SHORT SERIES REPORT

Increased AAI mode pacing threshold after termination of atrial fibrillation by acute administration of disopyramide phosphate

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Aims We studied changes in atrial pacing threshold after termination of atrial fibrillation (AF) by acute administration of disopyramide phosphate (DP) to elucidate the suitable setting for atrial pacing output before AF termination.

Methods and results Four patients with sick sinus syndrome implanted with AAI mode pacemakers were examined. Disopyramide phosphate (2 mg/kg body weight) was injected intravenously for termination of a total of eight AF episodes. The maximal pacing threshold after AF termination (5.2 ± 0.8 V at 0.45 ms) was significantly higher than that at baseline (1.3 ± 0.2 V at 0.45 ms; P < 0.01) and the average increment was 433 ± 68%. During a period free from AF, an acute administration of DP did not increase the atrial pacing threshold and serum disopyramide levels were not toxic.

Conclusion The increased atrial pacing threshold observed after AF termination cannot be explained by the action of DP alone. However, our results suggest that atrial pacing output should be set at the maximum value before DP is administered to induce AF termination in patients with AAI pacemaker-dependent bradyarrhythmias.

KEYWORDS
Antiarrhythmic drug; Atrial fibrillation; Disopyramide phosphate; Pacing failure; Pacing threshold; Sick sinus syndrome

Introduction

An increased pacing threshold after administration of antiarrhythmic drugs (AADs)¹⁻⁷ is a condition that is often encountered and a severe problem for patients with pacemaker-dependent bradyarrhythmia. Most of the reports regarding this condition are about ventricular pacing threshold and chronic administration of AADs, whereas there are few studies of atrial pacing threshold or acute administration of AADs for termination of tachyarrhythmia.

We previously reported a case of atrial pacing failure following termination of atrial fibrillation (AF) by acute administration of disopyramide phosphate (DP), a class Ia AAD.⁸ In that patient, a dramatic increase in atrial pacing threshold was the main feature of the case; therefore, we investigated the degree and mechanism of the increase in atrial pacing threshold after AF termination by acute administration of DP in four other subjects. Further, we attempted to determine a suitable setting of atrial pacing output before administration of DP based on the degree of changes in pacing threshold.

Methods

Patients

Four patients with implanted AAI pacemakers (Dash, model 292-03 R, Sulzer Intermedics Inc., Freeport, TX, USA), chosen according to the pacemaker criteria reported by Nielsen et al.,⁹ were enrolled in this study. When the device was implanted, atrial pacing threshold was <1.0 V at 0.45 ms in all of the patients. A total of eight episodes of paroxysmal AF was studied.

Measurement of atrial pacing threshold after AF termination by acute administration of DP

Before beginning the experiments, during the period free from AF, atrial pacing thresholds were measured (Thbase) by pulse amplitude (V) at a fixed pulse duration of 0.45 ms using a pacemaker programmer (RX 5000 programmer 522-12, Sulzer Intermedics Inc.) with the patient in a supine position. Beta-blockers were administered to control the ventricular rate of paroxysmal AF in all of the patients (Table 1).

During each episode of paroxysmal AF, the pacing output was first set at a maximum of 8.1 V with a pulse duration of 1.0 ms. Next, DP at a dose of 2 mg/kg body weight (maximum dose, 150 mg) was administered intravenously over 10 min. Arterial blood pressure using a sphygmomanometer and QT intervals with an electrocardiographic (ECG) monitor were recorded.

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simultaneously at 5 min intervals. After recognizing AF termination on the ECG monitor, the pacing threshold at 0.45 ms was measured in a non-invasive manner using the pacemaker programmer after 3, 5, 10, 15, and 20 min. The maximum atrial pacing threshold was defined as \( T_{\text{max}} \), whereas the increment was defined as \( \frac{T_{\text{max}}}{T_{\text{base}}} \times 100\% \). The time from AF termination to \( T_{\text{max}} \) was determined as time to \( T_{\text{max}} \) (min).

To measure serum levels of disopyramide, potassium, and creatinine, blood samples were obtained via the median cubital vein just after AF termination, then centrifuged at 3000 rpm for 5 min. The level of disopyramide was measured using an enzyme immunoassay.

Measurement of atrial pacing threshold after AF termination by acute administration of DP

One week after the second episode of paroxysmal AF in each patient, during a period free from AF, atrial pacing threshold was measured after acute administration of DP to assess the effect of DP. After the time required to terminate AF during the second episode, measurements of atrial pacing threshold were started and blood samples were obtained using the same method noted above. We measured pacing threshold before administration of DP (\( T_{\text{base}} \)) and maximal pacing threshold after administration of DP (\( T_{\text{max}} \), V), and also determined the increment \( \frac{T_{\text{max}}}{T_{\text{base}}} \times 100\% \).

Statistical analysis

The results are shown as mean ± SE. Student’s \( t \)-test was used to compare values between \( T_{\text{base}} \) and \( T_{\text{max}} \) within each group and an unpaired \( t \)-test was used to compare all values between the groups. Differences with a \( P \)-value of less than 0.05 were considered statistically significant.

Results

Patient characteristics

The patient characteristics are shown in Table 1. Two patients had mild arterial hypertension, whereas none had a history of angina pectoris or heart failure or had been receiving AADs over the long term. Serum levels of potassium (3.9–4.5 mEq/dL) and creatinine (0.5–0.8 mg/dL) were within normal limits.

Measurement of atrial pacing threshold after acute administration of DP during a period free from AF

Atrial pacing threshold did not increase significantly after an acute administration of DP during the period free from AF (Figure 1). The increment was 158 ± 14%; however, \( T_{\text{max}} \) (2.3 ± 0.6 V) was not higher than \( T_{\text{base}} \) (1.4 ± 0.2 V, \( P = NS \)) (Figure 2B). The serum level of disopyramide was 4.1 ± 0.5 \( \mu \)g/mL (Table 2).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Drugs</th>
<th>Type of pacing lead</th>
<th>LAD (mm)/EF (%)</th>
<th>Follow-up (months)</th>
<th>Duration of AF (h)</th>
<th>Rate of AF (bpm)</th>
<th>( T_{\text{max}} ) (V)</th>
<th>( T_{\text{after} 20 \text{min}} ) (V)</th>
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<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>SSS</td>
<td>Metoprolol</td>
<td>Tine</td>
<td>28/68</td>
<td>1st</td>
<td>30</td>
<td>8</td>
<td>90</td>
<td>2.5</td>
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<td></td>
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<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>SSS, HTN</td>
<td>Bisoprolol</td>
<td>Tine</td>
<td>32/72</td>
<td>1st</td>
<td>6</td>
<td>4</td>
<td>120</td>
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<td>100</td>
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<tr>
<td>3</td>
<td>67</td>
<td>M</td>
<td>SSS, HTN</td>
<td>Bisoprolol</td>
<td>Tine</td>
<td>30/67</td>
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<td></td>
<td>Steroid (-)</td>
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<td>26</td>
<td>0.5</td>
<td>110</td>
<td>5.4</td>
</tr>
</tbody>
</table>

SSS, sick sinus syndrome; HTN, hypertension; LAD, left atrial dimension on echocardiography; EF, ejection fraction on echocardiography; 1st, first episode of paroxysmal atrial fibrillation; 2nd, second episode of paroxysmal atrial fibrillation; \( T_{\text{max}} \), maximal pulse amplitude atrial pacing threshold at 0.45 ms after AF termination; \( T_{\text{after} 20 \text{min}} \), pulse amplitude atrial pacing threshold at 0.45 ms 20 min after AF termination.
Ia12 and Ib13 AADs have been reported to increase ventricular as well as metabolic and electrolyte disorders,6 can have an effect on pacing threshold compared with other AADs. In another report, Bianconi et al speculated that the increase in ventricular pacing threshold after acute administration, and the serum level of disopyramide serum (a) after termination of AF by acute administration of DP, and (b) after acute administration of DP during the period free from AF. Disopyramide toxicity has also been shown to cause greater increases in ventricular pacing threshold after acute intravenous administration.7 In the present study, the serum levels of disopyramide corresponded to the therapeutic level reported by Niarchos.16 Therefore, the increase in atrial pacing threshold observed in our patients was not due to disopyramide toxicity.

To assess the effect of DP alone, atrial pacing threshold was measured after an acute administration of DP during a period free from AF. We found a relatively lower increase of atrial pacing threshold as with that measured after AF termination, whereas the serum concentrations of disopyramide were similar throughout the study. The effects of AF alone on atrial pacing threshold are considered to be involved in the mechanisms that increase atrial pacing threshold. A recent report found a rise in atrial and ventricular stimulation thresholds after direct current cardioversion for AF termination,17 thus AF itself may be a cause of the increase in pacing threshold after its termination. Then, we speculated that the electrophysiological characteristics of the atrium might change in the presence of both DP and AF. Soriano et al.18 reported rate-dependent ventricular pacing failures with propafenone. The same mechanism may exist in the atrial myocardium related to reversible electrical remodelling19 in the presence of DP and AF. However, correlation between duration or rate of AF and Thmax is unclear in study patients (Table 1). Furthermore, the interaction of beta-blocker and DP should also be considered. Propranolol has been reported not to cause clinically important changes in the ventricular pacing threshold,20 but up to now, there are no published data on the interaction of beta-blocker and AADs.

In the present study, the average increment was >300% after AF termination by an intravenous administration of DP. In addition, the time to Thmax was relatively short (4.1 ± 0.9 min). Pacing output is commonly set at two or three times the pacing threshold11 as a safety margin; however, the present results suggest that atrial pacing output should be set at maximum before administration of DP for AF termination in patients with AAI pacemaker-dependent bradyarrhythmias.

### Table 2

<table>
<thead>
<tr>
<th>Increment (%)</th>
<th>Time to Thmax (min)</th>
<th>Serum disopyramide (µg/mL)</th>
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<tbody>
<tr>
<td>(a) 483 ± 68 (250–810)</td>
<td>4.1 ± 0.9 (3–10)</td>
<td>4.4 ± 0.6 (2.5–7.1)</td>
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<tr>
<td>(b) 158 ± 14 (133–200)</td>
<td>3.5 ± 0.5 (3–5)</td>
<td>4.1 ± 0.5 (2.9–5.4)</td>
</tr>
</tbody>
</table>

Average values are expressed as means ± SE. Increment, Thmax/Thbase × 100; serum disopyramide, serum level of disopyramide.
Conclusion

Atrial pacing threshold was increased an average of >400% after AF termination by acute administration of DP in patients with AAI pacemakers. This phenomenon could not be explained by DP alone; however, this may have been more related to AF. Nevertheless, great care must be taken when DP is administered for AF termination in patients with AAI pacemaker-dependent bradyarrhythmias.

References