Sotalol vs metoprolol for ventricular rate control in patients with chronic atrial fibrillation who have undergone digitalization: a single-blinded crossover study


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**Aims** To compare the effects of sotalol and metoprolol on heart rate, during isotonic (ITE) and isometric (IME) exercise and daily activities, in digitalized patients with chronic atrial fibrillation.

**Methods and Results** The study had a randomized, single-blinded, crossover design. Twenty-three patients with chronic atrial fibrillation received placebo for 4 weeks, followed by a 4-week period of treatment with sotalol and metoprolol in random order. At the end of each period, the patients were assessed with 24-h ECG monitoring, a cardiopulmonary exercise test and a handgrip manoeuvre.

Both agents produced a lower heart rate than placebo at rest and at all levels of isotonic exercise ($P<0.001$) without affecting oxygen uptake. Sotalol produced a lower heart rate than metoprolol only at submaximal exercise (116 ± 9 bpm for sotalol vs 125 ± 11 bpm for metoprolol, $P<0.001$). During isometric exercise, sotalol produced a lower maximum heart rate than did metoprolol (113 ± 22 vs 129 ± 18 bpm, respectively). Both agents produced a lower mean heart rate than placebo over 24 h ($P<0.001$ for all), while sotalol produced a lower mean heart rate than metoprolol during the daytime ($P<0.01$).

**Conclusion** Sotalol is a safe and effective agent for control of heart rate in digitalized patients with atrial fibrillation. Sotalol is superior to metoprolol at submaximal exercise, resulting in better rate control during daily activities.

**Key Words:** Chronic atrial fibrillation, sotalol, metoprolol, exercise, Holter monitoring.

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**Introduction**

Beta-blockers have been shown to be effective for the control of heart rate at rest and during exercise in patients with chronic atrial fibrillation$^{[1-5]}$. Indeed, a recent study assumes that the combination of beta-blocker and digoxin is the most effective regimen, reflecting a synergistic effect on the atrioventricular (AV) node of the vagomimetic actions of the cardiac glycoside and the prolongation of AV node refractoriness by beta-blockers$^{[6]}$. However, the use of beta-blockers is limited by a range of adverse reactions, of which the most serious is their negative inotropic action.

Sotalol is a non-selective beta-blocker that also has a class III action (prolongation of action potentials)$^{[7-9]}$. This property could contribute to sotalol’s ability to prolong AV node refractoriness and thus to control the ventricular response in chronic atrial fibrillation more effectively than a conventional beta-blocker. Furthermore, sotalol is considered to have a less negative inotropic action than conventional beta-blockers, and this could be an additional reason for its administration.

However, in spite of its theoretical advantages, the superiority of sotalol over conventional beta-blockers in controlling heart rate in patients with chronic atrial fibrillation has not been proven to date. The aim of this study was to assess the effects of sotalol at rest and during programmed exercise and daily activities in a group of patients with chronic atrial fibrillation who had
undergone digitalization, and to compare the results with those of a conventional beta-blocker, metoprolol.

Methods

Study patients

Twenty-three patients (13 men, 10 women, mean age 63 ± 8 years) with atrial fibrillation for >1 month (defined in this study as chronic atrial fibrillation) made up the study group. These patients were selected from a total population of 146 inpatients with chronic atrial fibrillation who were examined in the authors’ department in a 2-year period. Fifteen of them had a history of unsuccessful electrical attempts to restore sinus rhythm, and eight patients relapsed after electrical cardioversion, even though they received propafenone to prevent atrial fibrillation recurrence. All patients were carefully evaluated by history, physical examination, ECG, chest X-ray and echocardiography, and satisfied the following selection criteria: no history or signs of heart failure; absence of severe valvular heart disease; no evidence of ischaemic heart disease; no evidence of renal, hepatic, endocrine, pulmonary or neurological disease; no history of un-toward reaction to any of the medications used in the present study; and the ability to undergo a treadmill exercise test.

All patients were treated with digoxin and were given anticoagulation therapy with acenocoumarol (INR 2.5–3.5). While receiving digoxin therapy, these patients were required to have a resting heart rate >90 bpm.

All patients gave their consent to the protocol, which was approved by the local Ethics Committee for Human Research.

Study design

The study had a randomized, single-blinded, crossover design. It consisted of an initial 4-week placebo treatment period (2 tablets twice daily), followed by randomization to either metoprolol or sotalol treatment for a 4-week period, and then (after a placebo washout for 1 week) the alternative medication for the same length of time.

The digoxin treatment was maintained throughout the study. The dosage was adjusted until the serum concentration came within the range 0.8–2.0 ng·ml⁻¹ before the study commenced.

At the end of each treatment period, patients were assessed with 24-h ECG monitoring, a maximal, symptom-limited cardiopulmonary exercise test, an isometric exercise test with a handgrip dynamometer, and evaluation of subjective wellbeing and adverse events.

Drug schedules

Before the study, an open-label titration phase established the optimal therapeutic dose of sotalol or metoprolol for each patient enrolled, as determined by a decrease in resting heart rate to ≤70 bpm.

Sotalol was initiated at a dose of 40 mg twice daily. The dose was titrated up in 40–80 mg increments every 48–72 h until the target reduction in heart rate was achieved. The final maintenance dose of sotalol was adjusted downwards if adverse effects were noted by the patients, or if the rate-corrected QT interval exceeded 500 ms.

Metoprolol therapy was initiated at a dose of 25 mg twice daily. The dose was titrated up in 25–50 mg increments every 48–72 h with the same aim. Treatment with any antiarrhythmic agent except digoxin was stopped for at least five half-lives before the study commenced.

Exercise protocol

Before the start of the study, all patients underwent a trial cardiopulmonary exercise test in order to familiarize themselves with the equipment and the procedure. Patients exercised on a calibrated, motor-driven treadmill (Max-1, Marquette, Milwaukee, USA) with an incremental exercise workload using a modified Naughton protocol. A rhythm strip lasting 6 s was recorded at rest (after standing for 2 min) and at the end of each minute during exercise and until the fourth minute of recovery, in order to evaluate the heart rate, with a paper speed of 25 mm·s⁻¹. A six-lead ECG was also recorded at a paper speed of 50 mm·s⁻¹ at rest, at submaximal and at maximal exercise. The longest QT interval in any of the six leads was recorded and averaged from the measurement of six consecutive QRS-T complexes. The QT interval was corrected (QTc) for rate using Bazett’s formula, as follows: QTc = QT/√RR, where RR is the preceding RR interval.

Blood pressure was measured with a cuff sphygmomanometer at rest and at 2-min intervals during the exercise test.

Gas exchange analysis and determination of anaerobic threshold

During testing, the patients breathed atmospheric air through a low-resistance mask. The partial pressures of respiratory O₂ and CO₂ were measured using a special gas analyser (Oxycon A, Mijnhard). The signals were processed through analogue-to-digital conversion for breath-by-breath gas exchange analysis. The gas analyser was recalibrated before each test. Gas exchange variables were measured continuously and averaged at 30-s intervals during the 2-min rest period and throughout the test. The variables measured included oxygen uptake (VO₂, ml·kg⁻¹·min⁻¹), respiratory exchange ratio (RER, VCO₂/VO₂) and oxygen pulse (oxygen uptake/heart rate). These parameters were determined at submaximal exercise (speed 3 mph, 0% grade), at the anaerobic threshold and at peak exercise. The gas exchange anaerobic threshold, determined as outlined by Beaver et al., was taken as the mean of estimations performed by two independent observers who were unaware of the patient’s treatment or other data.
Isometric exercise
To evaluate the ventricular response to isometric exercise, a sustained handgrip test was performed. First, the subjects tested their maximal voluntary contraction, then, after a break of at least 2 min, the patients were asked to maintain their contraction at 30% of maximum for 150 s under continuous ECG monitoring. Heart rate was determined at rest and every 30 s on 6 s rhythm strips.

Statistical analysis
Continuous data are summarized as mean ± standard deviation. The effect of the three different treatment schemes on heart rate changes over time was assessed with repeated measures analysis of variance with two factors: one for temporal effect (at 24 levels for the circadian variation, nine levels for the isometric exercise test and six levels for the isotonic) and one for treatment effect (three levels). The isotonic exercise test had nine levels (one resting and eight consecutive 30-s intervals during the test). In case of significant findings, post hoc tests were also performed. Separate subanalyses were also performed to examine the day–night (7:00–23:00) and night (23:01–6:59) effect. A P value <5% was the criterion for significance in all statistical comparisons.

Results
All patients completed the study uneventfully. No patient converted to sinus rhythm, but all maintained a resting heart rate ≤70 bpm. Thirteen of them had no evidence of underlying heart disease, eight had hypertensive cardiovascular disease (signs of left ventricular hypertrophy on the echocardiogram or ECG), and two patients had surgically corrected mitral stenosis. All patients were in NYHA class I or II, and their mean ejection fraction was 53 ± 5%.

The mean drug dosages were 206 ± 37 mg. day−1 for sotalol and 182 ± 44 mg. day−1 for metoprolol.

Ventricular rate changes during isometric exercise
According to ANOVA with repeated measures, there were time, group and interaction effects (P<0.001) on heart rate changes during exercise. For placebo, the exercise curves showed a curvilinear course, with an initial sharp rise followed by a gradual increase. Metoprolol gave a similar pattern, but the values were lower throughout the period of observation. For sotalol, the exercise curve showed a smoother, more linear path, with mean values significantly lower than those of metoprolol during the first 4 min of exercise. By the fifth minute, the heart rate on sotalol had almost reached the value on metoprolol (Fig. 1).

The mean exercise parameters and gas exchange variables at different exercise levels are shown in Table 1. The mean exercise duration was similar in all treatment groups. Both sotalol and metoprolol produced a lower mean heart rate than placebo at all exercise levels (P<0.001 for all). Sotalol gave a lower mean heart rate than metoprolol at submaximal exercise (P<0.01), whereas at other levels, there was no difference.

There were no significant differences in blood pressure between the three treatment groups at all exercise levels. VO2 was similar in all three groups, at all exercise levels.

Ventricular rate changes during isometric exercise
Repeated measures ANOVA showed that there were also significant time, group and interaction effects (P<0.001 for all) on changes in heart rate during isometric exercise (Fig. 2).

For all three treatments, heart rate followed an increasing course during the first 90 s and then remained at a plateau for the following 60 s. Heart rate was much higher under placebo than under the other two treatments throughout the period of observation (quadratic trend), with a steeper rise during the first 30 s. Sotalol and metoprolol had a similar pattern of changes, more or less linear. However, although heart rate started out at the same level, it quickly diverged, increasing at a slower rate under sotalol. The maximum heart rate

Figure 1 Time course of heart rate during isotonic exercise in patients with chronic atrial fibrillation receiving sotalol (▲), metoprolol (●) and placebo (■). The changes during the first 8 min were chosen because all the exercise tests contained complete data for this duration. During the early stages of exercise (until the fourth minute), the difference between sotalol and metoprolol is apparent.
Table 1  Exercise parameters and gas exchange variables at rest, submaximal exercise, anaerobic threshold and maximal exercise in patients with chronic atrial fibrillation under treatment with placebo, metoprolol and sotalol

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metoprolol</th>
<th>Sotalol</th>
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<tbody>
<tr>
<td><strong>Resting</strong></td>
<td></td>
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<tr>
<td>HR (bpm)</td>
<td>96 ± 7</td>
<td>66 ± 9‡</td>
<td>67 ± 6‡</td>
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<td>Systolic BP (mm Hg)</td>
<td>140 ± 19</td>
<td>131 ± 11</td>
<td>127 ± 12</td>
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<tr>
<td>QT (ms)</td>
<td>308 ± 40</td>
<td>316 ± 45</td>
<td>378 ± 44‡‡</td>
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<tr>
<td><strong>Submaximal exercise</strong></td>
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<tr>
<td>VO₂ (ml·kg⁻¹·min⁻¹)</td>
<td>16.1 ± 1.8</td>
<td>15.4 ± 2.1</td>
<td>15.8 ± 2.8</td>
</tr>
<tr>
<td>O₂ pulse (ml·beat⁻¹)</td>
<td>7.8 ± 1.1</td>
<td>8.4 ± 0.8‡</td>
<td>9.1 ± 0.9‡‡</td>
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<td>RER</td>
<td>0.88 ± 0.12</td>
<td>0.89 ± 0.10</td>
<td>0.88 ± 0.08</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>149 ± 10</td>
<td>125 ± 11‡‡</td>
<td>116 ± 9‡‡</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>149 ± 15</td>
<td>142 ± 25</td>
<td>140 ± 20</td>
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<tr>
<td>QT (ms)</td>
<td>280 ± 41*</td>
<td>290 ± 42*</td>
<td>350 ± 43‡‡</td>
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<tr>
<td><strong>Anaerobic threshold</strong></td>
<td></td>
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<tr>
<td>Time (s)</td>
<td>380 ± 34</td>
<td>392 ± 27</td>
<td>375 ± 19</td>
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<tr>
<td>VO₂ (ml·kg⁻¹·min⁻¹)</td>
<td>18.2 ± 1.7</td>
<td>17.5 ± 1.8</td>
<td>17.9 ± 2.1</td>
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<td>O₂ pulse (ml·beat⁻¹)</td>
<td>8.3 ± 0.8</td>
<td>9.1 ± 1.1‡</td>
<td>9.6 ± 0.9‡‡</td>
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<td>RER</td>
<td>0.93 ± 0.12</td>
<td>0.92 ± 0.12</td>
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<td>HR (bpm)</td>
<td>157 ± 16</td>
<td>137 ± 6‡‡</td>
<td>134 ± 8‡‡</td>
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<td>Systolic BP (mmHg)</td>
<td>165 ± 15</td>
<td>153 ± 12</td>
<td>148 ± 9</td>
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<td><strong>Maximal exercise</strong></td>
<td></td>
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<tr>
<td>Time (s)</td>
<td>608 ± 51</td>
<td>589 ± 37</td>
<td>592 ± 49</td>
</tr>
<tr>
<td>VO₂ (ml·kg⁻¹·min⁻¹)</td>
<td>23.8 ± 1.4</td>
<td>22.2 ± 1.3</td>
<td>22.8 ± 1.3</td>
</tr>
<tr>
<td>O₂ pulse (ml·beat⁻¹)</td>
<td>9.1 ± 0.6</td>
<td>10.2 ± 0.6‡</td>
<td>10.6 ± 0.7‡‡</td>
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<tr>
<td>RER</td>
<td>1.08 ± 0.2</td>
<td>1.09 ± 0.1</td>
<td>1.05 ± 0.2</td>
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<tr>
<td>HR (bpm)</td>
<td>183 ± 16</td>
<td>150 ± 14‡‡</td>
<td>152 ± 13‡‡</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>181 ± 25</td>
<td>172 ± 25</td>
<td>170 ± 20</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>250 ± 24*</td>
<td>252 ± 39*</td>
<td>260 ± 37*</td>
</tr>
</tbody>
</table>

*P<0.001 QT duration at exercise vs resting.
†P<0.01 sotalol vs metoprolol.
‡P<0.001 sotalol or metoprolol vs placebo.
BP, blood pressure; bpm, beats per minute; HR, heart rate; RER, respiratory exchange ratio; VO₂, oxygen uptake.

Ventricular rate control over 24 h

Regardless of treatment, heart rate showed a significant circadian pattern, with higher values during the day than at night (time effect P<0.001 for all). However, the particular course of heart rate changes over the 24-h period was strongly treatment dependent (treatment and interaction effect P<0.001 for all). Under placebo, mean heart rate was higher throughout than in the other two groups, with a steeper rise in the morning until 13:00, then a steeper fall from the early afternoon until 23:00. Sotalol and metoprolol had similar effects on mean HR, except during the early afternoon (13:00–16:00) when heart rate was higher in the metoprolol group (Fig. 3).

Side-effects

During the open-label phase, no patient suffered side-effects that would necessitate exclusion from the study. Nor was it necessary to withdraw medication from any patient during the study because of side-effects. There was no evidence of sotalol-associated torsade de pointes or proarrhythmia during either the study or the open-label phase.

Figure 2  Time course of heart rate during isometric exercise in patients with chronic atrial fibrillation receiving sotalol (△), metoprolol (●) and placebo (■). There are clear differences between the three treatments, in terms of both the patterns of change and the values of heart rate.

under placebo was 155 ± 20 bpm, significantly higher than that for metoprolol (129 ± 18 bpm, P<0.001) and sotalol (113 ± 22 bpm, P<0.001). The difference between metoprolol and sotalol was also significant (P<0.01).

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The QT interval on sotalol was longer than on the other two treatments at rest ($P<0.001$ for both). It shortened significantly as the exercise level increased in all three treatment groups, until at maximal levels there were no differences between the groups. At submaximal exercise, however, the QT interval on sotalol was longer than on the other two treatments ($P<0.001$ for both, Table 1). No significant changes were observed in the corrected QT interval during exercise and there were no differences between the groups either at rest or during exercise (data not shown).

**Discussion**

**Ventricular rate control at rest and during exercise**

This study first of all confirms the findings of previous studies, that sotalol, combined with digoxin, is a safe and very effective means of controlling heart rate, both at rest and during exercise, in patients with chronic atrial fibrillation\[11\-14]\). According to the present results during exercise, this therapeutic combination reduces heart rate at all levels, achieving a linear increase in heart rate and eliminating the abrupt increase which is seen in atrial fibrillation during the early stages of exercise. It should also be noted that, despite the significant reduction in heart rate that sotalol causes, exercise performance was not significantly affected. As oxygen pulse, which reflects stroke volume, increases under sotalol, this suggests that the study population were able to use their stroke volume reserve to compensate for the negative chronotropic effects of sotalol. The study’s major finding, however, was that the effects of sotalol on exercise show certain differences from those of conventional beta-blockers, such as metoprolol, that are targeted at low levels of exercise. Specifically, while the two agents have the same effect on exercise capacity and heart rate at maximal levels, in the early stages of exercise, sotalol maintains a lower heart rate than does metoprolol. It is important to note that this lower heart rate under sotalol was accompanied by slightly higher levels of O$_2$ consumption. A possible explanation of this is the different effects of the two agents on myocardial function, given that previous investigators have reported that sotalol has a lesser negative inotropic action than conventional beta-blockers, or even a positive inotropic effect on the myocardium\[7\-9]\). As a result, the more negative chronotropic effect of sotalol at that stage may be counter-balanced by a better use of the stroke volume reserve compared with metoprolol. The fact that oxygen pulse was significantly higher on sotalol than on metoprolol during only the initial stages of exercise, first of all reinforces the above hypothesis.

To the authors’ knowledge, there is only one study in which it was observed that the heart rate in patients with chronic atrial fibrillation increased at the start of an isometric exercise test and remained high throughout the test\[15\]. This pattern corresponds to that reported from previous observations in normal subjects, suggesting that it is due to an initial vagal withdrawal and to the increased sympathetic tone which exists during isometric exercise.

The present study showed that the increase in heart rate during isometric exercise in patients with chronic atrial fibrillation is large and digoxin is insufficient for rate control. In contrast, agents with antiadrenergic properties seem to be able to control the heart rate response during isometric exercise in these patients. In this case, sotalol appears to be superior to conventional beta-blockers, causing a greater decrease in heart rate. The most likely explanation for this is that the cardiac stimulation during isometric exercise does not reach sufficient levels for the class III action of sotalol to disappear altogether.

**Ventricular rate control during daily activities**

This study used 24-h Holter recordings to investigate the effectiveness of the studied medications on ventricular rate control during patients’ daily activities. The results showed that during the day, when sympathetic tone is increased, digoxin is insufficient for rate control in patients with chronic atrial fibrillation. Sotalol, however, was shown to be effective in achieving this aim, and was superior to a conventional beta-blocker, especially during the daytime. The most likely explanation of this is that during daily activities the patients do not reach maximum exercise levels and so sotalol retains its class III action.

**Methodological considerations**

Both drugs were administered after the patients had been digitalized. Digoxin has traditionally been used for
control of heart rate in these patients, but its relative importance has declined because, as the present findings show, although it reduces the resting heart rate, it fails to control exercise-induced tachycardia\(^{[1,3,6,18-22]}\). However, the administration of digoxin in combination with other medications has been proved to produce a greater decrease in heart rate than either digoxin or the additional agent alone. Furthermore, it allows for the use of smaller dosages of the drugs and thus fewer side-effects\(^{[6,18-22]}\).

### Safety

The present study showed that both sotalol and metoprolol are relatively safe when used for rate control in patients with chronic atrial fibrillation. In the case of sotalol, however, previous studies have reported a significant proarrhythmic effect, especially in patients with underlying heart disease\(^{[7,8,16,17]}\). The fact that patients with compromised left ventricular function were excluded from the present study is likely to have had a significant effect on the findings regarding the safety of sotalol. Another important factor is that the drug was administered in combination with digoxin, so that only relatively small dosages needed to be given.

### Study limitations

The fact that these patients had good left ventricular function must clearly have influenced the results concerning the effects of the two drugs on exercise performance. It is well known that conventional beta-blockers do not affect exercise capacity in atrial fibrillation patients with good left ventricular function, but reduce it in patients with atrial fibrillation and impaired left ventricular function. Given the weaker negative inotropic action of sotalol, it seems likely that its advantages over beta-blockers might become even more apparent in patients with compromised left ventricular function, especially at low levels of exercise. Further studies will be necessary in order to investigate this question.

### Study implications

Currently, there are three major classes of pharmacological agents that are used for controlling the ventricular rate in patients with chronic atrial fibrillation: digitalis glycosides\(^{[1,3,6,18-22]}\), beta-blockers\(^{[1-5]}\) and calcium channel blockers\(^{[3,6,19,21-25]}\). However, in many patients, adequate rate control either cannot be achieved with the range of drugs available, or requires such large doses of the drug in question that the adverse reactions detract from the beneficial effects. Therefore, there is still a need for a safer, better tolerated and more effective drug for ventricular rate control in these patients.

The present study suggests that this position could be filled by sotalol, a non-selective beta-blocker that also has a class III effect. According to the results of this study, this agent, combined with digoxin, is safe and is more effective in controlling heart rate than conventional beta-blockers in patients with chronic atrial fibrillation during daily activities, when the patient does not reach maximal levels of exercise. Further studies are needed to compare the effectiveness of sotalol in controlling ventricular rate in patients with chronic atrial fibrillation, with that of other treatments, such as calcium channel blockers.

### References


