Comparison of the Effects of Na\(^+\) and K\(^+\) Channel Blockers on the Electrophysiological Properties of the Pulmonary Veins in Patients with Atrial Fibrillation

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Introduction: We assessed the effects of pilsicainide, a pure Na\(^+\) channel blocker, and nifekalant, a pure rapid delayed rectifier potassium current (IKr) blocker, on the electrophysiological characteristics within the pulmonary vein (PV) and at the PV-left atrial (LA) junction.

Methods and Results: We used a basket catheter for PV mapping in 38 patients with paroxysmal atrial fibrillation (AF). Programmed stimulation was performed in the distal PV and PV-LA junction before and after the infusion of pilsicainide (1 mg/kg; \(n = 24\)) or nifekalant (0.3 mg/kg; \(n = 14\)). Both drugs significantly prolonged the effective refractory period (ERP) of the distal PV and PV-LA junction. Pilsicainide significantly decreased the ERP heterogeneity of the PV and PV-LA junction (from 36 ± 43 to 9 ± 60 ms, \(P < 0.05\)). In contrast, nifekalant significantly increased the ERP heterogeneity of the PV and PV-LA junction (from 38 ± 34 to 60 ± 46 ms, \(P < 0.01\)). Pilsicainide significantly prolonged the conduction time (S1-A1) from the distal PV to the PV-LA junction (from 42 ± 12 to 63 ± 26 ms, \(P < 0.001\)), whereas this did not change with nifekalant.

Conclusions: In AF patients, pilsicainide has antiarrhythmic effects mainly on the distal PV by modifying the ERP and conduction properties. In contrast, nifekalant has antiarrhythmic effects mainly on the PV-LA junction by modifying the ERP.

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Key words: Nifekalant, Pulmonary vein, Atrial fibrillation, Pilsicainide, Electrophysiology

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias seen clinically. Based on the guidelines of the ACC/AHA, both Na\(^+\) channel blockers (class I antiarrhythmic drugs) and K\(^+\) channel blockers (class III antiarrhythmic drugs) can be used to treat AF. However, recent studies have mainly focused on their effects on atrial muscle. The mechanism of arrhythmogenicity in the pulmonary vein (PV) has been explained in previous reports.\(^1,2\) Furthermore, some reports have suggested that the atrial myocard-
dium in the PV sleeves is important for the initiation and maintenance of AF.\(^5,20,21\) In fact in patients with paroxysmal AF, there is a high likelihood that the AF can be cured with PV isolation.\(^1–4\) Kumagai et al. demonstrated the effect of a Na\(^+\) channel blocker, pilsicainide, on the PV.\(^6\) However, the effects of these antiarrhythmic drugs on the PV are not well known. A multielectrode basket catheter can be a very useful tool for detailed PV mapping and isolation.\(^7\) Therefore, in this study we evaluated the electrophysiologic effects of pilsicainide, a pure Na\(^+\) channel blocker (class Ic drug), and nifekalant, a pure rapid delayed rectifier potassium current (IKr) blocker (class III drug), on the PV in AF patients.

**Methods**

**Patient characteristics**

The patients were divided into two groups: a pilsicainide group and a nifekalant group. The pilsicainide group consisted of 24 patients (20 men) with a mean age of 59 ± 8 years, and the nifekalant group consisted of 14 patients (12 men) aged 54 ± 12 (n.s.) with paroxysmal AF who underwent an electrophysiological study. None of the patients had previously undergone PV isolation. There were no significant differences between the two groups with regard to AF history, hypertension, diabetes mellitus, mitral regurgitation, coronary artery disease, cardiomyopathy, left atrial dimension, ejection fraction or PV diameter (Table 1). All antiarrhythmic drugs were discontinued for the duration of at least five drug-serum half-lives before the study. Informed consent was obtained from all patients before the study.

**Catheter positions**

Three multipolar electrode catheters (Daig Corp., USA) were positioned in the right atrial appendage (RAA), the His bundle area (His), and the distal coronary sinus (CS), respectively, and a 31-mm, 64-pole basket catheter (EP Technologies, USA) was placed in the left superior PV. All catheters positioned in the left atrium (LA) were inserted by septal puncture. Next, the basket catheter was placed in the PV, and the proximal basket catheter electrodes (electrodes 7, 8) were then placed in the PV-LA junction by PV angiography performed with an angiocatheter (6-French, Baxter, USA) or a long sheath (SL-1, Daig Corp., USA) (Figure 1). Later, an electrode catheter for the His was introduced into the left atrial appendage (LAA) through the same transseptal puncture site. Intravenous heparin was administered in a single bolus of 5000 IU and then at 1,000 IU per hour (continuous venous infusion) after the atrial transeptal procedure.

**Electrophysiological study and stimulation protocol**

**Control study**

During sinus rhythm, the effective refractory periods (ERPs) were measured at the RAA and

| Table 1 | Comparison of Parameters Between Pilsicainide and Nifekalant Groups |
|---------|-----------------------------|-----------------------------|
|         | Pilsicainide (n = 24)       | Nifekalant (n = 14)         | \(p\)       |
| Age     | 59 ± 8                      | 54 ± 12                     | n.s.       |
| Male/Female | 20/4                      | 12/2                       | n.s.       |
| AF history (years) | 3 ± 2                  | 3 ± 4                       | n.s.       |
| Hypertension | 1(4%)                  | 1(7%)                        | n.s.       |
| Diabetes mellitus | 2(8%)               | 0(0%)                        | n.s.       |
| MR      | 10(42%)                    | 3(21%)                      | n.s.       |
| CAD    | 3(13%)                     | 1(7%)                        | n.s.       |
| CM     | 1(4%)                      | 2(14%)                       | n.s.       |
| LAd (mm) | 38 ± 5                    | 39 ± 6                       | n.s.       |
| EF(%)   | 64 ± 10                    | 64 ± 9                       | n.s.       |
| PV diameter | 19 ± 3                | 19 ± 5                       | n.s.       |


**Figure 1** Basket catheter-guided pulmonary vein (PV) mapping.

A basket catheter was positioned in the PV. Distal pacing was performed from the distal electrode pair (bipoles 1, 2) and PV-left atrium (LA) junctional pacing was implemented at the proximal pacing pair (bipoles 9, 10). The proximal electrode (bipoles 7, 8) was located at the PV-LA junction.
LAA and at the intra-PV and LA-PV junction. The ERPs of the RAA and LAA were measured using a multipolar electrode catheter, and intra-PV mapping was performed with a basket catheter. PV mapping consisted of measurement of the conduction time of intra-PV and the ERP of the distal PV and PV-LA junction and ERP heterogeneity. We defined ERP heterogeneity as the difference between PV-LA junction and PV distal ERPs within the same PV. Intra-PV pacing was performed from the distal (electrodes 1, 2) and proximal (electrodes 7, 8) electrode pairs of all splines of the basket catheter. It was also used to pace 2 or 3 different sites within the PV and PV-LA junction, including the bilateral, inferior, superior and posterior walls. The conduction time from the distal PV to the PV-LA junction was measured from the pacing artifact to the atrial potentials recorded during the drive cycle. The stimulus strength was determined at twice the diastolic threshold by a programmed stimulator (SEC-3102, Nihon Kohden, Japan). Bipolar intracardiac electrograms were recorded at a filter setting of 30 to 500 Hz and stored digitally on a polygraph (Labosystem DUO, Bard, USA) simultaneously with the surface ECG. Stable pacing sites were determined only if the threshold was <5 V. After a basic drive cycle of 8 stimuli at 600 ms, an extrastimulus was applied and automatically decremented in 10 ms steps. We confirmed the reproducibility of the measurement, especially in the distal PV. When AF was induced by the extrastimulus, we terminated AF by DC shock and repeated the measurement. The ERP was defined as the longest coupling interval at which a premature stimulus failed to capture local muscle (Figure 2).

**Drug study**

After the control study, the pilsicainide group was given a loading dose of 1 mg/kg of pilsicainide over 5 minutes, and the nifekalant group was given a loading dose of 0.3 mg/kg of nifekalant over 5 minutes. After drug administration, the parameters

![Figure 2](image1.png)

*Figure 2* Programmed stimulation was performed from the distal PV using a basket catheter. All proximal (bipoles 7, 8) electrograms with the basket catheter spline in the left superior PV are shown. A: Before pilsicainide. The maximum drive cycle conduction time (S1-A1) was 60 msec. Atrial fibrillation (AF) was induced when an extrastimulus (S2) is decremented to 100 msec. ERP of the distal PV is 100 msec. B: After pilsicainide. Maximum S1-A1 was prolonged to 102 msec. When S2 was decremented to 250 msec, AF was not induced. ERP of the distal PV was prolonged to 240 msec.
were measured repeatedly. If AF was not terminated within 5 minutes of drug infusion, AF was terminated by DC shock, and the measurements were repeated after 10 minutes. All measurements were finished within 40 minutes after the completion of drug infusion.

**Statistical analysis**

Continuous variables are expressed as mean ± SD. Paired or unpaired values were compared by Student’s t-test, the Mann-Whitney U test or the chi-square test, as appropriate. p < 0.05 was considered statistically significant.

**Results**

**Pilsicainide group**

There were no significant differences in ERP before loading between the pilsicainide and nifekalant groups (distal PV: 189 ± 51 vs 189 ± 37, n.s., PV-LA junction: 217 ± 42 vs 220 ± 46, n.s.). Pilsicainide prolonged distal PV ERPs from 189 ± 51 ms to 209 ± 55 ms (p < 0.002) and PV-LA junction ERPs from 217 ± 42 ms to 227 ± 60 ms (p < 0.01). ERPs of distal PVs were shorter than those of the PV-LA junction (189 ± 51 ms vs 217 ± 42 ms). Therefore, pilsicainide significantly decreased the ERP heterogeneity of the PV and PV-LA junction, defined as the difference between the PV-LA junction and PV distal ERPs within the same PV (36 ± 43 ms vs. 9 ± 60 ms, p < 0.05). Pilsicainide significantly prolonged the maximum conduction time during the drive cycle from the distal PV to the PV-LA junction (Maximum S1-A1, 42 ± 12 ms to 63 ± 26 ms, p < 0.001). Pilsicainide significantly prolonged RAA and LAA ERPs (RAA: from 232 ± 22 ms to 246 ± 24 ms, p < 0.02, LAA: from 234 ± 27 ms to 249 ± 24 ms, p < 0.01) (Table 2).

In three cases, after the injection of pilsicainide, electrograms in the PV gradually disappeared from the PV-LA junction side, which suggested pharmacological LA-PV conduction block during AF (Figure 3).

**Nifekalant group**

As noted above, there were no significant differences in the ERP at baseline between the pilsicainide and nifekalant groups (distal PV: 189 ± 51 ms vs 189 ± 37 ms, n.s., PV-LA junction: 217 ± 42 ms vs 220 ± 46 ms, n.s.). Nifekalant prolonged PV distal ERPs from 189 ± 37 ms to 197 ± 53 ms (p < 0.05) and PV-LA junction ERPs from 220 ± 46 ms to 253 ± 55 ms (p < 0.001). Therefore, nifekalant significantly increased the ERP heterogeneity of the PV and PV-LA junction (from 38 ± 34 ms to 60 ± 46 ms, p < 0.01). No significant change in the maximum conduction time during the drive cycle from the distal PV to the PV-LA junction was seen in the nifekalant group (from S1-A1, 38 ± 12 ms to 43 ± 17 ms, n.s.). Nifekalant significantly prolonged RAA and LAA ERPs (RAA: from 236 ± 26 ms to 279 ± 53 ms, p < 0.01; LAA: 239 ± 34 ms to 277 ± 47 ms, p < 0.02 (Table 2). In

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Table 2  Comparison of Parameters Between Pilsicainide and Nifekalant Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pilsicainide (n = 24)</th>
<th>Nifekalant (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre-i.v.</td>
<td>post-i.v.</td>
</tr>
<tr>
<td>ERP (msec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distal PV</td>
<td>189 ± 51</td>
<td>209 ± 55</td>
</tr>
<tr>
<td>PV-LA junction</td>
<td>217 ± 42</td>
<td>227 ± 60</td>
</tr>
<tr>
<td>RAA</td>
<td>232 ± 22</td>
<td>246 ± 24</td>
</tr>
<tr>
<td>LAA</td>
<td>234 ± 27</td>
<td>249 ± 24</td>
</tr>
<tr>
<td>heterogeneity</td>
<td>36 ± 43</td>
<td>9 ± 60</td>
</tr>
<tr>
<td>Conduction (Max S1-A1) (msec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distal to proximal</td>
<td>42 ± 12</td>
<td>63 ± 26</td>
</tr>
<tr>
<td>proximal to distal</td>
<td>42 ± 7</td>
<td>55 ± 13</td>
</tr>
<tr>
<td>Induced AF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distal PV</td>
<td>10</td>
<td>6.7</td>
</tr>
<tr>
<td>PV-LA junction</td>
<td>3.8</td>
<td>11.5</td>
</tr>
</tbody>
</table>

ERP: effective refractory period, PV: pulmonary vein, LA: left atrium, right atrial appendage, LAA: left atrial appendage.
two cases, after the injection of nifekalant, electrograms in the LA were gradually organized, except for intra PV electrograms (Figure 4).

**Discussion**

Our main findings are as follows. First, pilsicainide increased ERP in PV, decreased the ERP heterogeneity of the PV and PV-LA junction, and prolonged the conduction time within the PV. Second, nifekalant increased PV-LA junction ERP and significantly increased the ERP heterogeneity of the PV and PV-LA junction. Nifekalant did not affect conduction properties within the PV.

Electrophysiological effects of pilsicainide on the PV-LA junction and distal PV

Pilsicainide, a class Ic antiarrhythmic drug, was originally developed in Japan. It has pure Na⁺ channel-blocking action with slow recovery kinetics. At high concentrations, it shows minimal-to-moderate inhibition of ionic currents passing through Ca²⁺ and K⁺ channels, although this effect should be negligible at a plasma concentration that is effective for the treatment of arrhythmias. Some previous studies using wavelength theory have explained the inducibility and stability of AF. Class I and III antiarrhythmic drugs have antifibrillatory effects on AF, as shown using wavelength theory in a previous study. Other reports have demonstrated that pilsicainide decreased intra-atrial conduction velocity and significantly increased atrial ERP and the wavelength. A few clinical reports have found that this drug is effective for terminating paroxysmal and persistent AF. However, Wijffels et al. reported that pharmacologic cardioversion of AF cannot be explained by the prolongation of wavelength. Jais et al. demonstrated that patients with AF had distinctive electrophysiological properties for arrhythmogenicity. Recently, reentry formation has been demonstrated at the PV-LA junction, and PV distal ERP was shorter than PV-LA junction ERP.
ERP, while the conduction delay was longer than that at the PV-LA junction. In this study, similar results were seen with programmed stimulation. Thus, the difference between the characteristics of the distal PV and the PV-LA junction may play a very important role in both the onset and maintenance of AF. However, previous studies were unclear regarding the effects of antiarrhythmic drugs on the atrium and the PV and PV-LA junction. In this study, we noted that pilsicainide significantly increased the ERPs of both the distal PV and the PV-LA junction and prolonged the conduction delay within the PV (a greater delay was seen in the distal PV than that in the PV-LA junction). The heterogeneity in ERPs between the distal PV and PV-LA junction suggests arrhythmogenicity. In this study, we observed a decrease in ERP heterogeneity of the PV and PV-LA junction after the injection of pilsicainide. These findings may suggest an antiarrhythmic effect through the enhancement of an arrhythmic substrate. Thus, pilsicainide affected AF not only in the atria but also in the PV and PV-LA junction. Pharmacological PV isolation was achieved by prolonging conduction at the PV-LA junction, and AF was immediately terminated (Figure 3). Therefore, conduction delay by pilsicainide might terminate AF caused by reentry formation within PVs or the PV-LA junction. In addition, ERP prolongation by pilsicainide might prevent AF caused by PV foci. These effects of pilsicainide on the PV-LA junction and distal PV might explain one of the important mechanisms in the prevention and termination of AF by this class Ic drug.

Electrophysiological effects of nifekalant on the PV-LA junction and distal PV

Nifekalant, a class III antiarrhythmic drug, was also originally developed in Japan. It is a comparatively pure I Kr-channel blocker. However, nifekalant also has a weak inhibitory effects on the adenosine triphosphate-sensitive potassium channel current (I_{K_ATP}) and Na^+-activated potassium channel current (I_{K_Na}). Watanabe et al. demonstrated that nifekalant prolonged ERP and the duration of the monophasic action potential in the human ventricle, but did not affect the intra-atrial conduc-

Figure 4  Changes in PV electrograms by nifekalant.
The PV and left atrial potentials show irregular electrograms before the injection of nifekalant (left). However, while the atrial potential changed to a comparatively regular potential, PV electrograms were not affected by the injection of nifekalant during AF. Thus, a PV-to-LA discrepancy was observed (right).
tion time. Several atrial studies have found that nifekalant increased the atrial effective refractory period (AERP) and the wavelength for atrial reentry, and terminated arrhythmia, and may be effective for preventing AF due to prolongation of the AERP. In this study, we observed that nifekalant increased the ERP of the PV-LA junction more than that of the distal PV and did not significantly change the intra-PV conduction time. Thus, the effect of nifekalant mainly involves prolongation of the ERP of atrial muscle including the PV-LA junction compared to the distal PV without changing the conduction time. The inhibition of distal PV foci by an increase in PV ERP may be weaker than that in the PV-LA junction in comparison with the effects of pilsicainide, since the prolongation of ERP in distal PV by nifekalant was weaker than that in the PV-LA junction. In addition, as a unique effect of nifekalant, we noted a PV-to-LA discrepancy just before AF termination (Figure 4). This phenomenon was completely opposite that in the case of pilsicainide, and may be due to shortening of the action potential duration and refactoriness and suppressing automaticity in the PV by nifekalant. In this study, ERP heterogeneity of the PV and PV-LA junction after the injection of nifekalant was significantly increased. AF may have been terminated due to the effect of prolonged ERP of atrial muscle including the PV-LA junction and the prevention of PV-LA junction and/or non-PV foci. The effect of nifekalant on atrial muscle including the PV-LA junction and distal PV might explain one of the important mechanisms in the prevention and termination of AF by this class III drug.

Limitations of the study

There are several limitations in our study. First, pharmacologic isolation and PV-to-LA dissociation were not always observed. Second, we measured these parameters with only one PV and did not simultaneously observe the effects on other PVs. Thus, the effects of pilsicainide and nifekalant on other PVs are unclear. Third, pilsicainide is associated with use-dependent block, and nifekalant is characterized by its use-dependent block of $I_{\text{Na}}$. Nifekalant is also characterized by its reverse use-dependent prolongation of action potential durations. However, we used a BCL of only 600 msec when measuring ERP and conduction time. Therefore, different results may be obtained when different short cycle lengths are used. Last, we only measured the conduction time of PV, and thus the effect on the conduction time in the atrium is still unknown.

Conclusion

In conclusion, these results demonstrate that a Na$^+$ channel blocker and a K$^+$ channel blocker have different antiarrhythmic effects at the PV and PV-LA junction. Conduction delay by pilsicainide might terminate AF caused by reentry formation within PVs or the PV-LA junction, and the prolongation of ERP by pilsicainide might prevent AF caused by PV foci. In contrast, the main antiarrhythmic effect of nifekalant may be the termination of AF due to prolongation of the ERP of atrial muscle including the PV-LA junction and the prevention of AF through acting on the PV-LA junction and/or non-PV foci. The mechanism for the difference in the effects of these drugs on PV and PV-LA junction is not clear. However, these findings may be important for understanding the antiarrhythmic effects of Na$^+$ channel blockers and K$^+$ channel blockers on AF.

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References