**Mexiletine and Disopyramide Suppress Ventricular Premature Contractions (VPC) Irrespective of the Relationship between the VPC and the Underlying Heart Rate**

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**SUMMARY**

The effects of mexiletine (300 mg/day, 24 patients) and disopyramide (300 mg/day, 20 patients) on ventricular premature contractions (VPCs) were studied using a 24-hour ambulatory electrocardiogram. The VPC frequency was evaluated as a function of the underlying heart rate (HR). The VPC-HR correlation was classified into 2 major types, depending on whether the frequency of the VPC increased with the increased HR (positive type) or not (nonpositive type). The effects of the drugs were assessed based on the VPC-HR correlation and on the percent reduction of the VPC frequency.

Mexiletine and disopyramide significantly decreased the frequency of the VPCs of both the positive and nonpositive types. Each drug was assumed to be effective when the percent reduction of the VPC frequency exceeded 70%. Mexiletine (300 mg/day) was 58.5% effective in positive type patients and 33.3% effective in nonpositive type patients, with a total efficacy of 45.8%. Disopyramide was effective in 50% of total cases with 44.4% in positive type patients and 54.5% in nonpositive type patients. However, the efficacy of these drugs on the 2 different types of VPCs was the same statistically. The findings strikingly contrasted those obtained with diltiazem and atenolol, which predominantly suppressed VPCs of the positive type which share similar characteristics with a triggered activity in vitro.

We conclude that the mode of action of class I antiarrhythmics on the VPCs differs from that of class II or IV antiarrhythmics, as viewed...
from the VPC-HR relationship, and that the difference probably comes from the different arrhythmogenesis for positive and nonpositive types of VPCs, in addition to the different electrophysiological actions of mexiletine and disopyramide.

**Key Words:**
Heart rate dependency, VPC-HR correlation, Antiarrhythmic drug effect, Triggered activity

**THERE** have been numerous studies to assess the efficacy of antiarrhythmic drugs on ventricular premature contractions (VPCs), using a 24-hour ambulatory electrocardiogram (ECG) monitoring system. Most of the studies, however, focused simply on the reduction of either the frequency of VPCs or the severity of the arrhythmias, and the mechanisms underlying the arrhythmias or the modes of drug action have not been investigated extensively.

The clinical efficacy of class I antiarrhythmic agents in suppressing ventricular tachyarrhythmias is well documented. The predominant antiarrhythmic action of this class of drugs has been attributed to the blockade of the Na channel, with resultant decreases in the conduction velocity followed by a bidirectional block of conduction with or without a prolongation of the effective refractory period in the ventricular muscle. It has been also reported that the Na channel blocking effect of the class I drugs depends on the stimulus frequency, or the heart rate.

Indeed, there is a distinct relationship between the frequency of VPCs and the underlying heart rate (HR) during routine daily activity. We previously analyzed the antiarrhythmic effects of diltiazem, atenolol and propranolol (unpublished observations) on VPCs, based upon the relationship between the frequency of VPCs and the underlying heart rate. Interestingly, the analysis disclosed that both drugs predominantly suppressed these VPCs which increased in frequency as the underlying heart rate was increased, thereby termed VPCs with "positive correlation".

As for the efficacy of class I drugs, most previous studies were concerned only with the percent reduction of the number of VPCs or the improvement of their severity, with little attention to the underlying heart rate (HR). In the present study, we examined whether or not the effects of mexiletine and disopyramide on VPCs were the same as those of diltiazem and atenolol using this new method of analysis, i.e., the VPC-HR relationship, and discussed the mode of action of mexiletine and disopyramide on VPCs.
Patients and Methods

Patients

Forty-five consecutive patients with more than 1,000 VPCs per day were enrolled in the present study. All patients gave informed consent. In all patients, clinical examinations were performed before entering the study, including a physical examination, blood chemistry, peripheral blood cell count, standard 12-lead ECG, cardiac echogram, phonocardiogram and chest x-ray examination.

Patients with acute myocardial infarction, decompensated heart failure, marked bradyarrhythmias, atrioventricular block of the second degree or more, atrial fibrillation, severe renal and/or liver function abnormalities were excluded. Of the 45 patients, 6 had hypertension, 4 had ischemic heart disease and 1 had aortic regurgitation. The remaining 35 patients had no organic heart diseases except for the frequent VPCs.

Of the 45 patients who entered the study, one in the mexiletine group dropped out as a result of gastrointestinal side effects. The data from the remaining 44 patients who completed the study protocol were accepted for analysis. Table I represents the profiles of these 44 patients.

Study protocol

This study was an open, randomized trial consisting of 3 periods: the control, the treatment and the wash-out periods (Fig. 1). The protocol started with a period with no antiarrhythmic drugs given (control period) for 1 week. All antiarrhythmic drugs including digitalis, calcium antagonists and beta blocking agents were discontinued at least 1 week before patient entry into the study. Patients were allowed to receive other drugs such as nitrates provided that the dose remained unchanged during the study.

Only patients with more than 1,000 VPCs/24 hours on both of two con-

Table I. Patient Profiles

<table>
<thead>
<tr>
<th></th>
<th>Mexiletine</th>
<th>Disopyramide</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>P</td>
</tr>
<tr>
<td>Number</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.7 ± 15.5</td>
<td>60.2 ± 13.5</td>
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<tr>
<td>Sex (M/F)</td>
<td>16/8</td>
<td>7/5</td>
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|                | Total      | P            | NP           |
|----------------|------------|--------------|
| Number         | 20         | 9            | 11           |
| Age (years)    | 58.5 ± 13.8| 63.7 ± 11.2  | 54.3 ± 14.3  |
| Sex (M/F)      | 9/11       | 5/4          | 4/7          |

P = positive type; NP = nonpositive type.
Fig. 1. The study protocol. In each patient, a 24-hour ECG monitoring (Holter) was carried out every week at the points indicated by arrows. The drugs were given at the dose of 300 mg/day for 2 weeks after the second control recording. In some patients, the doses were increased to 600 mg/day, successively. C1: the first control recording, C2: the second control recording, D1: Holter recording after 1 week treatment (300 mg/day), D2: Holter recording after 2 weeks treatment (300 mg/day), D3: Holter recording 1 week after treatment of 600 mg/day, Wa: wash out recording 1 week after 300 mg/day, Wb: wash out recording 1 week after 600 mg/day dosing. See text for further explanation.

Consecutive control recordings (Fig. 1, C1 and C2) were entered into the subsequent study. The patients were randomly divided into either a mexiletine group (24 patients) or disopyramide group (20 patients). Each group received either mexiletine or disopyramide orally at a dose of 100 mg 3 times daily for 2 weeks. Twenty-four hour ECG recordings were performed weekly (Fig. 1, D1 and D2). When the mean VPC frequency (see the section below for the calculation) decreased by 70% or more as compared with that of the control period (the average of 2 sets of control data C1 and C2), the drugs were considered to be effective and such patients were defined as responders.

In all the responders (21 patients) and about half of the nonresponders (10 of 23 patients), the drug was discontinued at the end of the 2-week treatment period. One week after discontinuation of the drug, the 24-hour ECGs were repeated (Fig. 1, Wa). In the remaining 13 nonresponders, the treatment was continued with the same drug but at an increased dose (600 mg/day) for an additional week and the 24-hour ECG repeated (Fig. 1, D3), after which the drug was discontinued, regardless of the efficacy on the VPCs. One week after the discontinuation, a 24-hour ECG was recorded (Fig. 1, Wb).

**Analysis of 24-hour ECG recordings**
Twenty-four hour ECG recordings were performed with a two channel Avionics recorder and analyzed with an Avionics computer system (DCG 7). This system yielded a mean hourly VPC frequency and mean daily heart rate. The relationship between the VPC frequency and the heart rate was
analyzed as reported previously. In brief, the heart rate and VPC frequency were tabulated for each minute over 24 hours. The VPC frequency per minute was calculated for each heart rate in 1-min increments using the following formula: \[ \frac{\text{number of VPCs in all minutes at a given heart rate}}{\text{number of minutes at the given heart rate}} \]. Only the heart rates recorded for more than 5 min over 24 hours were used for the analyses. The reliability of the analysis using this system was good and has been discussed elsewhere.

Since we observed no significant differences in the frequency of VPCs between the first (C1) and second control recordings (C2), the averaged value of the two recordings was adopted as a control. In the case of drug treatment, there was also no significant difference in the efficacy evaluated at the 1-week (D1) and 2-week treatment periods (D2) for both mexiletine and disopyramide. Therefore the data of the 2 recording periods were pooled and averaged (cf. Table I) and used as the data for 300 mg/day dosing.

**Statistical analysis**

The data are reported as mean±SD unless otherwise specified. The statistical analyses were performed with a paired or unpaired Student's t-test for the continuous variables and by the chi-square test for the discrete variables. A p-value of 0.05 or less was considered statistically significant.

**Results**

**Correlation between VPC frequency and heart rate, and the effect of mexiletine**

Twenty-four patients were treated with mexiletine (Mexiletine group). All patients showed a distinct relationship between VPC frequency and heart rate. The patterns of the relationships observed during the control period could be classified into 3 categories: (1) an increase in VPC frequency with increasing heart rates in 12 patients (positive correlation, Fig. 2A), (2) an increase in VPC frequency up to certain heart rates and a decrease at much higher heart rates in 11 patients (bidirectional correlation, Fig. 2B), and (3) an almost constant VPC frequency over the entire range of heart rates in 1 patient (flat correlation, Fig. 2C). The patients were divided into 2 groups according to whether they revealed a positive correlation (P group) or other correlations (nonpositive or NP group).

There were no significant differences between the P and NP groups in age, sex ratio or underlying heart diseases. The frequency of the VPC and the mean daily heart rate also were not significantly different between the groups. The VPC frequencies in the first and the second recordings during
Fig. 2. Illustrations of 3 different patterns of VPC-HR correlation. A: positive, B: bidirectional, C: flat type. The abscissa shows the mean heart rate/min and the ordinate, the frequency of VPC/min. See text for further explanation.

Table II. The Frequencies of VPC and Heart Rate in the Mexiletine and Disopyramide Treated Groups

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C2</th>
<th>(C1+C2)/2</th>
<th>D1</th>
<th>D2</th>
<th>(D1+D2)/2</th>
<th>Wa</th>
<th>Wb</th>
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<tr>
<td>Mexiletine</td>
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<tr>
<td>P</td>
<td>608.9 ± 575.1</td>
<td>517.3 ± 588.8</td>
<td>572.0 ± 570.3</td>
<td>361.0 ± 625.1</td>
<td>356.2 ± 596.2</td>
<td>359.6 ± 603.1</td>
<td>482.4 ± 475.1</td>
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<tr>
<td>NP</td>
<td>474.2 ± 420.0</td>
<td>513.8 ± 423.5</td>
<td>499.0 ± 488.1</td>
<td>402.5 ± 466.5</td>
<td>351.7 ± 391.3</td>
<td>377.2 ± 418.6</td>
<td>468.5 ± 454.7</td>
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<tr>
<td>Total</td>
<td>541.5 ± 497.3</td>
<td>510.5 ± 501.6</td>
<td>536.0 ± 486.5</td>
<td>381.8 ± 535.8</td>
<td>354.9 ± 487.5</td>
<td>368.4 ± 507.8</td>
<td>485.5 ± 454.8</td>
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<th>C1</th>
<th>C2</th>
<th>(C1+C2)/2</th>
<th>D1</th>
<th>D2</th>
<th>(D1+D2)/2</th>
<th>Wa</th>
<th>Wb</th>
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<tbody>
<tr>
<td>Disopyramide</td>
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<tr>
<td>P</td>
<td>449.6 ± 411.0</td>
<td>453.4 ± 332.2</td>
<td>451.2 ± 321.4</td>
<td>323.0 ± 412.3</td>
<td>292.7 ± 202.8</td>
<td>262.8 ± 259.7</td>
<td>411.5 ± 364.2</td>
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<tr>
<td>NP</td>
<td>688.6 ± 554.2</td>
<td>454.0 ± 321.0</td>
<td>571.3 ± 347.2</td>
<td>244.7 ± 347.3</td>
<td>236.1 ± 332.0</td>
<td>245.0 ± 276.5</td>
<td>267.8 ± 364.3</td>
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<tr>
<td>Total</td>
<td>581.1 ± 498.0</td>
<td>453.8 ± 317.3</td>
<td>574.2 ± 332.7</td>
<td>280.0 ± 369.7</td>
<td>226.1 ± 276.5</td>
<td>253.0 ± 291.0</td>
<td>348.8 ± 367.9</td>
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C1 and C2: pre-drug (control) recordings. D1 and D2: records during treatment. Wash: record after 1 week washout period. See Fig. 1 for abbreviations of C1, C2, D1, D2, Wa and Wb.

the control period (C1 and C2) are presented in Table II together with the data for the treatment periods (D1 and D2).

Mexiletine decreased the frequency of VPC in both P and NP groups, however, the effect was not accompanied by significant changes in the heart rate. In the P group, mexiletine (300 mg/day) significantly decreased the frequency of VPC from 572.9/hour to 359.6/hour (p<0.01) and in the NP group, from 499.0/hour to 377.2/hour (p<0.01). After washing out the drug, the VPC frequency increased to 482.4/hour in the P group and 488.6/hour in the NP group.

Figure 3 illustrates the percent changes in the total counts of VPC during mexiletine therapy in the P and NP groups. At the 70% level of VPC reduc-
Fig. 3. Effect of mexiletine on the frequency of VPCs of positive (A) and nonpositive types (B), before and after treatment with a dose of 300 mg/day or 600 mg/day. The ordinate shows the percent changes in the VPC frequency and the abscissa, the drug dose.

Fig. 4. Typical examples of mexiletine and the VPC-HR correlation pattern during control period. A: positive type, B: nonpositive type. The ordinate shows the frequency of VPCs and the abscissa, heart rate/min. Filled circles indicate the plots of control records, while unfilled circles represent after 2 weeks treatment by each drug.
tion, mexiletine (300 mg/day) was effective in 7 of 12 patients (58.3%) in the P group and in 4 of 12 patients (33.3%) in the NP group. The effectiveness was, however, not significantly different between the groups.

Figure 4 shows typical examples of the VPC-HR correlation recorded before and after mexiletine. In both groups, the VPC-HR correlation remained essentially unchanged after treatment (Fig. 4A and B). However, in the case of the P group (Fig. 4A), the VPC frequency at every heart rate value decreased, and the reduction in the VPC frequency was more pronounced in the higher heart rate range, thereby leading to the decrease in the slope of the correlation.

With an increased dose regimen of 600 mg/day to the 8 nonresponders (P: 4, NP: 4), mexiletine proved effective for all 4 patients tested (100%) in the P group and for only 2 of the 4 patients tested (50%) in the NP group (Fig. 3).

**Effects of disopyramide**

The effects of disopyramide were studied in 20 patients (Disopyramide group). The mean VPC frequency of the first and second control recordings (C1 and C2) of the 20 patients and those during the treatment periods (D1 and D2) are summarized in Table II.

The analysis of the VPC-HR correlation during the control period showed 9 patients with a positive, 9 patients with a bidirectional, and 2 patients with a flat correlation. There was no significant difference between the P and NP groups with respect to age, sex ratio, or incidence of organic heart disease. The VPC frequency and mean daily heart rate during the control periods (C1 and C2) were not significantly different.

For all 20 patients, disopyramide (300 mg/day) significantly decreased the total number of VPCs from 517.4/hour to 253.0/hour ($p<0.01$). The VPC frequency decreased from 451.5/hour to 262.8/hour ($p<0.01$) in the P group and from 571.3/hour to 245.0/hour ($p<0.01$) in the NP group. The washout recording revealed a recurrence of VPC frequency from 253.0/hour to 348.8/hour. No significant change in the mean daily heart rate was observed during treatment in either P or NP groups.

Figure 5 illustrates the percent changes in the VPC frequency during disopyramide treatment with 300 mg/day. The drug was effective in 4 of 9 patients (44.4%) from the P group (Fig. 5A) and in 6 of 11 patients (54.5%) from the NP group. However, there was no significant difference in the suppressive efficacy between the groups. Five nonresponders (P: 1, NP: 4) were treated with the increased dose regimen (600 mg/day), and only 2 patients of the NP group (50%) were subjected to a VPC reduction greater than 70%.
Comparison of the effects of mexiletine and disopyramide

There were no significant differences between the patients subjected to treatment with mexiletine or disopyramide in terms of age, sex ratio, incidence of organic heart diseases and VPC frequency during the control period. Judging from the percentage of patients who revealed a VPC reduction of more than 70% on the 300 mg/day dose regimen, the effectiveness of mexiletine (responders: 11 of 24 patients, 45.8%) and disopyramide (10 of 20 patients, 50%) was not statistically significant. In the P group, mexiletine was effective in 58.3%, and disopyramide was effective in 44.4%. In the NP group, mexiletine was effective in 33.3%, while disopyramide was effective in 54.5%.

In the group treated with either mexiletine (300 mg/day) or disopyramide (300 mg/day), there was no significant difference between the responders and nonresponders in terms of age, sex ratio or incidence of heart disease. However, both the VPC frequency and the mean daily heart rate were significantly less in responders than in nonresponders in the mexiletine group. However, no such tendency was noted in the disopyramide-treated group.

Side effects

One patient on mexiletine suffered from abdominal pain and nausea,
and treatment was discontinued. In the other 44 patients, no side effects requiring removal from the trial were found, not were any distinct proarrhythmic effects noted.

**DISCUSSION**

The elucidation of the underlying electrophysiological mechanisms of ventricular tachyarrhythmias seems to be more difficult since the introduction of triggered activity as one possible mechanism.\(^{11},^{12}\) In addition, the results of a clinical electrophysiological study are now less decisive than they have been.\(^{13}\)–\(^{15}\)

In the present study, we evaluated the antiarrhythmic action of mexiletine and disopyramide on VPCs from the view point of VPC-HR correlation, which has not been done previously and may promise to increase understanding of the mode of action of antiarrhythmic drugs.

**The effect of mexiletine and disopyramide on the frequency of VPC and the VPC-HR correlation**

In this study, the class I antiarrhythmic drugs, mexiletine (300 mg/day) and disopyramide (300 mg/day), were effective in 45.8% and 50% of the patients, respectively, with frequent VPCs (>1,000 VPCs/day). These results are consistent with previous reports.\(^{16}\)–\(^{20}\) The present study further disclosed that both drugs suppressed both positive and nonpositive type VPCs. The findings are in striking contrast to those of class II (atenolol) and IV drugs (diltiazem), since both atenolol and diltiazem predominantly suppressed the VPCs with a positive correlation which share common characteristics with triggered activity in vitro. The latter two drugs revealed much less effect on the VPCs with a nonpositive correlation which may include reentry and abnormal automaticity.

In addition, the modes of action of mexiletine and disopyramide on the positive correlation are somewhat different from those of class II and IV drugs, although both drugs eventually suppressed VPCs as was reported for atenolol and diltiazem. First, mexiletine and disopyramide exerted their effects on the VPCs within 1 week after initiation of treatment. Moreover, the degree of suppression of the VPCs obtained after 1-week treatment was the same as that obtained after 2 weeks of treatment. In contrast, in cases with class II and IV drugs the suppression of VPCs was enhanced as the periods of the treatment were prolonged from 2 to 4 weeks.\(^{9}\),\(^{10}\)

Second, in cases of class I (this study) and class IV drugs, the slope of the VPC-HR correlation decreased concomitantly with the decrease in the VPC
frequency. However, in the case of class II drugs, the VPCs decreased first by decreasing the maximum heart rate developed in the daily activity of the patients, with the slope of the VPC-HR correlation remaining unchanged. The reduction of the slope appeared only after a much longer period of treatment (>3–4 weeks).

In the in vitro study, most class I drugs revealed a use-dependent inhibitory effect on the \( (\text{dV/dt})_{\text{max}} \) of the ventricular action potentials.\(^7\) The degree of the use dependency was attributable to the association and dissociation kinetics of the drugs to the Na channel.\(^7\),\(^21\) In the case of mexiletine, the rate of drug dissociation from the Na channel is rapid, so that the inhibitory effect on the Na channel is only pronounced at relatively higher stimulation rates or at rapid heart rates. On the other hand, disopyramide dissociates from the channel more slowly than mexiletine; consequently it can block the Na channel at a much slower stimulation frequency or heart rate than mexiletine does. In other words, disopyramide has a broader effective spectrum with respect to heart rate than mexiletine, in view of blocking efficacy on the Na channel.

This difference in use-dependency between mexiletine and disopyramide perhaps may explain their somewhat different effects on VPCs with different VPC-HR correlations. That is, mexiletine tended to be more effective on the positive correlation group (P: 58.3% vs NP: 33.3%), whereas disopyramide revealed no such predominancy on either group (P: 44.4% vs NP: 54.5%), although this trend did not reach statistical significance.

The possible antiarrhythmic mechanisms

The electrophysiological mechanisms of the ventricular arrhythmias include abnormal automaticity, re-entry and triggered activity (TA).\(^22\),\(^23\) Since the major electrophysiological effects of mexiletine\(^24\)–\(^26\) and disopyramide\(^27\)–\(^29\) include the inhibition of the sodium current in the Purkinje fibers and ventricular muscles and the suppression of diastolic slow depolarization in the Purkinje fibers, the drugs may suppress the VPCs derived from both the re-entry mechanism and the abnormal automaticity.

With regards to VPCs due to triggered activity (TA),\(^30\),\(^31\) if any, the sodium channel blockers such as mexiletine and disopyramide may also inhibit the TA by means of the following mechanisms. (1) The upstroke of the TA occurring from transient depolarization (TD) consists of the sodium inward current and therefore is sensitive to mexiletine and disopyramide. (2) Both mexiletine\(^32\) and disopyramide\(^33\) reportedly have an inhibitory effect on the calcium current with a resultant decrease in \([\text{Ca}^{2+}]_i\). (3) Lidocaine, a class I drug, decreases \([\text{Na}^+]_i\) and ultimately decreases \([\text{Ca}]_i\) via Na-Ca
exchange with eventual suppression of both TD and TA. Similar effects could be expected for disopyramide and mexiletine. (4) Both drugs may directly affect either the Na-Ca exchange system or the nonspecific cation channels carrying the transient inward current. On the basis of these considerations, mexiletine and disopyramide are expected to suppress VPCs regardless of the mechanism, e.g., re-entry, automaticity or triggered activity.

In the present study, most patients had no underlying heart disease. Further studies should be performed to elucidate whether or not the same line of results can be obtained in patients with ischemic or other organic heart diseases.

We believe that the analyses of the VPC-HR correlations and the test of antiarrhythmic agents on these correlations provide an important clue to solving the mechanism of ventricular tachyarrhythmias and to predicting the efficacy of certain antiarrhythmic drugs.

**References**

13. Wellens HJJ: Value and limitations of programmed electrical stimulation of the heart in the
37. Cannell MB, Lederrer WJ: The arrhythmogenic current \( I_{r1} \) in the absence of electrogenic sodium-calcium exchange in sheep cardiac Purkinje fibers. J Physiol 374: 201, 1986