Clinical Study of the Acute Effects of Intravenous Nifekalant on the Defibrillation Threshold in Patients With Persistent and Paroxysmal Atrial Fibrillation

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Background Antiarrhythmic agents are considered to have significant effects on the defibrillation energy requirement, so this study investigated the effects of nifekalant on defibrillation.

Methods and Results Forty-two patients with persistent atrial fibrillation (AF) underwent electrical cardioversion via intracardiac electrode catheters prior to and after the intravenous administration of nifekalant. The success rate of the defibrillation and change in the defibrillation threshold using sequential incremental defibrillation energy deliveries was investigated. In addition, the parameters that could predict the beneficial effects of nifekalant were also assessed. Nifekalant significantly decreased the defibrillation energy requirement in 13 of the 42 cases, and nifekalant also converted AF to sinus rhythm with an identical energy to that of the last unsuccessful defibrillation in 21 of 42 cases. The success of defibrillation seemed to be dependent on significant prolongation of the intracardiac atrial electrogram intervals during AF by the nifekalant.

Conclusions Intravenous nifekalant significantly improved the electrical defibrillation efficacy in patients with persistent AF that was resistant to defibrillation, without any serious adverse effects. (Circ J 2008; 72: 76–80)

Key Words: Antiarrhythmic agent; Atrial fibrillation; Defibrillation; Defibrillation threshold; Nifekalant

Various factors have been suggested for altering the energy requirements for ventricular defibrillation in animals and humans, including underlying heart disease, changes in autonomic tone, acid–base and electrolyte imbalances, and various antiarrhythmic agents1–7 With regard to the effects of antiarrhythmic drugs on the defibrillation threshold (DFT), studies have shown that drugs which prolong the cardiac repolarization, but do not affect the conduction velocity, lower the DFT. Nifekalant hydrochloride is a pure class III antiarrhythmic drug that inhibits the rapid component of the delayed rectifier potassium current, transient outward potassium current, and inward rectifier potassium current without affecting the inward sodium current, inward calcium current, or β-adrenergic activity.8,9 A previous report demonstrated that nifekalant significantly decreased the DFT of ventricular fibrillation in canine hearts10 so the aim of this study was to determine whether short-term intravenous administration of nifekalant would alter the DFT in humans with paroxysmal and persistent atrial fibrillation (AF).

Methods

Study Population Between 2003 and 2005, we enrolled a total of 42 patients with persistent and paroxysmal AF lasting longer than 24 h, and which was refractory not only to antiarrhythmic drugs, but also to external cardioversion, and who had subsequently underwent internal catheter cardioversion with and without the concomitant administration of nifekalant. The research protocol was approved by the institutional ethics committee. Patients were excluded if they were less than 18 years old, had a corrected QT interval >450 ms or QRS duration >140 ms, had third-degree atrioventricular block or a serum potassium level <3.5 mmol/L. Written informed consent was given by all patients prior to cardioversion and nifekalant administration. The average duration of paroxysmal AF was 46.8±8.2 h (ranging from 35.8 to 49.5 h). All patients were refractory to direct current cardioversion in the control state, and necessitated further therapeutic interventions, such as administration of nifekalant, in order to restore sinus rhythm (SR).

Defibrillation Procedure The patients were placed under general anesthesia, which was maintained with ultra-rapid barbiturates. Under fluoroscopic guidance, 2 multipolar electrode catheters were introduced from the right femoral vein and positioned at the lateral wall of the right atrium and inserted into the coronary sinus (Fig 1). The internal leads were connected to a battery-operated external cardioverter-defibrillator (DVX, Tokyo, Japan) that could be preset to deliver a variable amount of energy from 5 to 100 joules in 5 J increments. The defibrillating pulse was in the form of a truncated exponen-
Acute Effects of Nifekalant for AF

DFT Testing

The initial test used 5 joules and if that was unsuccessful, a 10- to 20-J shock was then tried. Unsuccessful attempts were followed by a 25- to 30-J shock in some patients. The defibrillation trials were separated by at least 5 min. The DFT was defined as the lowest energy that was able to terminate the AF. When 10–30 J failed to terminate the AF, 0.4 mg/kg of nifekalant was administered intravenously over 10 min. Blood pressure, QT interval, QRS complex duration and cycle length of the intracardiac electrograms during AF were measured before and after drug administration, then the same protocol to determine the DFT was repeated. The initial energy was either always less than the last unsuccessful attempt by 10 J or was the same as the last attempt. When the attempt failed to terminate the AF, the energy was increased by 10 J until the AF was terminated by the shocks.

Determinants of Successful Defibrillation

Intracardiac electrograms recorded from the distal electrodes of the catheter positioned in the right lateral atrium were analyzed before and after intravenous administration of nifekalant in all the patients. The average intervals of the intracardiac atrial electrograms (AE-AE) during AF were measured in 20 consecutive beats in a random fashion. We compared the change in the average AE-AE interval be-

![Fluoroscopic images of the electrode catheter position](image1)

Table 1 Clinical Characteristics of the Patients With Persistent and Paroxysmal Atrial Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>42</th>
<th>36 (85%)/6 (15%)</th>
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<tbody>
<tr>
<td>Total no. of patients</td>
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<tr>
<td>M/F</td>
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<tr>
<td>Age (years; average)</td>
<td></td>
<td>62.3±10.3</td>
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<tr>
<td>LA diameter (mm; average)</td>
<td></td>
<td>42.0±3.9</td>
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<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td>60.4±12.1</td>
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<tr>
<td>Valve disease (mitral stenosis)</td>
<td>2/47 (6%)</td>
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![Defibrillation energy comparison](image2)

Fig 1. Fluoroscopic images of the position of the electrode catheter. RA, right atrium; CS, coronary sinus; LAO, left anterior oblique projection; RAO, right anterior oblique projection.

Fig 2. Defibrillation energy of the last attempt before nifekalant was administered because of failure of defibrillation and that for successful defibrillation after nifekalant.
between successful and unsuccessful cases of electrical defibrillation.

**Statistical Analysis**

All data are presented as the mean values ± standard deviation. Differences between groups were compared by Wilcoxon signed-ranks test. A p value of less than 0.05 was considered significant.

**Results**

**Patient Population**

The study group comprised 42 patients (average age 61.9±10 years; range, 43–78 years). The average ejection fraction was 56.4±13.8% (range, 47–61%); 3 patients had mitral valve stenosis and 4 had coronary heart disease (Table 1). All patients were taking antiarrhythmic agents; 22 were receiving pilsicainide, 11 propafenone, 7 cibenzoline, and 2 flecainide. Other drugs being taken were ß-blocking agents in 25 patients, digoxin in 31, and verapamil in 8.

**Effects of Nifekalant on DFT**

There was variability among the patients in the energy required for defibrillation, ranging from occasional successful defibrillation with 10 J in 11 patients, to 30 Joules for even just an occasional defibrillation in the other patients after intravenous administration of nifekalant. In 39 of the 42 patients, defibrillation was successful and normal SR resumed. Failure to defibrillate or immediate re-initiation of AF occurred in the other 3 patients, even after administration of intravenous nifekalant. In 1 patient, the final energy level was 50 J, given according to the physician’s discretion when 30 J failed to terminate AF.

In 21 patients, an identical electrical energy requirement to the last unsuccessful one was able to defibrillate the AF to SR after intravenous administration of nifekalant. In 5 patients, the electrical energy level required for successful defibrillation after the nifekalant was greater than that of the last unsuccessful attempt. In 13 patients, nifekalant significantly decreased the energy level required for successful defibrillation. The mean decrement in the DFT in response to intravenous nifekalant for each patient was 9.5±7 J. Fig 2 compares the defibrillation energy of the last attempt before nifekalant was administered, because of failure of defibrillation, and that for successful defibrillation after nifekalant. Although there was no significant difference in the DFT between before and after intravenous nifekalant, nifekalant had a significant effect in lowering the defibrillation energy requirement because the majority of the cases in this study were successfully defibrillated with the same or a lower energy level than that of the last unsuccessful attempt after nifekalant but not before.

**Determinants of Successful Defibrillation**

We investigated the factors that might influence the efficacy of defibrillation of AF. The AE-AE interval during AF was analyzed in order to compare cases of successful and unsuccessful defibrillation. The AE-AE interval during AF was compared before and after administering intravenous nifekalant. In 38 of 39 patients, the average AE-AE interval was significantly prolonged from 167.9±40.3 ms to 260.4±40.1 ms after nifekalant (p<0.001) (Fig 3A). The average AE-AE interval was significantly prolonged from 155±16 ms to 283±18 ms after intravenous nifekalant in patients with successful electrical defibrillation (Fig 3B). In contrast, in the patients with an unsuccessful defibrillation there was no significant difference in the average AE-AE interval after intravenous nifekalant (from 181±21 ms to 204±23 ms) (Fig 3C).

**Adverse Effects**

In all patients, the QT interval significantly prolonged after nifekalant (380±37 vs 489±86 ms, p<0.01). After successful defibrillation of AF, cardiac arrest with a maximum
duration of 6 s was provoked in 3 patients but did not require treatment (Fig 4). No other serious arrhythmias associated with nifekalant infusion were observed.

Discussion

Major Findings

The major findings of this clinical study are that (1) the DFT of AF significantly decreased after intravenous administration of nifekalant in the majority of the study patients, and (2) the average AE-AE interval after nifekalant was significantly more prolonged in cases of successful AF defibrillation than in unsuccessful cases.

Effects of Nifekalant on Electrical Defibrillation of AF

We found that intravenous nifekalant was effective in terms of lowering the DFT in patients who demonstrated significant prolongation of the AE-AE interval after drug administration. Murakawa et al demonstrated that the DFT of ventricular fibrillation decreased as the fibrillation cycle length prolonged during intravenous nifekalant administration10 and in the present study, we also observed an inverse relationship between the fibrillation cycle length during AF and the DFT. In general, the DFT for atrial flutter is relatively lower than that for AF11 Prolongation of the AE-AE interval suggests conversion of AF to an atrial flutter-like excitation pattern in the atrium, which would render it more amenable to defibrillation. This study did not uncover the actual mechanism of the improvement in the DFT for AF by intravenous administration of nifekalant, and it may be the main factor in successful AF defibrillation.

Previous Studies

The concomitant use of antiarrhythmic drugs and an implantable cardioverter defibrillator is an important tool for managing patients with refractory supraventricular and ventricular arrhythmias. Regarding the class III antiarrhythmic agents, which are the most widely used drugs for the various kinds of arrhythmias, Oral et al demonstrated that intravenous ibutilide increased the success of cardioversion and decreased the cardioversion energy requirement!2 In addition, Lai et al also reported that intravenous sotalol decreased the cardioversion energy requirement for chronic AF.13 In contrast, drugs that block the cardiac sodium channels and do not affect potassium conductance increase the energy required for successful defibrillation!3,14,15 and aof the class III antiarrhythmic agents, only amiodarone significantly increases the DFT.16-18

Nifekalant hydrochloride has proven to be an effective antiarrhythmic agent for treating life-threatening refractory ventricular tachyarrhythmias, such as ventricular tachycardia and ventricular fibrillation, by lowering the DFT!9-22 even in the cases with out-of-hospital cardiopulmonary arrest.23

Proposed Mechanism for Effect of Nifekalant

Ujheyi et al considered that failure of defibrillation may be caused by (1) unidirectional conduction block as a result of increased refractory dispersion; (2) unidirectional conduction velocity slowing; or (3) a short impulse wavelength and an excitable gap.24 In the present study, nifekalant exerted its pharmacological action by decreasing the dispersion of the AE-AE interval during AF, without affecting conduction velocity or the wavelength of conduction. Nifekalant has little pharmacological effect on the wavelength of fibrillatory excitation in the cardiac tissue. Therefore, this pharmacological effect might be the principal mechanism of the results in the present study; however, the precise mechanism of the decrease in the DFT by class III agents remains unclear.

Study Limitations

Flaker et al demonstrated that repeated shocks had a “sensitizing” effect on cardiac tissue, allowing for more successful defibrillation with repeated shocks.25 However, in that study the defibrillation energy determinant tests were carried out with a time interval of 30 s, whereas we separated them by at least 5 min and this interval may be long.
enough to eliminate the sensitizing effect of repeated defibrillations.

We did not investigate a control groups from the same patient population, so a prospective randomized study might be necessary to assess the potential effects of nifekalant on the defibrillation energy requirement.

The DFT is a simple and quantitative estimate of the success of defibrillation, with a predictable relationship to the dose–response curve, and the percent of the success curve should have a sigmoid shape. In our study, the DFT was determined by a sequence of incremental test shocks, so the shift in this sigmoid-shaped curve obtained with multiple shocks needs to be assessed, which is not clinically difficult.

Conclusions

Intravenous nifekalant successfully improved the defibrillation efficacy and prevented any immediate recurrence of AF. The success of defibrillation can be predicted by a significant prolongation of the AE-AE interval after nifekalant administration. This finding suggests that using nifekalant to increase the success rate should be considered when AF is refractory to electrical defibrillation. To evaluate the efficacy of nifekalant more precisely in patients resistant to electrical defibrillation, a randomized prospective study is required.

Disclosure

None.

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References