The Effect of Propafenone on Premature Ventricular Contractions (PVCs)

An Analysis Based on Heart Rate Dependency of PVCs

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SUMMARY

The effect of 450 mg/day propafenone for two weeks on premature ventricular contractions (PVCs) was studied in combination with an assessment of heart rate (HR) dependency of PVCs using Holter ECG monitoring in patients with more than 720 PVCs per day. The PVC-HR correlation was classified into positive (P), bidirectional (B), and flat and negative (FN) correlation groups. The positive group included only patients in whom PVC frequency increased with a heart rate increase, while the bidirectional group included patients with PVCs whose frequency increased at low heart rates and decreased at high heart rates. The FN group contained both flat (PVC frequency was almost fixed regardless of heart rate changes) and negative (PVC frequency decreased as heart rate increased) correlations. The effectiveness of propafenone was 70% in the positive group and 50% in the nonpositive group which included both bidirectional (67%) and FN (0%) groups, using a > 70% PVC reduction as a criterion of efficacy. From this, we concluded that propafenone is effective in patients showing either positive or bidirectional PVC-HR correlation. The coupling interval (CI) of PVCs was also prolonged by propafenone as a whole. The present study suggests that there are differences in the mechanism of PVC development in patients with flat or negative correlation and those with a positive or bidirectional correlation. Thus, this type of analysis contributes to an understanding of the action of antiarrhythmic agents, and may allow the prediction of their efficacy on PVCs. (Jpn Heart J 2001; 42: 701-711)

Key words: Propafenone, Ventricular premature contractions, Heart rate dependency, Holter ECG

ANTIARRHYTHMIC drugs, which suppress cardiac sodium channels, are subdivided into classes Ia, b, and c1) and slow, intermediate and fast kinetic drugs
according to the Sicilian Gambit. Propafenone, a class Ic and intermediate kinetic drug, is currently used in cases of variable supraventricular tachyarrhythmias as well as ventricular tachyarrhythmias since it has a broad antiarrhythmic spectrum.

Few noninvasive studies have been performed, however, using ambulatory ECG monitoring to investigate the action of propafenone in relation to the mechanisms of ventricular arrhythmias on Japanese patients. Furthermore, previous studies using propafenone have not provided a satisfactory outcome using Holter ECG monitoring for predicting the different types of heart rate dependency of ventricular arrhythmias. Recently, propafenone has been used for the treatment of atrial fibrillation. Although propafenone has been assumed to have a β-blocking action, little data have been presented suggesting the contribution of such a β-blocking action in the analyses of the results. In the course of general usage of propafenone, its β-blocking action seems to be an important factor in the choice of antiarrhythmic drugs for the treatment of supraventricular tachyarrhythmias.

We recently developed a new method of analyzing the correlation between ventricular premature contraction (PVC) and heart rate (HR), and used this to determine the effect of diltiazem and atenolol on the PVCs. This analysis is useful to characterize PVCs sensitive to the Ca antagonist diltiazem, and β-blockers such as atenolol and propranolol. Atenolol suppressed PVCs whose frequency increased with an HR increase, what we called a positive PVC-HR correlation. PVCs with other types of heart rate dependency were not suppressed by atenolol. Diltiazem exhibited effects similar to those of atenolol.

We also investigated the efficacy of the class I antiarrhythmic drugs disopyramide (class Ia, slow kinetic drug) and mexiletine (class Ib, fast kinetic drug). Both disopyramide and mexiletine showed a broad spectrum of antiarrhythmic actions, which was markedly different from those of atenolol and diltiazem. However, class I agents differ from each other regarding their effect on action potential and also have different kinetics with respect to cardiac sodium channels.

An analysis of the effects of class Ic drugs, such as propafenone, on PVCs using this method might therefore be important from the clinical point of view, especially as propafenone is known to exhibit β-blocking activity. The aim of the present study was to analyze the effects of propafenone on PVCs with respect to the different types of PVC-HR correlation in patients with frequent PVCs using 24-hour Holter ECG monitoring.
PATIENTS AND METHODS

Patients: Thirty consecutive patients with more than 720 PVCs per day at the end of a control or a washout period who visited our hospital and our branch hospitals were enrolled in the present study. All patients gave informed consent. Physical examination, blood biochemistry, peripheral blood cell count, standard 12 lead ECG, cardiac echogram, and chest X-ray examinations were performed in all patients before entry.

Patients with acute myocardial infarction, decompensated heart failure, marked bradyarrhythmias, second-degree or higher atrioventricular block, atrial fibrillation, electrolyte imbalance, and severe renal and/or hepatic dysfunction were excluded. Of the 30 patients, 4 had hypertension, 7 ischemic heart disease, 3 dilated cardiomyopathy, and 1 diabetes mellitus. The remaining 15 patients had no organic heart diseases except for the frequent PVCs.

Study protocol: Patients who were not undergoing antiarrhythmic therapy entered the open study directly. For those already undergoing treatment, all antiarrhythmic drugs including digitalis were discontinued and a 2-week washout period was instituted before entry to the study. This was followed by a 2-week treatment period with propafenone (Pronon, Toa Eiyo Ltd., Tokyo, Japan) at a dose of 450 mg/day. Patients were allowed to receive other drugs such as organic nitrates provided that the dose remained unchanged throughout the study. Twenty-four-hour Holter ECG recordings were performed before administration of propafenone (baseline recording) and then again at the end of 2 weeks of propafenone treatment. Propafenone was considered to be effective when the PVC frequency decreased by 70% or more compared with baseline recording.

Analysis of 24-hour ECG recordings: Twenty-four-hour Holter ECG recordings were performed with a two-channel Avionics recorder and analyzed using an Avionics computer system (DCG 7). This system yielded mean hourly PVC frequency, mean hourly coupling interval (CI) and mean daily heart rate. The relationship between the PVC frequency and the heart rate was analyzed as reported previously.\(^{10-12}\) In brief, the heart rate and PVC frequency per minute were calculated for each heart rate in 1 minute increments using the following formula: (number of PVCs in all minutes at a given heart rate)/(number of minutes at the given heart rate). Only the heart rates recorded for more than 5 minutes over 24 hours were used for the analyses. Analysis using this system has been previously shown to be reliable.\(^{10-12}\) The CI of PVCs was also calculated by measuring the CI of each PVC and averaged during each minute. The CI was then averaged every 10 HR increase from 50/min, namely from 50 to 110/min, and the slope between CI and HR was assessed.

Statistical analysis: Data are reported as the mean±SEM unless otherwise spec-
ified. Analysis of PVC frequency was performed using the common logarithm, log (mean hourly PVC frequency + 1) to ensure a normal distribution. The statistical analyses were performed with a paired or unpaired Student's *t*-test for continuous variables and by the chi-square test for discrete variables. A *p* value less than 0.05 was considered statistically significant.

**RESULTS**

**Correlation between PVC frequency and heart rate:** In the baseline recording, patients revealed one of the following distinct types of correlation between PVC frequency and heart rate, (1) positive correlation: PVC frequency increased as heart rate increased (*n*=10, Figure 1P), (2) bidirectional correlation: PVC frequency increased at low heart rates and decreased at high heart rates (*n*=15, Figure 1B), (3) flat correlation: an almost fixed PVC frequency irrespective of heart rate change (*n*=2, Figure 1F), and (4) negative correlation: PVC frequency decreased as heart rate increased (*n*=3, Figure 1N). The patients were divided into 3 major groups: the positive, bidirectional, or flat and negative (FN) groups. The positive group included only those with a positive correlation, and the bidirectional group those with only a bidirectional correlation, while the FN group contained both flat and negative correlations. There were no statistically significant differences among the 3 groups with respect to sex, concomitant cardiovascular complications, and PVC frequency and mean daily heart rate (Table), except for age between the P and FN groups (0.01).

**Effect of propafenone on ventricular premature contractions:** The frequency of PVCs was transformed into log (PVCs/h+1) to ensure a normal distribution as described in the statistical analysis section. Propafenone decreased log (PVC frequency +1) in both the positive and bidirectional groups: from 2.39±0.16 to 1.16±0.31 (*p*<0.01) and from 2.37±0.09 to 1.09±0.30 (*p*<0.01), respectively. This decrease in PVC frequency was not accompanied by statistically significant changes in heart rate in either group: from 78.7±3.1 to 72.7±2.9 bpm and from 77.4±2.6 to 77.6±3.3 bpm, respectively. In contrast, propafenone did not decrease the PVC frequency or heart rate in patients with either flat or negative PVC-HR correlations. The log PVC frequency was 2.02±0.27 in the baseline recording and 1.94±0.16 after propafenone in the FN group. The heart rate changed from 85.6±4.1 to 81.0±4.6 bpm after treatment (Figure 2).

The efficacy of propafenone was assessed using the criterion of a 70% or greater reduction in PVC frequency (Figure 3). Propafenone (450 mg/day) was effective in 7 of 10 patients (70%) in the group showing a positive correlation and in 10 of 15 patients (67%) in the group showing bidirectional correlation, while it was ineffective in all 5 patients either showing either a flat or negative correla-
**Table 1. Patient Profile**

<table>
<thead>
<tr>
<th></th>
<th>P Group</th>
<th>B Group</th>
<th>FN Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Age (Mean±SEM)</td>
<td>67.5±3.7</td>
<td>57.9±3.4</td>
<td>47.0±3.8*</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/5</td>
<td>6/9</td>
<td>4/1</td>
</tr>
<tr>
<td>Complication (%)</td>
<td>50</td>
<td>53.3</td>
<td>60</td>
</tr>
<tr>
<td>Heart Rate (/min) (Mean±SEM)</td>
<td>78.7±3.1</td>
<td>77.4±2.6</td>
<td>85.6±4.1</td>
</tr>
<tr>
<td>(upper: before, lower: after drug)</td>
<td>72.7±2.9</td>
<td>77.6±3.3</td>
<td>81.0±4.6</td>
</tr>
<tr>
<td>Log (PVC/h+1)</td>
<td>2.39±0.16</td>
<td>2.37±0.09</td>
<td>2.02±0.27</td>
</tr>
</tbody>
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* p<0.01 versus P group. No significant difference between P versus B, B versus FN group.

**Figure 1.** Illustration of the four different types of PVC-HR correlation. P=positive; B=bidirectional; F=flat; N=negative correlations. See text for further explanation.
Figure 2. Effect of propafenone 450 mg/day on mean PVC and heart rates in groups showing positive (P), bidirectional (B), and flat or negative (FN) PVC-HR correlations. The frequency of PVC/h is transformed into the common logarithm. * $P < 0.05$ versus pretreatment.

Figure 3. Percent change in PVC frequency after treatment with propafenone 450 mg/day in individual patients. P=positive; B=bidirectional; FN=flat or negative PVC-HR correlation. The dotted line shows the 70% reduction level of PVC frequency.
tion. There was no statistically significant difference in efficacy when comparing the positive and bidirectional groups. In the previous papers, we have summarized both the bidirectional and FN groups into a nonpositive (NP; types other than P type or P group) group. With the grouping, the efficacy of propafenone in the nonpositive group was 50%.

Effect of propafenone on coupling interval of PVCs: We analyzed the CI of PVCs on Holter ECG by averaging every 10 HR divisions. In other words, the, CI at 50, 60, 70, 80, 90, 100, and 110/min HR was calculated and averaged. Propafenone increased CI from 462±47 to 510±50 ms ($p<0.01$). Furthermore the slope of the CI to HR also decreased from -1.87±0.80 to -2.77±1.94 as a whole. In each type, the CI increased from 430±42 to 506±67 ($p<0.1$), 476±50 to 517±57, and 485±34 to 508±21 ms in the positive, bidirectional and FN groups, respectively. The CI-HR slope changed from -2.275±0.895 to -4.170±2.354, -1.810±0.306 to -1.686±0.634, and -1.476±0.792 to -1.762±1.118, in the P, B and FN groups, respectively. These changes in the CI and CI-HR slope in the respective PVC-HR correlation groups are not statistically significant. Typical changes in the CI and CI-HR slope as a whole are shown in Figure 4.

Side effects: No side effects due of propafenone were noted during the study.

Figure 4. The analysis of coupling interval in P (positive correlation), B (bidirectional correlation) and FN type (flat and negative correlations).
**DISCUSSION**

Although many papers have been published regarding the efficacy of propafenone on PVCs,\textsuperscript{5-9} few have analyzed its mode of action.\textsuperscript{16,17} To our knowledge, the present study is the first report which describes the action of propafenone on PVCs in terms of its heart rate dependency, as well as assessing its effect on CI. The type of PVC-HR correlation was evaluated in 30 patients with frequent PVCs using 24-hour Holter ECG recording and the effect of propafenone on this correlation was analyzed. Propafenone was effective in 17 of 30 patients (57%), a result consistent with those reported previously.\textsuperscript{5-9} In addition, the present study showed the equivalent effectiveness of propafenone on the groups with either a positive ($n=10$, 70%) or bidirectional ($n=15$, 67%) type of PVC-HR correlation. However, propafenone was not effective in any of the 5 patients (0%) with negative or flat correlations. The present finding is important since this method might be used to discriminate patients sensitive to propafenone from those who are not. Therefore, the present analysis is worth continuing to elucidate the mode of action of antiarrhythmic drugs on ventricular tachyarrhythmias and the underlying mechanisms.

**Comparison of the actions on P and NP types among class I agents:** The present study shows that propafenone, 450 mg/day, is effective against PVCs with positive and bidirectional correlations with heart rate, 70% on a positive and 67% on bidirectional (10/15). With the other grouping, namely positive and nonpositive groups, propafenone was effective 50% in 20 nonpositive group patients (10/20) including bidirectional, flat and negative correlations of PVC-HR correlations. According to our previous data, mexiletine was 58.3% effective in the positive group at 300 mg/day and 68.8% effective at 600 mg/day, while 33.3% effective in the nonpositive group at 300 mg/day and 37.5% effective at 600 mg/day, respectively. Disopyramide was 44.4% effective in the positive group and 54.5% effective in the nonpositive group at 300 mg/day.\textsuperscript{11} Thus mexiletine showed predominance on P type and disopyramide showed predominance on NP type, with the reserve that no statistical significance was noted and the number of patients tested was small. The present results show that propafenone was effective in both the positive group and nonpositive group almost equally with no predominance in either group. This finding is in clear contrast with those of mexiletine and disopyramide, and reflects a possible beta-adrenergic blocking action of propafenone.

**Electrophysiological mechanism of PVCs and actions of propafenone:** We previously reported\textsuperscript{10,11} that atenolol (a class II antiarrhythmic drug) and diltiazem (a class IV antiarrhythmic drug) suppressed PVCs that show a positive correlation, but poor efficacy against those showing nonpositive PVC-HR correlations, i.e., PVC-HR correlations such as bidirectional. *In vitro* studies have shown that stim-
ulation at higher heart rates increases the amplitude of delayed after-depolarization (DAD), leading to an increased probability of reaching the threshold for triggered activity.\textsuperscript{17} DAD is related to intracellular calcium overload and is suppressed by both calcium antagonists and $\beta$-blockers. These findings suggested that tachyarrhythmias derived from DAD play a role in the genesis of positive-type PVCs. Indeed, we recently analyzed the features of PVCs showing a positive correlation with heart rate and identified two groups.\textsuperscript{18} One group showed a delay in the increase in PVC frequency following an abrupt and sustained heart rate increase and in the other group there was no such delay. Diltiazem was predominantly effective against PVCs whose frequency increased with a delay following the increase in heart rate. We concluded that PVCs, which exhibited a delayed response to the increase in heart rate, may be strongly related to tachyarrhythmia originating from DAD.\textsuperscript{18}

The effect of propafenone on CI was also interesting. In the present study, CI was only prolonged significantly in the P group, but not in either the B or FN group. The reason for the difference is certainly not clear in the study, however, the Na blocking action and $\beta$-blocking action may cooperate to prolong the CI in the P group. The result may be consistent, assuming that the PVCs in the P group are related to triggered activity. The changes in CI may depend on the mechanisms of the development of PVCs, in the sense that, it is necessary to analyze CI distinctly by their dependence on heart rate. Further elaborate analysis is necessary to clarify the effects of antiarrhythmic agents on CI. The findings that propafenone was equally effective in both positive and bidirectional correlation type patients may be an expression of its $\beta$-blocking action together with prolongation of the CI and the decrease in the CI-HR slope. The nominal decreases in HR in both the P and FN groups also support this interpretation of a $\beta$-blocking action of propafenone.

There seemed to be several features associated with the bidirectional correlation: the ascending arm (acceleration phase), the descending arm (deceleration phase), and the inflection point between these two arms (see Figure 1b). This could be interpreted as tachycardia progression and regression phases. In addition, a critical heart rate for the development of PVCs appears to exist: the level at which the inflection heart rate appears seems to be important for the assumption of the electrophysiological mechanisms involved in the induction of PVCs, namely whether the heart rate was in the low or high range. This consideration is clearly warranted for studying the data obtained on the electrophysiological action of nicorandil,\textsuperscript{19-21} since we have reported that this drug suppresses PVCs with bidirectional correlation when the inflection appeared at rather low heart rates.\textsuperscript{22}

Therefore, the electrophysiological mechanism of PVCs with a bidirectional
correlation may not be single but multiple, such as re-entry, automaticity, and tachyarrhythmia originating early after-depolarization (EAD). Whatever the mechanisms are, it seems that such PVCs are dependent on fast sodium channels since class Ia, b, c drugs are generally effective on PVCs with bidirectional correlation, while calcium antagonists and β-blockers are not.

The electrophysiological mechanisms involved in the induction of PVCs with flat and negative correlations are still not clear. PVCs with a negative correlation seem to be bradycardia-dependent, since no PVCs appear at higher heart rates. Therefore, tachyarrhythmia originating from early afterdepolarization and automaticity may be the mechanisms for negative correlation. Regarding PVCs with flat correlation, re-entry and/or abnormal automaticity may be possible mechanisms. Further study is necessary to elucidate the electrophysiological background of PVCs with different PVC-HR correlations. In particular, studies using drugs with a specific action on cardiac ionic channels, such as a specific potassium channel blocker, would be promising in elucidating the mechanisms.

The major electrophysiological effects of propafenone include inhibition of cardiac sodium currents, and probably calcium currents, as well as β-blocking activity. These actions of the drug could suppress PVCs dependent on either re-entry or automaticity. Similar analyses were also reported in recent papers, suggesting the importance of analysis of the heart rate dependency of PVCs.

**CLINICAL IMPLICATIONS**

The present study revealed that propafenone suppresses PVCs with positive and bidirectional correlations, but not PVCs with flat or negative correlations. Evaluation of the PVC-HR correlation may therefore be useful for predicting the responses of patients with PVCs to propafenone and other cardiac antiarrhythmic drugs.

**REFERENCES**