Electrical Remodeling in Persistent Atrial Fibrillation May Be Mediated by Changes in the \( \text{IK}_{\text{ATP}} \) Channel

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The goal of this study was to measure the effective refractory period (ERP), the conduction velocity (CV) and the wavelength (WL) after cardioversion in patients with persistent atrial fibrillation (AF) and to determine the effects of the adenosine triphosphate sensitive potassium channel (\( \text{IK}_{\text{ATP}} \)) opening agent, nicorandil, on those parameters in patients with persistent AF.

METHODS: Patients with AF underwent elective cardioversion followed by measurement of ERP and CV before and after administration of nicorandil. Parameters were measured again one week later, and the ERP and the CV was used to calculate WL.

RESULTS: ERP was significantly shorter immediately after termination of AF than at the 1-week time point (193.4 vs. 228.7 msec \( p < 0.01 \)). While there was no significant difference in ERP immediately after termination of AF when comparing measurements taken before and after the administration of nicorandil, ERP at the 1-week time point was shorter after nicorandil administration than before nicorandil administration (193.4 vs. 191.4 msec, n.s.; 228.7 vs. 217.2 msec, \( p < 0.01 \)). Further, WL was higher at the 1-week time point after nicorandil administration than before nicorandil administration.

CONCLUSIONS: These data indicate that the electrical remodeling that occurs after cardioversion is at least partially mediated by changes in \( \text{IK}_{\text{ATP}} \) channel behavior. Further, the electrophysiologic properties, that is, nicorandil prolonging the WL, may be of benefit in reducing the recurrence rate of AF.


Key words: Atrial fibrillation, Remodeling, Nicorandil, Conduction velocity

Introduction

The adenosine triphosphate (ATP)-sensitive potassium channel (\( \text{IK}_{\text{ATP}} \)) is activated by low intracellular concentrations of ATP and acts to shorten action potential duration (APD). Nicorandil, a specific agonist of \( \text{IK}_{\text{ATP}} \) channel, decreases the effective refractory period (ERP) under hypoxic or ischemic conditions in ventricular muscle cells, but the effect of nicorandil in the atria following atrial fibrillation (AF) remains unclear.

In 1995, Alessie et al. described a goat model of electrical remodeling induced by high-frequency atrial stimulation. Specifically, continued high-frequency atrial stimulation induced AF, and the duration was extended in proportion to the length of the stimulation period. Further, the presence of the
AF itself contributed to its persistence. These experimental studies showed that intracellular calcium overload and shortening the atrial ERP were important factors contributing to the persistence of AF.\(^4\) Other studies demonstrated that the levels of Kir6.2 mRNA, which encodes for a portion of the IK\(_{\text{ATP}}\) protein, was decreased in patients with paroxysmal AF\(^7\) and that the IK\(_{\text{ATP}}\) current density was down-regulated in patients with chronic AF.\(^8\) However, the precise role of IK\(_{\text{ATP}}\) in electrical remodeling remains unclear.

Maintenance of AF is dependent on the presence of simultaneous reentrant waves. Animal experiments and computer simulations indicate that AF is maintained by multiple independent wavelets that irregularly activate atrial cells at very high rates.\(^9\) The minimal size of a reentrant wave is related to the wavelength (WL), which is defined as the product of the local refractory period and the local conduction velocity (CV). Rapid atrial activation reduces CV\(^13\) and increases WL thereby promoting development or maintenance of AF. However, IK\(_{\text{ATP}}\) channel activation reduces rest potential and may increase CV and reduce WL, thereby decreasing the vulnerability to AF.

Therefore, the goal of this study was to measure the ERP, CV, and WL after cardioversion and to determine the effects of nicorandil on WL in patients with persistent AF.

**Methods**

**Subjects**

The patient population consisted of one female and eleven males (mean age, 58.9 ± 12.2 years; range, 29 to 72 years). Eight of the 12 patients had AF (AF group) that had persisted for at least 30 days (mean duration, 94.9 ± 81.1 days; range, 30 to 279 days; mean age, 60.6 ± 8.1 years), while the other four patients (control group) did not experience any episodes of AF (mean age, 55.5 ± 19.2 years). The mean left atrial diameter (LAD), as determined by echocardiography, was 39.9 ± 5.8 mm in all patients and was 41.8 ± 5.6 and 36.2 ± 4.6 mm in the AF and control subgroups, respectively (\(p < 0.1\)).

Co-morbid conditions included hypertension (n = 4) and ischemic heart disease (n = 1), and there was no significant difference in age, gender or co-morbid conditions when comparing the two groups of patients. All patients were classified as New York Heart Association functional class I or II, with no clinical or instrumental signs of cardiac failure. (Tables 1 and 2)

The duration of AF before participation in the current study was determined by regular electrocardiography (ECG) and ambulatory Holter ECG monitoring. All patients remained hospitalized during the study. After cardioversion, patients were monitored by continuous ECG to detect any recurrence of atrial fibrillation.

Written informed consent was obtained from all patients, and the Showa University School of Medicine approved all protocols.

**Electrophysiological Study**

Electrophysiological studies (EPS) were performed immediately after cardioversion (Day 1) and seven days later (Day 7). Cardioversion was performed on the body surface following intravenous anesthesia with thiopental and diazepam. Two catheters were inserted via the femoral vein and used for EPS studies: a basket-type catheter (EPT

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<th>Gender (M/F)</th>
<th>All patients ((n = 12))</th>
<th>AF Group ((n = 8))</th>
<th>Control Group ((n = 4))</th>
<th>(p) value</th>
</tr>
</thead>
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<td>Female</td>
<td>11/1</td>
<td>8/0</td>
<td>3/1</td>
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<td>Age (years)</td>
<td>58.9 ± 12.2</td>
<td>60.6 ± 8.1</td>
<td>55.5 ± 19.2</td>
<td>n.s.</td>
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<tr>
<td>AF duration (days)</td>
<td>—</td>
<td>94.9 ± 81.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>39.9 ± 5.78</td>
<td>41.8 ± 5.6</td>
<td>36.2 ± 4.6</td>
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<tr>
<td>EF (%)</td>
<td>63.1 ± 7.4</td>
<td>60.4 ± 7.2</td>
<td>68.5 ± 4.2</td>
<td>n.s.</td>
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<tr>
<td>Heart disease (n)</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
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<td>3</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1</td>
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<td>0</td>
<td>—</td>
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<td>Lone AF</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>—</td>
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</table>

Data are presented at the mean value ± SD or number of patients. AF = atrial fibrillation; F = female; M = male; EF = left ventricular ejection fraction; LAD = left atrial diameter. A total of twelve patients, consisting of 11 men and one woman, with a mean age of 58.9 years and a range of 29 to 73 years were studied. Mean duration of AF was 94.9 days, with a range of 30 to 279 days. Left atrial diameter was 39.9 mm, as measured by ultrasound.
Corp.; 64 electrodes, 32 pairs of bipolar leads; 48 or 60 mm diameter based on echocardiographic measurements of the LAD) placed in the right atrium, and a standard 8-pole electrode catheter for measurement of the electrical potential of the bundle of His. The 48 and 60 mm basket catheters possessed eight splines, containing eight electrodes with 5 and 4 mm inter-electrode distances, respectively. Surface ECG and endocardial signals, acquired by bipolar leads, were monitored continuously and stored on a computer-based digital amplifier/recorder system (CardioLab®, Pruka Engineering Inc., Houston, TX, USA) on optical disks for offline analysis. Intracardiac electrograms were filtered from 30 to 500 Hz and measured using computer-assisted calipers at a sweep speed of 400 mm/sec.

ERP measurements

ERP was measured using 32 pairs of bipolar leads within the basket catheter that was located in the right atrium. In all, ERP was measured at 802 points in the right atrium immediately and one week after cardioversion. ERP was determined by the longest coupling interval in which an atrial premature stimulus was not captured after a seven-beat basic stimulation with 400 and 600 msec basic cycles.

The pacing voltage (10 volts) was determined from the results of our previous study in which the diastolic threshold was between 5 and 7 volts using the basket catheter under the same conditions used in the current study.

Administration of nicorandil

Nicorandil infusion was performed as described previously.14) Briefly, 12 milligrams (mg) of nicorandil was administered intravenously after baseline ERP measurements. ERP was measured again within 15 minutes after nicorandil infusion (Day 1 with nicorandil). The same protocol was repeated one week after AF termination (Day 7 with nicorandil) (Figure 1).

Conduction velocity analysis

The distal bipolar (1–2) of each spline of the basket catheter was paced, and the activation time from the distal (3–4) to the proximal bipolar (7–8) was measured. The conduction velocity was calculated as the activation time divided by the distance from the distal (3–4) to the proximal bipolar (7–8). Conduction time was measured at cycle lengths of

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age</th>
<th>Gender</th>
<th>AF duration (days)</th>
<th>LAD (mm)</th>
<th>EF (%)</th>
<th>Anti-arrhythmic drug</th>
<th>OHD</th>
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<td>IHD</td>
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<td>30</td>
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<td>HT</td>
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<tr>
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<td>64</td>
<td>M</td>
<td>39</td>
<td>42.2</td>
<td>52.0</td>
<td>Cibenzoline</td>
<td></td>
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<tr>
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<td>71</td>
<td>M</td>
<td>279</td>
<td>42.5</td>
<td>63.0</td>
<td>Bepridil</td>
<td></td>
</tr>
<tr>
<td>No. 5</td>
<td>59</td>
<td>M</td>
<td>60</td>
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<td>51.0</td>
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<tr>
<td>No. 6</td>
<td>68</td>
<td>M</td>
<td>66</td>
<td>47.0</td>
<td>55.0</td>
<td>Cibenzoline</td>
<td></td>
</tr>
<tr>
<td>No. 7</td>
<td>47</td>
<td>M</td>
<td>120</td>
<td>44.6</td>
<td>69.0</td>
<td>none</td>
<td>HT</td>
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<tr>
<td>No. 8</td>
<td>57</td>
<td>M</td>
<td>52</td>
<td>46.0</td>
<td>59.0</td>
<td>Cibenzoline</td>
<td>HT</td>
</tr>
<tr>
<td>No. 9</td>
<td>67</td>
<td>F</td>
<td>—</td>
<td>31.0</td>
<td>73.0</td>
<td>Verapamil</td>
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<tr>
<td>No. 10</td>
<td>54</td>
<td>M</td>
<td>—</td>
<td>37.2</td>
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<tr>
<td>No. 11</td>
<td>29</td>
<td>M</td>
<td>—</td>
<td>34.6</td>
<td>70.0</td>
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<td></td>
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<tr>
<td>No. 12</td>
<td>72</td>
<td>M</td>
<td>—</td>
<td>42.0</td>
<td>68.0</td>
<td>Verapamil</td>
<td>HT</td>
</tr>
</tbody>
</table>

Subjects consisted of 12 patients with atrial fibrillation for at least 30 days who subsequently underwent elective cardioversion. EPS had been performed immediately after AF converted to sinus rhythm. AF = atrial fibrillation; F = female; M = male; EF = left ventricular ejection fraction; LAD = left atrial diameter; OHD = organic heart disease, IHD = ischemic heart disease, HT = hyper tension.

Figure 1 Time course of electrophysiologic (EPS) measurements. EPS measurements were obtained immediately after cardioversion (Day 1) and before and after administration of nicorandil (Day 1 with nicorandil). One week later, measurements were repeated using the same protocol (Day 7, and Day 7 with nicorandil).
600 msec after stable capture for at least three seconds.

**Statistical Analysis**

Data are presented as mean ± SD. Differences in continuous variables were analyzed by the Wilcoxon Signed Rank Test or the Mann-Whitney U Test when independent. Atrial wavelength was defined as the distance traveled by the atrial impulse during the atrial effective refractory period as follows: wavelength = ERP × conduction velocity. Differences were considered significant at \( P < 0.05 \), and tendency at \( P < 0.1 \).

**Results**

1. Atrial refractoriness

**Figure 2** shows the results of the electrophysiological studies performed immediately after and seven days after cardioversion. The average ERP values on days 1 and 7 in the AF group were 193.4 ± 21.6 msec (172.5–237.1 msec) and 228.7 ± 33.2 msec (184.5–282.5 msec), respectively, and the average ERP in the control group was 213.2 ± 19.1 msec (196.1–237.1 msec). The ERP value was significantly shorter immediately after cardioversion than on day 7 (\( P < 0.01 \)). While the ERP on day 7 tended to be longer in the AF group when compared to the control group, this difference did not reach the level of statistical significance (Figure 2, left panel). The ERP values immediately after cardioversion were similar when comparing values obtained before and after nicorandil administration (193.4 ± 21.6 msec; range, 172.5–238.9 msec vs. 191.4 ± 20.7 msec; range, 171.3–232.3 msec). However, the ERP values obtained one week after cardioversion were lower in the AF group after administration of nicorandil (217.2 ± 26.8 msec; range, 180.9–264.1 msec) than before administration of nicorandil (228.7 ± 33.2 msec; range, 184.5–282.5 msec) (\( P < 0.01 \)). Further, ERP was lower in the control group after administration of nicorandil than before administration of nicorandil, but this difference did not reach the level of statistical significance (200.1 ± 17.1 msec; range, 182.9–217.1 msec vs. 213.2 ± 9.1 msec; range, 196.1–237.1 msec, n.s.). The response to nicorandil decreased immediately after cardioversion but recovered after one week (Figure 2, right panel).

2. Conduction velocity

Conduction velocity was relatively slower in the AF group immediately after cardioversion when compared with conduction velocity in the control group (1.12 ± 0.09 vs. 1.43 ± 0.36 m/sec; \( P < 0.1 \)), but there was no significant difference in conduction velocity when comparing values obtained immediately after cardioversion and those obtained one week later in the AF group. Conduction velocity significantly increased after nicorandil administration immediately after and one week after cardioversion in the AF group (1.12 ± 0.09 vs. 1.26 ± 0.12 m/sec, \( p < 0.05 \), 1.08 ± 0.10 vs. 1.19 ± 0.12 m/sec \( p < 0.05 \), respectively) (Figure 3).

3. Wavelength

WL was relatively shorter immediately after cardioversion in the AF group when compared with the control group (216.4 ± 31.8 vs. 309.0 ± 101.8 mm; \( p < 0.1 \)), and WL was longer seven days after cardioversion when compared to immediately after cardioversion in the AF group (216.4 ± 31.8 vs.
Nicorandil administration increased WL immediately after cardioversion (216.4 ± 31.8 to 240.6 ± 34.8 mm; *p < 0.05*) and seven days after cardioversion (251.3 ± 45.0 to 262.5 ± 45.2 mm; *p < 0.05*) (Figure 4). The WL was shorter immediately after cardioversion in the AF group than in the control group, and this difference persisted at the 7-day time point.

**Discussion**

**Major Findings**

The present study demonstrated that the ERP response to nicorandil decreased immediately after cardioversion but recovered after one week. These data suggest that electrical remodeling in patients with persistent AF is mediated by the IK<sub>ATP</sub> channel and that this difference resolved after patients were maintained in normal sinus rhythm for a period of one week.

Further, the WL was shorter immediately after cardioversion when compared to seven days after cardioversion or to patients in normal sinus rhythm. Further, nicorandil administration resulted in an increase in WL. Because WL is a major determinant of the vulnerability to developing and maintaining AF, these data suggest that nicorandil may prevent the recurrence of AF after cardioversion.

**Atrial Refractoriness**

Other studies have demonstrated that rapid depolarizations result in increased cytosolic Ca<sup>2+</sup> concentration (calcium overload) and ERP shortening in cardiac myocytes<sup>4,16–19</sup> via changes in I<sub>CaL</sub>, I<sub>To</sub> and I<sub>Na</sub> and that inhibition of I<sub>Na</sub> results in decreased conduction velocity. Further, Balana et al. reported that chronic AF was associated with down-regulated IK<sub>ATP</sub> currents<sup>8</sup> and Brundel et al. reported that mRNA levels of Kir6.2, which encodes for a portion of the IK<sub>ATP</sub> protein, are reduced in patients with
persistent AF. They also demonstrated that the reduction in levels of Kv4.3, Kv1.5 and Kv3.1, which encode for portions of the I_{F}, I_{M} and I_{ACh} channels, could be reversed by maintenance of sinus rhythm.

One study reported that atrial blood flow increases 2- to 3-fold within 5 seconds after initiation of atrial fibrillation, but others have reported that rapid atrial rates result in reduced atrial blood flow after six weeks in a pacing model. Since oxygen consumption increases with rapid atrial excitation, rapid atrial rates likely result in myocardial hypoxia, which is consistent with reports of decreased intracellular creatinine phosphate levels in the context of atrial fibrillation. This energy depletion may lead to a decrease in the intracellular ATP concentration and subsequent activation of I_{K_{ATP}} channels, thereby shortening APD, suppressing inward calcium current during excitation, and preventing atrial cell calcium overload.

The present study demonstrated that ERP was shortened in the context of AF but normalized after one week of normal sinus rhythm, which is consistent with published reports of ERP shortening and its time course by electrical remodeling after atrial fibrillation. Further, the present study demonstrated that nicorandil administration did not affect ERP immediately after cardioversion but did shorten ERP at the 7-day time point. This change in the response to nicorandil may occur via a decrease in I_{K_{ATP}} channel gene expression that subsequently leads to a reduction in the current density of I_{K_{ATP}}. Alternatively, it is possible that the I_{K_{ATP}} channels were already activated by relative ischemia, which would limit any further increase in response to nicorandil.

Conduction Velocity and Wavelength

The WL is defined as the distance traveled by the depolarization wave and can be determined by multiplying the CV by the ERP. A shortened wavelength in the atrium results in increased vulnerability to development and maintenance of AF. Sodium channel blockers (class I anti arrhythmic drugs) prolong the refractory period and decrease conduction velocity, thereby countering the change in WL and promoting conversion to normal sinus rhythm. L-type calcium channel blockers, such as verapamil, decrease intracellular Ca overload and electrical remodeling but also shorten the refractory period and decrease conduction velocity. Thus, verapamil may prevent electrical remodeling but not AF recurrence.

Any increase in the I_{K_{ATP}} current shortens the APD, which subsequently limits calcium entry during excitation and prevents calcium overload. Furthermore, the I_{K_{ATP}} current repolarizes the resting potential, thereby increasing the sodium current and conduction velocity. These effects of the I_{K_{ATP}} channel oppose the effects of shortened wavelength.

Clinical implication

The present study demonstrated that nicorandil shortens ERP, increases conduction velocity, and prolongs the wavelength. These data suggest that nicorandil may be useful in preventing the recurrence of AF following cardioversion.

Limitations

Because of the methodological risk inherent in the trans-septal approach, the present study conducted EPS measurements in the right atrium alone. This may be insufficient, as recent studies reported that AF is propagated mainly from the pulmonary vein and left atrium. Further, physical limitations prevented contact of all the splines of the basket catheter to the right atrial wall, which prevented optimal assessment of EPS parameters.

References


Asano T Electrical remodeling involved IKATP and nicorandil improves wavelength