DAY-TO-DAY VARIATION OF THE FREQUENCY OF VENTRICULAR PREMATURE CONTRACTIONS DEPENDS ON VARIATION OF HEART RATES

Shigeru Tsumabuki, M.D., Morio Ito, M.D., Makoto Arita, M.D.*
Tetsunori Saikawa, M.D.*, and Sukenobu Ito, M.D.**

To examine the manner in which spontaneous variation in the frequency of ventricular premature contractions (VPCs) relates to the variation of heart rate (HR), 68 patients with frequent VPCs were studied, by using 24-hour ECG recordings. All patients had more than 40 VPCs/hour on an initial 24-hour ECG recording and a second recording was made within 2 months (mean: 15 days). For each patient, the HR-dependency of VPCs was evaluated. Plots of VPC frequency per minute (VPCs/min) vs. HR were made at 1-beat/min steps for all HRs recorded for at least 5 min during 24 hours.

Based on the patterns of correlation between VPCs/min and HR observed at the first recording, patients were divided into 2 groups: 1) 26 with a positive correlation or the P group (a linear increase in VPCs/min with increasing HRs) and 2) 42 with a non-positive correlation or the NP group. The NP group included: 1) an increased VPCs/min at low HRs and a decrease at high HRs (38 patients), 2) a linear decrease in VPCs/min with increased HRs (2 patients) and 3) constant VPCs/min at all HRs (2 patients). The patterns of correlation were reproducible at the second recording period in 65 of 68 patients (96%). Variability in the VPC frequency per 24 hours between two 24-hour recording periods was significantly greater in the P than in the NP group, while the variability in the mean daily HR was similar between the 2 groups. Thus, the 95% confidence limit for spontaneous reduction in the VPC frequency was greater for the P (67%) than for the NP group (50%). The percent change in VPC frequency per 24 hours at the second recording period relative to the first (y) showed a significant positive relationship with the percent change of mean daily HR (x) in both P (y = 5.9x + 17.6, r = 0.80, p < 0.001) and NP (y = 1.8x - 4.6, r = 0.34, p < 0.05) groups. However, the correlation coefficient and the slope of regression were significantly greater in the P than in the NP group. These observations indicate that the spontaneous variation of HR is a pivotal determinant of VPC variation, particularly in cases of the P group.

Key words:
Ventricular premature contractions
Heart rate
Ambulatory ECG recording
Spontaneous variation

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Department of Laboratory Medicine, *Department of Physiology, and **First Department of Internal Medicine,
Medical College of Oita, Oita, Japan
Supported by the Kimura Memorial Heart Foundation Research Grant for 1987
Mailing address: Morio Ito, M.D., Department of Laboratory Medicine, Medical College of Oita, 1-1506,
Idaigaoka, Hazama-machi, Oita-gun, Oita 879-86, Japan

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AMBULATORY electrocardiographic (ECG) recording has become a standard method to monitor the efficacy of antiarrhythmic drug therapy. However, the assessment of drug efficacy on ventricular premature contractions
(VPCs) is complicated by a large degree of spontaneous variations in their frequency\(^1\)\textendash\(^6\). The mechanisms involved in VPC variability are not well understood. Animal\(^7\),\(^8\) and clinical studies\(^9\),\(^10\) showed that heart rate is an important determinant of the frequency of ventricular arrhythmias. Recently Winkle\(^11\) and Ito et al\(^12,13\) evaluated VPC frequency as a function of underlying heart rate during routine daily activity, using the ambulatory ECG recordings. They found that in most patients with frequent VPCs there was a definite relationship between VPC frequency and heart rate and this relationship differed from one patient to another. Accordingly, it is suggested that spontaneous variation in VPC frequency may depend on variation in heart rate and the degree of VPC variability may differ between patients with different VPC frequency-heart rate relationships. However, studies so far reported on the day-to-day variability of VPC frequency have focused simply on the total number of VPCs\(^1\)\textendash\(^6\). The evaluation of VPC frequency as a function of heart rate is expected to provide new and important information concerning the mechanisms of spontaneous variation in VPC frequency. We examined: 1) how the spontaneous variation in VPC frequency relates to the variation in heart rate; and 2) whether the degree of VPC variability differs according to the heart rate-dependency of VPCs.

**METHODS**

**Patients**

Sixty-eight patients with frequent VPCs were studied. To be included in this study, they had to have more than 40 VPCs per hour averaged over 24 hours on an initial ambulatory ECG recording and to have a second recording within 2 months after the initial recording. The second recordings were made 1\textendash}55 days (mean \(\pm\) SEM: 14.5 \(\pm\) 1.3 days) after the initial recording. Both recordings were made after discontinuing all antiarrhythmic drugs including digitalis, for at least 1 week beforehand. All patients had sinus rhythm. Patients with an intraventricular conduction disturbance or AV block of second or higher degrees were excluded. Nine patients had cardiac diseases (ischemic heart disease in 4, idiopathic cardiomyopathy in 3, valvular heart disease in 1 and ventricular septal defect in 1). The others had no cardiac abnormalities detectable by history, physical examination, 12-lead ECGs, echocardiogram and chest X-ray.

**Analysis of 24-hour ECG Recordings**

Twenty-four-hour ECG recordings were made with a two-channel Avionics recorder (Model 445B) and were analysed with the Avionics computer system (Dynamic Electroscanner DCG 7). With this system, we determined the mean VPC frequency per hour (total number of VPCs during 24 hours/24) and the mean heart rate per minute (total number of heart beats during 24 hours divided by total minutes (1440) during 24 hours). These 2 values are expressed hereafter by using the terms: “mean VPC frequency” and “mean heart rate”, respectively.

With the use of another computer system in conjunction with the Avionics system, we obtained tabular and graphic information concerning the relationship between VPC frequency and heart rate. The methods were the same as described previously\(^12\). In brief, the heart rate and VPC frequency were tabulated for each minute during 24 hours. The number of minutes at each heart rate (in a bin of 1 beat/min) and the total number of VPCs in these minutes were determined. VPC frequency per minute for each heart rate was calculated by the formula: number of VPCs in all minutes at a given heart rate/number of minutes at the same heart rate. The obtained heart rate and VPC frequency per minute are expressed using abbreviations, that is “HR” for the heart rate and “VPCs/min” for the VPC frequency, to avoid confusion with “mean VPC frequency” and “mean heart rate”, as mentioned above. VPCs/min was plotted vs. HR for all HRs recorded for at least 5 min during 24 hours. Accuracy of this system has been described\(^12\). Based on the relationship between VPCs/min and HR observed at the first recording period, patients were divided into 2 subgroups: 26 patients with a positive relationship (P group) and 42 patients with a non-positive relationship (NP group). The definition of positive and non-positive relationship is given in the Results section.

**Statistical Analyses**

Statistical comparison of data between the 2 monitoring periods or between P and NP groups was made using the Wilcoxon rank sum test for mean VPC frequency and VPCs/min, Student’s t test for other continuous variables, and chi square test for discrete variables. With regard to HR and VPCs/min, we selected for analysis the maximum, medium and minimum HRs of all HRs recorded for at least 5 min during 24 hours,
as well as VPCs/min at these HRs. The medium HR was calculated by the formula: (maximum HR + minimum HR)/2.

For each patient, the percent changes of both mean VPC frequency and mean heart rate were calculated as (value on the second recording/ value on the first recording – 1) x 100. The relationship between these 2 values was examined for each of the 2 patient groups using linear regression analysis.

Confidence limits for spontaneous variation in the mean VPC frequency between the two 24-hour periods were estimated for P and NP groups as well as for all the patients studied. We used an analysis of variance according to the methods described by Morganroth et al. In brief, the analysis was carried out using natural logarithms, ln (mean VPC frequency + 1), to induce a normal distribution and equal variances. Using the pooled estimate of the between-days variability (Vbd), we calculated a 95% confidence interval. This confidence interval represents the minimum difference required to demonstrate a significant difference between the 2 recordings at the 5% level for a 2-sided test. The confidence interval (D) was obtained by the formula:

\[ D = 2\sqrt{Vbd \left(1/n_1 + 1/n_2\right)} \]

where \(n_1\) and \(n_2\) are the number of days in the first and the second recording periods, respectively. In the present study, \(n_1 = n_2 = 1\). The percent reduction in mean VPC frequency from the first recording period to the second was calculated as follows:

\[ D = \ln(2nd \text{ record}) - \ln(1st \text{ record}) \]

Therefore,

\[ e^D = \frac{2nd \text{ record}}{1st \text{ record}} \]

The percent reduction in VPC frequency equals:

\[ 100 \left(1 - \frac{2nd \text{ record}}{1st \text{ record}}\right) \text{ or} \]

\[ 100 \left(1 - e^{-D}\right) \]

Variabilities of both mean VPC frequency and mean heart rate were compared between P and NP groups, using the approach proposed by Pratt et al. For each patient, the variance was estimated for the log-transformed counts of mean VPC frequency and the natural counts of mean heart rate. These estimates were used as the response variables. The modified 2-sample t-test was used to compare the variabilities between the 2 patient groups.

Data given are the mean ± SEM, unless otherwise specified. A p-value of less than 0.05 was considered statistically significant.

RESULTS

1. Relationship between VPC Frequency and
Heart Rate and the Reproducibility

In all patients there was a clear relationship between VPC frequency (VPCs/min) and heart rate (HR), and the patterns of relationship observed at the first 24-hour monitoring period could be classified into several broad categories. Included were: 1) an increase in VPCs/min with increasing HRs (positive correlation, 26 patients; Fig. 1, closed circles), 2) an increase at relatively low HR range and a decrease at high HR range (bidirectional correlation, 38 patients; Fig. 2A, B and C, closed circles), 3) a decrease in VPCs/min with increasing HRs (negative correlation, 2 patients; Fig. 2D, closed circles), 4) fairly constant VPCs/min over the entire range of HRs (flat correlation, 2 patients; Fig. 2E, closed circles). Bidirectional correlation tended to flatten at a high HR range, in some patients (Fig. 2C, closed circles). We divided 68 patients in 2 groups depending on the patterns of relationship between VPCs/min and HR: 26 patients with a positive correlation (P group) and 42 patients with the other (non-positive) correlations (NP group).

At the second recording period, 25 out of 26 patients (96%) of the P group and 40 out of 42 patients (95%) of the NP group again showed a positive (Fig. 1) and a non-positive correlation (Fig. 2), respectively. In the remaining 3 patients, the pattern of correlation changed from a positive to a bidirectional one (1 patient) or from a bidirectional to a positive one (2 patients). Three in the NP group showed a transition within the same category of non-positive pattern as follows: 2 cases of bidirectional type changed to the negative type (Fig. 2B) and 1 of the flat type became the bidirectional type (Fig. 2E).

In Fig. 3, the averages of VPCs/min at the maximum, medium and minimum HR were plotted vs the averages of the respective HRs for P (panel A) and NP group (panel B). In both the first and the second recording periods, the
Spontaneous Variability of Ventricular Premature Contractions

Fig. 3. Plots of averaged frequencies of ventricular premature contractions (VPCs) at the maximum, medium and minimum heart rates vs. averages of the corresponding heart rates in patients with positive (A) and non-positive correlations (B). Closed and open circles with bars represent mean ± SEM of the data for the first and the second monitoring periods, respectively. All 3 points of heart rates and VPC frequencies were statistically similar between the two monitoring periods.

TABLE 1 CLINICAL DATA AND FINDINGS OF 24-HOUR AMBULATORY ECG RECORDINGS IN 68 PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 68)</th>
<th>P group (n = 26)</th>
<th>NP group (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>51.7 ± 1.9</td>
<td>54.5 ± 3.1</td>
<td>49.9 ± 2.4</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>39/29</td>
<td>13/13</td>
<td>26/16</td>
</tr>
<tr>
<td>Interval (days)*</td>
<td>14.5 ± 1.3</td>
<td>13.8 ± 1.5</td>
<td>14.9 ± 1.9</td>
</tr>
<tr>
<td>Mean VPC frequency (hour⁻¹)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st recording</td>
<td>536 ± 56</td>
<td>618 ± 113</td>
<td>486 ± 57</td>
</tr>
<tr>
<td>2nd recording</td>
<td>462 ± 51</td>
<td>512 ± 95</td>
<td>432 ± 57</td>
</tr>
<tr>
<td>Mean heart rate (min⁻¹)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st recording</td>
<td>74.1 ± 1.0</td>
<td>73.5 ± 1.5</td>
<td>74.5 ± 1.3</td>
</tr>
<tr>
<td>2nd recording</td>
<td>72.5 ± 1.2</td>
<td>71.5 ± 2.0</td>
<td>73.2 ± 1.5</td>
</tr>
</tbody>
</table>

P group = patients with a positive correlation, NP group = patients with non-positive correlation. Interval = interval between the 2 ambulatory ECG recordings, Mean VPC frequency = frequency of ventricular premature contractions per hour averaged over 24 hours. Mean heart rate = heart rate per minute averaged over 24 hours. *Data are expressed as the mean ± SEM.
maximum, medium and minimum HRs were statistically identical between the 2 groups. In either the P or the NP group, these 3 HRs and the VPCs/min at these HRs did not differ significantly between the 2 monitoring periods. However, individual patients showed various degrees of change in these parameters. Accordingly, the relationship curve shifted from one recording to the next (Fig. 1 and 2). In 20 patients (10 of the P group and 10 of the NP group), the relationship curves of the 2 recording periods were identical or “superimposable” (Fig. 1A and 2A). In 14 patients (10 of the P group and 4 of the NP group), the second curve spread out approximately in the extending direction of the initial curve (Fig. 1B and C). In this type of alteration, VPCs/min at a given HR was held almost unchanged between 2 recording periods, as was in case of “superimposable” relationship. In the remaining 34 patients (6 of the P group and 28 of the NP group), the second relationship curve deviated from the initial one in the vertical direction (Fig. 2B–E), resulting in the marked change in VPCs/min at a given HR between 2 recording periods. This type of alteration was noted only in 6 of 26 (23%) in the P group, but in 28 of 42 (67%) in the NP group (p < 0.01, chi square test). These results indicate that reproducibility of the relationship between VPCs/min and HR was better in the P than in the NP group.

There was no significant difference between P and NP groups with regard to age, sex ratio, interval between the 2 recording periods, mean VPC frequency and mean heart rate (Table I).

2. Day-to-day Variation in VPC Frequency and Heart Rate

Both the mean VPC frequency and the mean heart rate averaged for either the P or NP group showed no significant difference between the two 24-hour periods (Table I). However, individual patients showed considerable variation in these values between the 2 recording periods. The percent changes of mean VPC frequency ranged from −86% to +369% in the P group and from −82% to +134% in the NP group. The percent changes of mean heart rate were much less as compared to those of the mean VPC frequency, ranging from −30% to +36% in the P group and −20% to +17% in the NP group. In Fig. 4, the percent change of mean VPC frequency was plotted against the percent change of mean heart rate for P (panel A) and NP groups.
(panel B). In both groups, the percent change of mean VPC frequency showed a significant positive relationship with the percent change of mean heart rate. However, both the correlation coefficient and the slope of regression were significantly greater in the P group.

Variability in mean VPC frequency between the 2 recording periods was significantly greater in the P than in the NP group (p < 0.05). Here, the variability of the mean heart rate was statistically similar between the 2 groups. A 95% confidence limit of the percent reduction in the mean VPC frequency was estimated to be 67% for the P group and 50% for the NP group. For all the patients studied, the confidence limit was 58%.

DISCUSSION

1. Correlation between VPC Frequency and Heart Rate

Previous experimental as well as clinical reports revealed heart rate-dependent ventricular arrhythmias in ischemic or other conditions. There are patients in whom VPCs are either enhanced or suppressed by exercise. Recently, the relationship between VPC frequency and underlying heart rate was examined using 24-hour ambulatory ECG recordings. In the present study, we examined this relationship in 68 patients with frequent VPCs (> 40/hour) and found several patterns of relationship. Dominating patterns were positive (26 patients) and bidirectional relationship (38 patients). The patterns of relationship were reproducible in the majority of patients, from one recording to the next. These results are consistent with reported data. We divided 68 patients into 2 subgroups, depending on whether there was a positive (P group, 26 patients) or non-positive correlation (NP group, 42 patients).

The graphic patterns of relationship were reproducible, but in some patients, the VPC frequency-heart rate relationship curve shifted upward or downward or to the right or left. In most patients in the P group (20 of 26 patients, 77%), the VPC frequency-heart rate relationship of the second recording period was a mere extension of the initial relationship, leaving both the slope of relationship and the intercept on the HR-axis practically identical (Fig. 1). In contrast, in most patients in the NP group (28 of 42 patients, 67%), the relationships of 2 recording periods distinctly deviated (Fig. 2B-E). These results show that the reproducibility of the VPC frequency-heart rate relationship was better in the P group.

We reported that oral diltiazem suppressed VPCs in patients of the P group (P type VPCs), but had almost no effect on VPCs in patients of NP group (NP type VPCs). Animal experiments have shown that triggered activity is most prominent with high rates of pacing and is readily suppressed by calcium antagonists. Thus, triggered activity may, at least in some patients in the P group, play a role in the genesis of VPCs, as already stated.

2. Spontaneous Variability in VPC Frequency and Heart Rate

There is ample evidence of a considerable variation in VPC frequency between days in the absence of antiarrhythmic drugs. In the patients studied here there was also a large variation in VPC frequency between the two 24-hour recording periods (from 86% reduction to 369% increase). Several authors estimated the decline in VPCs required to establish an effect due to antiarrhythmic drug therapy rather than to spontaneous variation. Morganroth et al seem to have been the first to apply an analysis of variance to estimate the minimal VPC reduction necessary to demonstrate a drug effect. They claimed an 83% reduction in VPC frequency necessary to establish drug effect, if two 24-hour periods were compared. Pratt et al using a similar statistical approach, arrived at a similar conclusion. They reported that at least 78% of VPC reduction was needed to demonstrate a drug effect. Sami et al used a regression analysis and claimed that 65% was a necessary reduction. We utilized the statistical approach proposed by Morganroth et al and found the 95% confidence limit for a spontaneous reduction in VPCs to be 58% for all the patients studied, a figure slightly lower than that in other reports.

Previous studies concerning the spontaneous variation in VPC frequency were concerned with the number of ectopic beats. The present study seems to be the first to examine whether VPC variation can be explained by a relationship between VPC frequency and heart rate. In both the P and the NP groups, there was a significant positive relationship between the percent changes in the mean VPC frequency and the mean heart rate (Fig. 4). However, the correlation coefficient and the slope of linear regression were signifi-
cantly greater in the P group. This observation suggests that heart rate variation is a pivotal determinant of the VPC variation in both the P and the NP groups, but it is more so in the former. The linear increase of mean VPC frequency with an increase in mean heart rate in the P group can be well explained by the finding that, in most patients of this group, the VPC frequency-heart rate relationship of the second recording period was a mere extension of the relationship of the first recording period (Fig. 1).

In addition, the present study revealed that VPC variability between two 24-hour periods was significantly greater in the P than in the NP group, while the heart rate variability was similar between the two groups. Thus, the minimal percent reduction of VPC frequency needed to establish a significant drug efficacy at the 95% confidence limit was greater for the P group (67%) than for the NP group (50%). It has been reported that spontaneous variability in VPC frequency is influenced by several factors. VPC variation tends to be greater when the VPC frequency is less at the initial recording period,

the duration of monitoring period is short

or the interval between the 2 monitoring periods is prolonged. Recently, Pratt et al. reported that the patients with coronary artery disease had a greater VPC variability than in those without this ailment. We wish to add another factor which strikingly influences VPC variability, that is, heart rate-dependency of VPC frequency, since spontaneous variation in the P group is more marked than in the NP group. Most of the patients we studied had no underlying heart disease. Further studies should be done to confirm whether the same results will be obtained in patients with coronary or other organic heart diseases.

3. Implications

The evaluation of VPC frequency as a function of heart rate may be a new and important approach for studying the spontaneous variation in VPC frequency and antiarrhythmic drug efficacy. The present study shows that VPC variation is, largely, due to change in the mean heart rate and that even a slight change in heart rate can produce a relatively large variation in VPC frequency. This is particularly so for P type VPCs. Mean heart rate would be readily influenced by a variety of daily activities and environmental conditions, such as exercise, emotional stress and sleep. To minimize spontaneous VPC variability, these factors in daily life should be kept as constant as possible during different ambulatory ECG monitoring periods.

Antiarrhythmic drugs with negative chronotrophic effects are expected to be more effective in suppressing P than NP type VPCs. Indeed, we found that oral atenolol suppressed P type VPCs, but had little effect on NP type VPCs, although this drug caused the same degree of heart rate reduction in both P and NP groups. Likewise, oral diltiazem was effective only for the P group. However, these 2 drugs differ significantly with regard to effects on the relationship between VPCs/min and HR. At 2 week period of treatment, diltiazem caused little change in the range of HRs recorded during 24 hours, but produced a distinct decline of the slope of the relationship between VPCs/min and HR. In contrast, atenolol strikingly decreased the maximum HR with little alteration in the slope of the relationship between VPCs/min and HR, a phenomenon similar to that seen in the positive correlation curve in which the maximum HR decreased on the second recording, without the drug (Fig. 1A). These observations suggest that heart rate reduction per se plays an important role in suppression of VPCs by atenolol, while mechanisms other than heart rate change may underlie the effect of diltiazem since the main effect of diltiazem was to decrease the slope of the VPC frequency-heart rate relationship.

Thus, the analyses of the relationship between VPC frequency and heart rate should provide useful information for elucidating mechanisms of spontaneous VPC variation and the mode of action of antiarrhythmic agents and may provide a clue as to the choice of an antiarrhythmic drug.

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