ms, $P<0.001$) and placebo (*QTc* 324.86 ms vs 314.06 ms, $P<0.01$; *JTc* 245.04 ms vs. 232.69 ms, $P<0.001$). The *JTc* percent reduction increased progressively with each stage of exercise and correlated positively with exercise heart rate ($r=0.148$, $P<0.01$). The *JTc* percent reduction correlation with exercise heart rate did not exist with either propranolol or placebo. Conclusions: These results imply that with sotalol ventricular repolarization is progressively shortened after exercise. Thus the specific class III antiarrhythmic activity of sotalol, present as delay of ventricular repolarization, may be attenuated during exercise. Such findings may imply the need to consider other antiarrythmic therapy during periods of stress-induced tachycardia.

Key words: Sotalol, Exercise stress test, Ventricular repolarization
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INTRODUCTION

D,l-sotalol is a nonselective β-adrenergic receptor antagonist with class III antiarrhythmic activity. It has been widely used for treatment of both atrial and ventricular arrhythmias, and has been found to be an effective therapy to avoid atrial fibrillation post-cardiac surgery (Suttorp *et al*., 1991), and it may be the drug of choice for patients with inducible ventricular arrhythmias as documented in ESVEM (Roden, 1993).

Because of its Beta blocking activity, sotalol slows the sinus rate, prolongs the PR interval and increases the effective refractory period of the atrioventricular (AV) node. It exerts its antiarrhythmia activity by blocking the rapid component of the delayed rectifier potassium current (Ikr). This appears to be a reverse rate-dependent prolongation on the action potential duration (APD) and effective refractory period (ERP) of the myocardial cell. This effect can also be manifested as the reverse rate-dependent increase in QT and JT intervals on the electrocardiogram. Delay of ventricular repolarization is the principal action of the class III antiarrhythmic effect of sotalol (Vaughan Williams, 1985). Although there have been several animal studies which examine the rate-dependent delay of sotalol on ventricular repolarization, human studies have been performed mainly after slow pacing. Little information on the rate-dependent effect of sotalol under physiological stress has been reported. This study is designed to observe the rate-dependent effect of sotalol on QT and JT intervals during exercise and to consider the impact of these changes on its antiarrhythmic potential during periods of stress-induced tachycardia.

METHODS

The study subjects included 31 healthy volun-

teers (18 males, 13 females, age 40.50±6.7). Each had a chest X-ray, 24-h ambulatory ECG (electrocardiogram), echocardiogram, count of blood cell, serum electrolytes, blood sugar, liver function, renal function test and thyroid function tests to exclude organic heart disease or other systemic disease.

Volunteers were excluded if they had one of the following conditions:

1. Organic heart disease or other systemic disease or electrolyte disorder.
2. Presence of Sick Sinus Syndrome (Sinus bradycardia with Atrial tachyarrhythmia).
3. Preexcitation syndromes.
4. Atrioventricular or bundle branch block.
5. Asthma or other chronic respiratory disease.
6. Contraindications to exercise testing.
7. Suspected history of ischemic heart disease.
8. Previous positive or borderline positive treadmill ECG.
9. Taken any antiarrhythmic agent within the week prior to testing.
10. Resting systolic blood pressure <90 mmHg or resting heart rate <65 beats/min.
11. Uncooperative attitude during exercise testing.

Study design

The subjects were fasted for no less than 8 h and randomized to receive a single dose of sotalol, propranolol or placebo 3 h before the exercise test. Since 100 mg sotalol has activity equivalent to 30 mg propranolol (Antonaccio and Gomoll, 1993), these dosages were selected for both medications. Three hours after taking the medication, the treadmill exercise test was then performed according to the Bruce protocol on a TrackMaster (TM200E, MedGraphics Co., USA). Each subject performed the treadmill exercise test 3 times once after each medication with an intervening one-week interval. The medications were coded and an assistant investigator randomly determined the sequence of medication administration. Both the volunteer subjects and the investigators who supervised the exercise test were blinded to the medication sequence.

Treadmill exercise testing protocol

The Bruce protocol was followed for the exercise treadmill tests. Exercise testing was terminated at an age-predicted maximum heart rate. The same investigator who was blinded to the study medications supervised all exercise tests. A standard 12-lead ECG was recorded at rest and at the end of each exercise stage (3 min/stage) by a 12-lead synchronous cardiofax (HP1705A, HP Co., USA). The Cardiofax speed was 50 mm/s. Systolic blood pressure was measured with a cuff sphygmomanometer at rest and at the end of each exercise stage.

Measurement of ECG intervals

Two observers who were unaware of the treatment details and the identity of each patient independently performed the measurements. The ECG lead in which the onset and termination of the P-QRS-ST segment could be most easily identified was selected for measurement. Each observer measured the average duration of three consecutive P-QRS-ST segments at rest and at each stage of exercise. The results from the two observers were averaged and used for analysis.

1. QT and JT intervals: With exercise-induced tachycardia, the P wave may merge with the downward limb of the preceding T wave, which affects the exact measurement of the intervals. In order to avoid this effect, the QT interval was measured from the onset of the Q wave to the peak point of the T wave or the middle point between two peaks of the biphasic T wave (Wang *et al.*, 1995). The JT interval was calculated as the difference of the QT and QRS intervals.

2. The *QTc* interval was corrected for heart rate by using the equation:

$$QTc=QT+0.154(1-RR)$$ (Sagie *et al.*, 1992)

3. The *JTc* percent reduction from previous stage to present stage was expressed as (delta *JTc*%).

(delta *JTc*%)=[(*JTc* of previous stage–*JTc* of present stage)/*JTc* of previous stage]×100%

Statistical analysis

The significance of differences among mean ECG intervals using different medications was assessed by analysis of variance. Significant differences between mean values of two different stages during the same exercise test were assessed by paired-samples *T* test. Bivariate correlate analysis was used

to correlate the (delta *JTc*%) with exercise heart rate. All results were expressed as mean±1 standard deviation of the mean. Significant differences were considered when the probability of a type I error was <0.05.

RESULT

All subjects completed their exercise tests. Sinus rhythm was maintained during exercise in all subjects and all exercise tests were terminated because of either fatigue or dyspnea. There were no ECG ischemic changes.

Heart rate (HR)

The resting heart rate with sotalol was significantly lower than that with placebo (68.85±9.66 bpm vs 89.00±9.61 bpm, $P<0.001$). However the heart rate with sotalol was not significantly different from that with propranolol (68.85±9.66 bpm vs 70.44±9.54 bpm, $P>0.05$). To the peak of the exercise, the heart rate with sotalol was still significantly lower than that with placebo (132.56±18.00 bpm vs 164.19±18.26 bpm, $P<0.001$) and remained not significantly different from that with propranolol (132.56±18.00 bpm vs 131.96±13.17 bpm, $P>0.05$).

QRS intervals

The QRS intervals at rest and at peak exercise with sotalol were respectively 79±10.66 ms and 80.95±9.69 ms ($P>0.05$); with propranolol they were 81.04±10.65 ms and 82.80±9.82 ms ($P>0.05$) respectively, with placebo they were 81.37±11.00 ms and 80.71±10.28 ms ($P>0.05$).

JTc intervals

At rest, the *JTc* intervals after treatment with sotalol were significantly longer than the *JTc* after treatment with either propranolol or placebo (Table 1). In the early stage of the exercise, the *JTc* intervals both after treatment with sotalol and with propranolol showed resistance to the exercise-induced *JTc* reduction. With the exercise going on, the *JTc* intervals after treatment with both two medications showed progressive reduction. Although during exercise, reduction in *JTc* intervals was noted after all medications, the *JTc* reduction after medication with sotalol was greatest (Table 1). Changes of the *JTc* intervals during exercise are shown in (Fig.1).

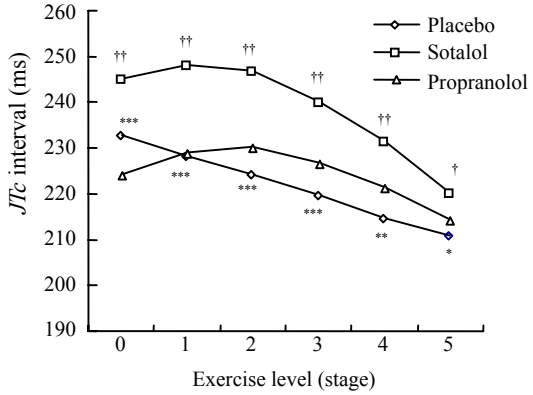

Fig.1 The changes of *JTc* interval during exercise after respective administration with sotalol, propranolol and placebo. The *JTc* with sotalol is significant longer than that with propranolol or placebo at rest and is more significantly shortened than that with propranolol or placebo during exercise. *Sotalol vs Placebo, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$; †Sotalol vs Propranolol, $^{\dagger}P<0.01$, $^{\dagger\dagger}P<0.001$

JTc percent reduction during exercise (delta *JTc*%)

The (delta *JTc*%) during exercise with sotalol medication positively correlated with the increasing heart rate during exercise ($r=0.148$, $P<0.01$).

DISCUSSION

The QT interval correlates closely with heart rate. Under static conditions with heart rate increase, the QT interval progressively decreases. When the QT interval was corrected according to heart rate by the

Table 1 Comparison of JT_C intervals and maximal percent reduction in *JTc* intervals during exercise after different medications

	Exercise level (stage)	*n*	Placebo (ms)	Sotalol (ms)	Propranolol (ms)
JT_C	Rest	31	232.69±4.04	245.04±5.00**††	224.17±4.09$^{\Delta}$
	Peak	31	210.97±3.89	220.11±3.59*†	214.45±3.81$^{\Delta}$
Maximal (delta *JTc*%)			5.73%±5.83%	8.83%±6.09%*†	2.70%±6.20%$^{\Delta\Delta}$

*Sotalol vs Placebo, $^{*}P<0.05$, $^{**}P<0.001$; †Sotalol vs Propranolol, $^{\dagger}P<0.01$, $^{\dagger\dagger}P<0.001$; $^{\Delta}$Propranolol vs Placebo, $^{\Delta}P<0.05$, $^{\Delta\Delta}P<0.01$

correction equation, the corrected QT interval (*QTc*) was almost a constant. The increase in cardiac sympathetic tone may accelerate the ventricular repolarization (Sager *et al.*, 1994; Markel *et al.*, 1993; Morady *et al.*, 1988), manifested as a reduction in the corrected QT interval (*QTc*). Due to increase in sympathetic tone, during exercise the *QTc* interval was shortened with increasing heart rate rather than remaining constant.

Although this study showed further progressive shortening in *JTc* interval with physiological exercise (with placebo), but also showed "exaggerated" *JTc* interval shortening after sotalol during the later exercise stage. This "exaggerated" *JTc* interval shortening during the later exercise stage implied a progressive attenuation of sotalol's effect on ventricular repolarization prolongation with physiological stress.

With slow heart rates, the rapid component of the delayed rectifier potassium current (Ikr) is the major factor in controlling ventricular repolarization. With a rapid heart rate, the slow component of the delayed rectifier potassium current (Iks) is the dominant ion current (Jurkiewicz and Sanguinetti, 1996; Dai, 1998). Sotalol selectively blocks the Ikr, so sotalol prolongs the ventricular repolarization more prominently during slow pacing than with rapid pacing (Nakaya *et al.*, 1993). Human studies showed that bradycardia increased and tachycardia decreased the sotalol's potential to prolong the QT interval (Shimizu *et al.*, 1996; Funck-Brentano *et al.*, 1991). This reverse rate dependence effect still has not been studied enough in humans under physiological stree of exercise.

Our study yielded the following findings:

1. Sotalol is an agent with both β-adrenoceptor antagonism and class III antiarrhythmic effects. From Fig.1 we note that sotalol's β-adrenoceptor blocking effects is similar to that of propranolol on the *QTc* and *JTc* intervals. In order to distinguish sotalol's class III antiarrhythmic effect on ventricular repolarization from its β-blocking effect, we used propranolol for comparison. The change in heart rate with exercise was similar after sotalol and propranolol treatment. This confirms that 100 mg sotalol has equivalent β-blocking activity to 30 mg propranolol (Antonaccio and Gomoll, 1993).

2. Through heart rate acceleration by physiologic exercise, the study revealed the attenuation of sotalol's prolongation of ventricular repolarization after exercise. From Fig.1 we note that although during the early stage sotalol presents resistance to this attenuation, which may due to its β-blocking effect, but after the second exercise stage (*HR*>84.77±10.55 bpm), the effect of sotalol on ventricular repolarization was more prominent attenuation than that of both placebo and propranolol, attenuation of not only sotalol's β-blocking effect, but also of its class III effect.

3. The ventricular repolarization period has significance for evaluating the antiarrhythmic effect of medications. Delay of ventricular repolarization is the principal action of the class III antiarrhythmic effect of sotalol (Vaughan Williams, 1985). We found from this study, that the effect of sotalol on delay of ventricular repolarization is progressively attenuated during the later stage of the exercise. Physiologic stress due to illness may result in similar sympathetic nervous system stimulation with resultant tachycardia just as with physical exercise. For example febrile illnesses which induce rapid heart rates also increase sympathetic stimulation. Further investigation is needed to determine if sotolal's antiarrythymic potential is thus attenuated in febrile states or under physiologic stress of illness.

SUMMARY

Though sotalol significantly prolongs ventricular repolarization in the resting state, during physiological exercise the refractory period of ventricular repolarization progressively decreases. Whether this significant shortening of ventricular repolarization may attenuate the antiarrythmic potential of sotalol under conditions of both exercise and illness induced tachycardia or not, it remains to be assessed by further clinical studies.

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