Discordant Repolarization Alternans-Induced Atrial Fibrillation is Suppressed by Verapamil

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**Background** Ventricular alternans of repolarization produces serious ventricular arrhythmias in experimental models. The present study investigated the role of alternans of atrial repolarization in patients with atrial fibrillation (AF).

**Methods and Results** Electrophysiological studies were performed in 19 patients without structural heart disease. Monophasic action potentials (MAP) were recorded with 2 Franz catheters during steady state pacing, starting at a cycle length (CL) of 400 ms with subsequent decrements of 10 ms. Duration from the onset of upstroke to 90% repolarization of the MAP were measured. If discordant alternans (DA) was present during pacing, verapamil was administered, and MAP measurements were repeated. Rapid pacing resulted in concordant alternans to DA in 13 of 19 (68%) patients. AF was initiated after the induction of DA in 8 of 13 patients (p=0.012). Verapamil treatment resulted in a significant decrease in the longest pacing CL at which DA was induced (207±19 vs 178±17 ms, p<0.0001).

**Conclusions** Rapid atrial pacing induced DA and was associated with initiation of AF. Furthermore, induction of DA was suppressed by verapamil. Reducing the spatiotemporal repolarization heterogeneity may be how the calcium-channel blockade prevents initiation of AF. (Circ J 2005; 69: 1368 – 1373)

**Key Words:** Atrial fibrillation; Spatiotemporal repolarization; Verapamil

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**Table 1 Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td>Population</td>
<td>19</td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>52±13</td>
</tr>
<tr>
<td>M/F</td>
<td>11/8</td>
</tr>
<tr>
<td>Induced arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>6</td>
</tr>
<tr>
<td>Atrioventricular nodal reentrant tachycardia</td>
<td>6</td>
</tr>
<tr>
<td>Atrioventricular reentrant tachycardia</td>
<td>5</td>
</tr>
<tr>
<td>Noninduced arrhythmia</td>
<td>2</td>
</tr>
<tr>
<td>Episodes of paroxysmal atrial fibrillation</td>
<td>5</td>
</tr>
</tbody>
</table>

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Electrical alternans is defined as a beat-to-beat change in the amplitude of the electrocardiogram (ECG) that repeats once every other beat and is generated by alternation of the action potential duration (APD) at the cellular level! Clinical studies suggest that there is a high correlation between large amplitude microscopic T wave alternans (TWA) and ventricular arrhythmias or sudden cardiac arrest.1,2 Discordant alternans (DA) is a phenomenon of 2 spatially distinct regions exhibiting APD alternans of opposite phases that is associated with TWA and arrhythmia induction. Pastore et al recently reported that DA produced spatial gradients of repolarization of sufficient magnitude to cause unidirectional block and reentrant ventricular fibrillation.3 Other studies have demonstrated that TWA is a fairly common phenomenon at high heart rates and that temporal variability of ventricular repolarization is associated with susceptibility to ventricular fibrillation.1,2

Atrial fibrillation (AF) is the most frequently encountered arrhythmia in clinical practice, but the precise mechanisms by which it is initiated and maintained are unclear. Previous studies demonstrated that long-term rapid right atrial pacing causes sustained AF, presumably because of pacing-induced electrical and anatomical remodeling. Neural remodeling may also play an important role in the generation and maintenance of AF.4,6,10

Recent reports have suggested that calcium entry blockers, such as verapamil, suppress atrial fibrillation11,12 and, in the canine myocardium, suppress monophasic action potential (MAP) alternans.13 Verapamil administration has resulted in attenuation of various phenomena, including short-term (<24 h) tachycardia-induced shortening, maladaptation of the atrial effective refractory period (AERP), dispersion of the AERP, and inducibility of AF.11,13

Based on these data, we hypothesized that the spatiotemporal variability of atrial repolarization may play an important role in the initiation of AF, similar to the phenomenon by which ventricular fibrillation is suppressed by verapamil. Thus, the aim of the present study was to determine the relationship in humans between inducibility of AF and spatiotemporal variability of atrial repolarization induced by rapid atrial pacing. Furthermore, we investigated the association of spatiotemporal variability of atrial repolarization induced by rapid atrial pacing and the effect of verapamil on the
atrial electrophysiologic properties.

**Methods**

**Patients**

Twenty-six consecutive patients underwent electrophysiologic study (EPS) for supraventricular tachyarrhythmias, and MAP was recorded clearly in 19 patients (Table 1). There was no evidence of structural heart disease by physical examination, chest X-ray or echocardiography, and there were not any electrolyte abnormalities, metabolic disorders or advanced systemic diseases that could affect cardiac function. The end-diastolic left atrial internal dimension was within 40 mm, and right atrium was smaller than the left atrium in all patients. Eleven patients had paroxysmal supraventricular tachycardia, and 6 had paroxysmal atrial flutter (AFL). In the remaining 2 patients, therapeutic arrhythmias could not be induced during the study despite a past history of palpitations.

Five patients had episodes of paroxysmal atrial fibrillation (PAF), which was diagnosed by documentation of the arrhythmia on ECG, and/or Holter ECG recordings. The ethics committee of Hyogo College of Medicine approved this study protocol, and written informed consent was given by all patients. Procedures were in accordance with institutional guidelines.

**Electrophysiological Study**

All patients underwent an EPS in a fasting and unsedated state, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the study. Femoral venous access was obtained under local anesthesia. After other electrophysiological examinations, a 5Fr hexapolar catheter (Daig, Supreme, Minnetonka, MN, USA) was placed in the high lateral right atrium (HRA) via the left femoral vein for rapid drive pacing, and 2 quadripolar Franz catheters (EP Technologies Inc, San Jose, CA, USA) were inserted through the right femoral vein under fluoroscopic control and positioned at 2 different sites (free wall and septal wall in the right atrium) to record MAP. The position of each MAP electrode was adjusted until an acceptable MAP signal was obtained. Programmed atrial stimulation was performed with a programmable stimulator (EPMed Systems, Inc, West Berlin, NJ, USA). Atrial pacing was performed using the HRA catheter set at twice the diastolic threshold. The pacing interval was initiated at 400 ms and then decreased in 10-ms steps until it reached 180 ms or until atrial capture failed or AF was initiated. MAPs were simultaneously recorded from the 2 sites. To obtain clear and stable MAP waveforms, recording was initiated after HRA pacing and continued for at least 1 min.

**Measurements**

The activation time (AT) was measured as the interval from the beginning of the pacing spike to the onset of the upstroke of the MAP. The APD was measured at 90% repolarization (APD90: from the onset of the upstroke to 90% repolarization of the MAP) at each site during rapid HRA pacing (Fig 1). Pacing artifact had no appreciable effect on MAP measurements.

All patients underwent MAP acquisition by an EPMed System, which records a digital signal at 500 Hz that can be viewed at 200 mm/s with adjustable gain control. Digital calipers, capable of measuring to within 1 ms (horizontal

![Fig 1. Action potential duration measured from the onset of the upstroke to 90% repolarization of the monophasic action potential during rapid high right atrium pacing. APD, action potential duration.](image)

![Fig 2. Changes in monophasic action potential at the right atrial septal and free walls caused by rapid atrial pacing. (Left) Alternans in action potential duration (APD90) of the free wall is in phase with the alternans at the septal wall during 250 ms pacing (concordant alternans). (Right) Alternans in APD90 of the free wall is out of phase with the alternans at the septal wall during 210 ms pacing (discordant alternans).](image)
axis) and 0.01 mV (vertical axis), were used to determine the AT and APD90. The intervals of AT and APD90 were measured in 3 consecutive beats at each site. In order to exclude ventricular excitation, measurement of AT and APD90 was started and analyzed when a greater than 3:1 atrioventricular (AV) block was present.

All measurements were conducted in duplicate by 2 separate investigators.

**Definition**

Because the error associated with measurements in AT and APD90 was 3±4 ms, only alternans >10 ms was considered significant. If the alternans in measurements at the free wall were in phase with the alternans at the septal wall in the right atrium, it was defined as concordant alternans (CA) (Fig 2, Left panel). If the free wall site alternated out of phase with the alternans at the septal wall in the right atrium, it was defined as DA (Fig 2, Right panel).

**Study 1**

At least 15 min before rapid HRA pacing, propranolol (0.2 mg/kg intravenously at 2 mg/min) and atropine (0.04 mg/kg intravenously over 2 min) were administrated to produce autonomic blockade. AT and APD90 of 3 consecutive beats were measured in every pacing interval at each site, and the occurrence of CA, DA and AF was noted. In addition, the differences in maximal pacing intervals were measured and compared in patients with and without PAF.

**Study 2**

Verapamil (0.1 mg/kg intravenously over 10 min) was administrated to patients who experienced DA during rapid HRA pacing. At least 15 min later, rapid HRA pacing was initiated, and the MAPs were recorded. As in study 1, the occurrence of CA or DA was noted. If DA was induced, maximal pacing intervals before and after administration of verapamil were measured and compared. If DA was not induced until 180 ms pacing, the maximal pacing interval for DA used for statistical analysis was designated as 170 ms. In addition, differences in the inducibility of AF and susceptibility to DA before and after administration of verapamil were compared.

**Data Analysis**

In study 1, Fisher’s exact probability test was used to determine significant differences. In study 2, the Wilcoxon matched paired test was used to compare data obtained before and after administration of verapamil. Continuous data were expressed as mean±SD, and a value of p<0.05 was considered statistically significant.

**Results**

The clinical characteristics of the 19 study patients are summarized in Table 1. The mean age was 52±13 years (range 40–77) and 57.8% were men. Five patients had episodes of PAF and 8 patients (42.1%) developed AF during rapid HRA pacing, but it remitted spontaneously within several minutes (mean duration of PAF 3.43±1.64 min).

**APD90 Alternans**

**Study 1**  CA was induced in 14 patients, and DA in 13 patients (Table 2). In the 13 patients in which DA was induced, DA was seen in the context of CA, but CA did not occur alone. The mean cycle length (CL) of the longest pacing intervals at which DA was induced was 207±19 ms. DA was induced in each of the 5 patients with documented PAF (Fig 3, Left). Inducibility of DA was not significantly different when comparing patients with and without documented PAF (100.0 vs 57.1%, respectively; p=0.128). In addition, the maximal pacing intervals at which DA was induced were not significantly different when comparing both groups (200.0±12.2 vs 211.2±22.3 ms, respectively; p=0.33).

In 8 of the 13 patients (61.8%) in which DA was induced, AF was also induced following DA (Fig 3, Right). Fig 4
illustrates the transition of DA into AF, which was seen in all patients with induced AF. AF did not occur in patients without DA. There were no significant differences in age, sex ratio and induced arrhythmias when comparing the 2 groups with and without induced DA. However, the maximal pacing intervals at which DA was induced were significantly different when comparing both groups with and without induced AF (215.0±20.0 ms vs 189.1±13.8 ms, respectively; p=0.004).

Study 2 Of the 13 patients in which DA was induced (Table 2), DA occurred in only 3 (23%) patients after administration of verapamil (Fig 5, Right). Verapamil treat-
Atrial Spatiotemporal Dispersion and Initiation of AF

The present study demonstrated that DA was induced by rapid atrial pacing in 13 patients (68.4%) and in all of them, CA preceded DA, and AF was always preceded by DA. In addition, initiation of AF only occurred following DA. Although the mechanism that triggers DA remains unclear, we speculate that localized conduction block secondary to increasing spatiotemporal dispersion of atrial repolarization with rapid atrial pacing is responsible for this phenomenon, which subsequently leads to AF.

Atrial Spatiotemporal Dispersion and Verapamil

Verapamil suppressed the inducibility of DA and susceptibility to AF in the present study. However, previous studies demonstrated that verapamil increased the duration of an induced AF episode and increased atrial vulnerability. By contrast, the present study demonstrated that the spatiotemporal variability of atrial repolarization was suppressed by verapamil and that the inducibility of AF was reduced. The discrepancy may be related to the method employed for long-term rapid atrial pacing; this study was performed in human models of recent-onset AF induced by rapid atrial pacing. Kinebuchi et al demonstrated that verapamil was found to prevent short-term rapid pacing-induced shortening of the AERP. Another study demonstrated that verapamil did not attenuate the AERP dispersion induced by long-term rapid atrial pacing, but verapamil attenuated the AERP dispersion induced by 1-day rapid atrial pacing, consistent with the findings from the present study.

The mechanism underlying the ability of verapamil to prevent changes in the atrial electrophysiological properties under short-term rapid atrial pacing is unclear. Lee et al reported that verapamil attenuated AERP dispersion by preventing AERP shortening. Others reported that verapamil shifted the MAP slope of the plateau upward and the slope of phase 3 downward, as well as demonstrating that verapamil suppressed the ST segment alternans concentrations that also influenced the slow inward current. Thus, it was concluded that transmembrane or intercellular movement of Ca2+ is involved in this process. In addition, Hirayama et al reported that delayed intracellular calcium cycling played a role in the concomitant occurrence of electrical alternans and that verapamil suppressed temporal electrical alternans in ventricular muscle. We presume that a similar phenomenon was induced in the human right atrium by rapid atrial pacing; temporal electrical alternans induced CA or DA, and that the effect was suppressed via a
verapamil-mediated reduction in intracellular calcium.

**Study Limitations**

First, we were unable to achieve critical pacing CLs under 170 ms. As a result, DA was induced in only 13 patients. Second, we did not perform an analysis of ADP90 until a greater than 3:1 AV block was achieved. However, when 3:1 AV block occurred, CA was already present in all patients. Therefore, we could not determine the longest pacing intervals required for initiation of CA. Third, fixation of both Franz catheters in stable sites during 1 session was technically difficult to achieve, making consecutive measurements of ADP90 at each pacing CL problematic. Therefore, we could not assess the relationship between local repolarization alternans and the pacing rate. Fourth, verapamil was only administered to patients who experienced DA during rapid HRA pacing. Therefore, we could not evaluate the effect of verapamil in patients without DA in study 1. Further work needs to be done for the purpose of demonstrating an association between the initiation of AF and verapamil.

**Conclusion**

DA induced by rapid atrial pacing was associated with the initiation of AF. Furthermore, DA and initiation of AF were suppressed by verapamil. Spatiotemporal repolarization heterogeneity may provide the substrate for initiation of AF and may be suppressed by calcium-channel blockers.

**References**