HEART RATE-DEPENDENT ALTERATION OF THE FREQUENCY AND COUPLING INTERVAL OF VENTRICULAR ARRHYTHMIAS AS MEASURED BY 24-HOUR ECG MONITORING

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Twenty-four hour ECG recordings of 132 patients with frequent (>1000/day) ventricular premature contractions (VPCs) were analyzed using a computerized system, designed to evaluate the relationships between 1) the VPC frequency and heart rate (HR) (VPC-HR relation), 2) the coupling interval (CI) of VPCs and HR (CI-HR relation), and 3) the incidence of ventricular tachycardia (VT) and HR (VT-HR relation). The patterns of the VPC-HR relation included: 1) an increase in VPCs with increasing HR (positive correlation, 43 patients), 2) an increase in VPCs at low HR range and a decrease at high HR range, with increasing HR (bidirectional correlation, 74 patients), 3) a decrease in VPCs with increasing HR (negative correlation, 7 patients) and 4) constant VPCs over all HRs (flat correlation, 8 patients). Patients were divided into 2 broad categories according to whether they had a positive correlation (P group, 43 patients) or the other correlations (non-positive or NP group, 89 patients). Of 132 patients, the CI-HR relation was negative in 129 (98%) and positive in only 3 (2%). Patients with frequent VTs (10 or more events over 24h) were significantly more frequent in the P (9 patients, 21%) than in the NP group (7 patients, 8%, p<0.05). However, mean HR, mean CI, total VPC counts and the slope of CI-HR relation were not significantly different between the groups. The VT-HR relation observed in 16 patients with frequent VTs were positive in 9 of the P group and in 2 of the NP group and non-positive in 5 of the NP group. We conclude that: 1) the incidence of VTs depends on underlying HR, as was the case for VPCs, 2) in most (88%) patients, the occurrence of VPC and VT reveals similar dependence on the underlying HR, and 3) the CI of VPCs shortens as HR increases in most (98%) patients.

The mechanisms of clinical ventricular arrhythmias has been suggested to be reentrant excitation or enhanced automaticity. However, recent studies of cellular electrophysiology have added another mechanism, that is, triggered activity arising from delayed afterdepolarizations (DADs).1,2 The causal relation between DADs and ventricular arrhythmias is a matter of intense interest3-7 However, convincing evidence of DADs as a cause of clinical ventricular arrhythmias is still lacking3,5,8

In this context, Winkle9 and Ito et al6,7 examined the relationship between the frequency of ventricular premature contractions (VPCs) and underlying heart rate using 24h ambulatory monitoring and found that there were distinct patient groups in whom VPCs

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were increased or decreased with increasing heart rate. In our previous reports\textsuperscript{6,7} diltiazem and atenolol suppressed the VPCs that increased at the higher heart rates, but had very little effect on VPCs which did not increase with increasing heart rates. Due to a resemblance of the former type of VPCs to the triggered activity seen in in vitro animal experiments\textsuperscript{1,2} with regard to the responses to heart rate change and pharmacologic interventions, these researchers claimed that the VPCs evoked under increased heart rates may be elicited by triggered activity arising from DADs\textsuperscript{6,7}.

DADs may underlie not only VPCs, but also ventricular tachycardia (VT). The trains of driven beats are frequently followed by a run of triggered activity and such multiple responses became more evident with more rapid stimulation rates\textsuperscript{1} The coupling interval (CI) of DADs to the previous action potential also depends on the stimulation rate. The CI shortened when the cycle length of the foregoing test pulse was shortened\textsuperscript{1,2,4,10} In contrast, in the case of reentrant arrhythmias, the CI lengthened with the shortening of the cycle length of foregoing stimulation\textsuperscript{3–5} In the programmed electrical stimulation study, such a difference in the CI response to the foregoing test pulse(s) has been used as an important criterion for differentiating the triggered activity from the reentry\textsuperscript{3–5} Thus, the evaluation of the frequencies of VPCs and VT, as well as the CI of VPCs, as a function of underlying heart rate would provide some clues for understanding of the mechanisms of ventricular arrhythmias.

The study aimed: 1) to elucidate the relationships of VPC frequency and the CI of VPCs to underlying heart rate in patients with frequent VPCs, using 24h ECG monitoring; 2) to examine the relationship between the incidence of VT and underlying heart rate in the same patients; and 3) to discuss the mechanisms of VPCs and VT with special attention to ventricular arrhythmias due to triggered activity arising from DADs.

METHODS

Patient profiles

Twenty-four hour ambulatory ECG recordings were made from 132 patients (79 men and 53 women) aged 13–85 years (mean ± SD: 51.5 ± 17.6 years). Patients were selected from those who underwent 24h ECG recordings at the Medical Laboratory Center, Medical College Hospital of Oita during the period from October 1982-January 1989. To qualify, patients were required to have a 24h ECG recording that was made after discontinuing all antiarrhythmic drugs for at least 5 half-lives and to have more than 1000 VPCs per 24h. If 2 or more recordings were available from one patient, the recording with the most frequent VPCs was chosen for analysis. Patients with atrial fibrillation or flutter, intraventricular conduction disturbance, WPW syndrome, congestive heart failure or acute myocardial infarction were excluded from the study. Based on history, physical examination, 12-lead ECGs, echocardiograms and chest X-ray films, 27 patients had ischemic heart disease (6 of them, old myocardial infarction); 21, hypertension; 5, idiopathic cardiomyopathy; 4, valvular disease; and one, ventricular septal defect. The remaining 74 patients had no sign of cardiac disease other than frequent VPCs. Patients studied here included some of those used in our previous studies\textsuperscript{6,7,11}.

Analysis of 24h ECG recordings

Twenty-four hour ECG was recorded with a 2-channel Avionics recorder (model 445B) and analyzed with the Avionics computersystem (DCG 7 Dynamic Electrosocaner). This system provided information about the VPC frequency, the incidence of the episodes of VT (3 or more successive VPCs) and “the CI of VPCs”. The CI between the preceding sinus beat and the first beat of couplet or VT run was also counted as “the CI of VPCs”. With this system, we obtained total VPC counts over 24h, mean heart rate (mHR, total heart beats over 24h/1440) and mean CI (mCI, the average of all CIs over 24h). The individual beats recorded during couplets or VT run were included in “the number of VPCs”. The total number of the VT episodes over 24h were counted manually using compressed ECG paper recordings.

With the use of the second computer (M-343, Sord Computer Systems) connected to
the Avionics system, we obtained tabular and graphic information about the relationships of VPC frequency, the CI of VPCs and the incidence of VT episodes to underlying heart rate. These were processed as follows:

(1) Relationship between VPC frequency and heart rate (VPC-HR relation): Methods of analysis were the same as reported previously. In brief, the heart rate and the number of VPCs were tabulated for each min over 24h. The number of min at each heart rate (in 1-beat/min increments) and the total number of VPCs in these min were counted. The averaged VPC frequency (per min) for the particular heart rate was calculated by the formula: [total number of VPCs in all min at a given heart rate][number of min at the same heart rate]. Then, the VPC frequency (per min) was plotted vs. the heart rate (per min) for all heart rates that were recorded for at least 5 min during 24h.

(2) Relationship between CI and heart rate (CI-HR relation): The heart rate was tabulated for each min during 24h. The number of CIs and the sum of these CIs were determined for each min over 24h. Mean CI for each heart rate was calculated by the formula: [sum of total CIs in all min at a given heart rate]/[number of CIs at the same heart rate]. Here, if the number of CIs included in a given heart rate was zero, this heart rate was excluded from analysis. Plots of mean CI (msec) vs. heart rate (per min) were made for every heart rates that occupied at least 5 min over 24h.

(3) Relationship between the incidence of VT episodes and heart rate (VT-HR relation): VT-HR relation was examined in 16 patients who had 10 or more VT episodes during 24h, using methods essentially the same as described for the evaluation of VPC-HR relation. Heart rate and the number of VT episodes were tabulated for each min over 24h. The number of min for a certain heart rate (at the bin of 10-beats/min) and the number of VT episodes in these min were determined. Mean incidence of VT episodes (per hour) was obtained for each heart rate by the formula: [60×(total number of VT episodes in all min at a given heart rate over 24h)/(number of min of this particular heart rate)]. Plots of the incidence of VT episodes (per hour) vs. heart rate (per min) were made at a bin of 10-beats/min for all heart rates recorded for at least 30 min over 24h.

Reproducibility of findings of 24h ECG recordings

To examine reproducibility of the findings of 24h ECG recordings, 49 patients (29 men and 20 women) aged 13−85 years (mean ± SD: 53.3 ± 17.2 years) were selected from 132 patients according to the following criteria: 1) They had two 24h ECG recordings made after discontinuing all antiarrhythmic drugs for at least 5 half-lives. 2) The interval of the 2 recordings was less than 100 days. 3) They had more than 1000 VPCs per 24h in the both recordings. The interval of the 2 recordings ranged 1−100 days (mean ± SD: 28.6 ± 26.8 days).

Accuracy of computer analysis

Accuracy of the computer analysis for VPC frequency and CI was evaluated in 10 patients with frequent VPCs, using randomly selected 100-min recordings, in which the computer-generated data were compared with the manually measured data. Manual measurements of CI were made on ECG papers recorded at a speed of 25 mm/sec. Errors (computer counts minus manual counts) estimated for each min were: −3.1 ± 2.8 beats/min (mean ± SD) for the heart rate, −0.9 ± 1.7 for the VPC frequency, and −10 ± 19 msec for the mean CI. Accuracy of the computer analysis of VT-HR relation was also evaluated in 9 patients with 10 or more VT episodes over 24h. Manual counts of the VT incidence were made for each min over 24h, using the compressed ECG paper recordings. Heart rate was determined for each min over 24h by the computer system. The incidence of VT episodes (per hour) for a given heart rate (at the bin of 10-beats/min) was calculated by the formula as stated above. There was highly significant correlation between the computer-generated and manual counts for the VT incidence (n=42, r=0.96, p<0.001). In all 9 patients, the patterns of VT-HR rela-
tion determined by manual method were the same as those made by the computer.

Statistical analyses
Results were reported in mean ± SD, unless otherwise specified. For the analyses of the frequencies of VPCs (per hour) and VT episodes (per 24h), the log-transformed data, i.e., log (arrhythmia frequency +1), were used to induce a normal distribution. Statistical comparison of data was made by Student’s t test and chi-square test. For individual patients, the CI-HR relation was analyzed by a linear regression analysis and the slope of regression (CI/HR slope) was determined. To examine the reproducibility of the findings of 24h ECG recordings, correlation coefficients between the data of the initial and the second recordings were determined by a linear regression analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

VPC-HR relation
In all patients, there was a distinct VPC-

HR relation and the patterns of the relationship could be classified into several categories. Included were: 1) an increase in VPC frequency with an increase in heart rates (positive correlation) in 43 patients (33%) (Fig. 1A), 2) an increase in VPC frequency at a relatively low heart rate range and a decrease at a high heart rate range (bidirectional correlation) in 74 patients (56%) (Fig. 1B), 3) a decrease in VPC frequency with increasing heart rates (negative correlation) in 7 patients (5%) (Fig. 1C), and 4) fairly constant VPC frequency over the entire range of heart rates (flat correlation) in 8 patients (6%) (Fig. 1D). We divided these patients into two broad categories, according to whether they had a positive (P group, 43 patients) or the other (non-positive) correlations (NP group, 89 patients).

CI-HR relation
In the majority of patients studied, the CI of VPCs was shortened with increasing heart rates, regardless of the patterns of VPC-HR relation (Fig. 1). A linear regression analysis of the CI-HR relation disclosed a significant negative correlation in 123 out of 132 pa-
patients (93%), a significant positive correlation in only 1 patient (1%) and no significant correlation in 8 patients (6%). The CI/HR slope was negative in 129 of 132 patients (98%) and positive in only 3 (2%). The values of individual CI/HR slopes in these patients, however, were scattered widely, ranging from 1.69 to -13.95 msec/beat/min (mean: -2.06 ± 1.91 msec/beat/min).

**VT-HR relation**

Sixteen of 132 patients (9 of the P group and 7 of the NP group) had 10 or more VT episodes during 24h and all of these patients showed a distinct VT-HR relation. All 9 patients of the P group had a positive VT-HR relation (Fig. 2A), whereas 7 patients of the NP group had various VT-HR relationships, i.e., a bidirectional correlation in 4 (Fig. 2B), a negative correlation in 1 (Fig. 2C) and a positive correlation in 2 (Fig. 2D).

**Comparison of other parameters between the P and NP groups**

Table I shows the clinical characteristics and the findings of 24h ECG recording in 132 patients. Age and the incidence of VT episodes were significantly greater in the P group than in the NP group. VT was recorded in 31 of 132 patients (23%). There was no statistical difference in the incidence of VT between the P (13 of 43 patients, 30%) and the NP groups (18 of 89 patients, 20%). However, the rate of evolution of frequent VT (10 or more VT episodes during 24h) was significantly higher in the P group (9 of 43 patients, 21%) than in the NP group (7 of 89 patients, 8%, p<0.05). There was no statistical difference in any of the other parameters, shown here (Table I), between the groups.

**Reproducibility**

In Table II are compared the data of the initial and the second 24h ECG recordings in 49 patients. For all the parameters studied, the data of the two recordings were statistically similar and showed statistically significant correlation. In the initial recording, 18 patients had a positive correlation and 31 patients showed a non-positive correlation. Of 18 patients with a positive correlation, 17 had the same positive correlation in the second recording and the pattern of VPC-HR relation changed to a bidirectional correlation in 1 patient. All of 31 patients with
TABLE I CLINICAL PROFILES OF THE PATIENTS STUDIED AND PARAMETERS OF 24H ECG RECORDINGS

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=132)</th>
<th>P group (n=43)</th>
<th>NP group (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>51.5±17.6</td>
<td>58.1±14.8</td>
<td>48.3±18.0**</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>79/53</td>
<td>24/19</td>
<td>55/34</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>58 (44%)</td>
<td>23 (53%)</td>
<td>35 (39%)</td>
</tr>
<tr>
<td>mHR (beats/min)</td>
<td>74.8±8.2</td>
<td>74.5±8.7</td>
<td>74.9±8.0</td>
</tr>
<tr>
<td>minHR (beats/min)</td>
<td>57.2±7.7</td>
<td>56.8±8.9</td>
<td>57.3±7.1</td>
</tr>
<tr>
<td>maxHR (beats/min)</td>
<td>100.0±11.9</td>
<td>99.0±12.5</td>
<td>100.4±11.7</td>
</tr>
<tr>
<td>log (VPCs+1)</td>
<td>2.49±0.44</td>
<td>2.50±0.41</td>
<td>2.48±0.46</td>
</tr>
<tr>
<td>log (VTs+1)</td>
<td>0.30±0.70</td>
<td>0.49±0.96</td>
<td>0.20±0.51*</td>
</tr>
<tr>
<td>Pts. with VT≥1</td>
<td>31 (23%)</td>
<td>13 (30%)</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>Pts. with VT≥10</td>
<td>16 (12%)</td>
<td>9 (21%)</td>
<td>7 (8%)*</td>
</tr>
<tr>
<td>mCI (msec)</td>
<td>467±83</td>
<td>449±67</td>
<td>476±89</td>
</tr>
<tr>
<td>CI/HR slope (msec/beat/min)</td>
<td>-2.06±1.91</td>
<td>-2.08±1.96</td>
<td>-2.05±1.90</td>
</tr>
</tbody>
</table>

P or NP groups: patients with positive or non-positive correlation between the frequency of ventricular premature contractions and heart rate; mHR=mean daily heart rate; minHR or maxHR=minimum or maximum heart rate of all heart rates recorded for at least 5 min over 24h; VPCs=frequency of ventricular premature contractions (per hour); VTs=the incidence of the episodes of ventricular tachycardias recorded during 24h; mCI=mean coupling interval; CI/HR slope=slope of the relationship between coupling interval and heart rate; *p<0.05 and **p<0.01 vs. P group. All averaged data are expressed as mean±SD.

TABLE II COMPARISON OF THE FIRST AND THE SECOND 24H ECG RECORDINGS IN 49 PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>First recording</th>
<th>Second recording</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>mHR (beats/min)</td>
<td>74.7±7.8</td>
<td>73.4±7.3</td>
<td>0.713</td>
</tr>
<tr>
<td>minHR (beats/min)</td>
<td>55.6±7.7</td>
<td>54.4±6.9</td>
<td>0.660</td>
</tr>
<tr>
<td>maxHR (beats/min)</td>
<td>100.6±11.4</td>
<td>99.3±11.4</td>
<td>0.692</td>
</tr>
<tr>
<td>log (VPCs+1)</td>
<td>2.56±0.35</td>
<td>2.50±0.38</td>
<td>0.604</td>
</tr>
<tr>
<td>log (VTs+1)</td>
<td>0.32±0.59</td>
<td>0.20±0.44</td>
<td>0.566</td>
</tr>
<tr>
<td>mCI (msec)</td>
<td>456±69</td>
<td>460±69</td>
<td>0.914</td>
</tr>
<tr>
<td>CI/HR slope (msec/beat/min)</td>
<td>-2.01±1.36</td>
<td>-2.11±1.51</td>
<td>0.736</td>
</tr>
</tbody>
</table>

Abbreviations are the same as in Table I. For all the parameters, the data of the first and the second recordings were statistically similar and showed a significant correlation (p<0.01).

a non-positive correlation on the initial recording again showed a non-positive correlation on the second recording. Of 31 patients with a non-positive correlation, the initial pattern of VPC-HR relation wasbidirectional in 27, negative in 2 and flat in 2. Seven of these 31 patients (23%) showed a transition within the same category of non-positive correlation as follows: 2 cases of a bidirectional type and one of a flat type changed to a negative type, one of a negative type and one of a flat type changed to a bidirectional type, and 2 of a bidirectional type became a flat type.

DISCUSSION

VPC-HR and CI-HR relations

In the present study, we examined the VPC-HR and CI-HR relations in 132 patients with frequent VPCs using 24h ECG recordings and found several patterns of VPC-HR relation. Dominating patterns were positive (43 patients, 33%) and bidirectional correlation (74 patients, 56%). These results are consistent with those re-
ported previously. We divided all the patients into two much broader categories, depending on whether they had a positive (P group, 43 patients) or a non-positive correlation (NP group, 89 patients).

The present study showed that the CI shortens with increasing heart rates in the majority of patients, and that the CI/HR slope differed markedly from one patient to another. This confirmed the results of previous studies, conducted using patients with various cardiac diseases while Surawicz et al. reported more frequent occurrence of a negative than a positive relationship between the preceding RR interval and CI. Furthermore, our present analyses disclosed that there was no statistically significant difference in the value of CI/HR slope, between the P and NP groups.

In this study, we examined the reproducibility of the findings of 24h ECG recordings in 49 patients. For all the parameters, including mCI and CI/HR slope, the data of the initial and second recordings were statistically similar and showed statistically significant correlation. With respect to the patterns of a positive and a non-positive VPC-HP relation, reproducibility was noted in 48 of 49 patients (98%). However, the change of pattern within the same category of a non-positive correlation was observed in 7 of 31 patients (23%). The present results concerning the reproducibility of the patterns of VPC-HP relation were the same as reported previously.

**VT-HP relation**

We examined the VT-HP relation in 16 patients (9 of the P group and 7 of the NP group) with frequent VTs (10 or more events during 24h). All 9 patients of the P group had a positive VT-HP relation, while 2 out of 7 patients of the NP group had a positive VT-HP relation, with the remaining 5 patients showing a non-positive VT-HP relation. Several investigators examined the heart rate just prior to the occurrence of VT or ventricular fibrillation. Kempf et al. reported that VT or ventricular fibrillation associated with sudden cardiac death was frequently preceded by an increase in heart rate. By examining patients with repetitive monomorphic idiopathic VT, Zimmermann et al. found faster heart rates before evolution of VT than before evolution of isolated VPCs. On the other hand, Lie et al. found that patients with acute myocardial infarction had inconsistent heart rate changes immediately before the development of ventricular fibrillation, that is, sinus tachycardia, normal sinus rhythm, or bradycardia due to complete AV block. To our knowledge, the present study is the first to document the incidence of VT episodes as a function of the underlying heart rates. Our results showed that there are 3 different patient categories in whom VT most likely occurs under high heart rates, low heart rates or the heart rates inbetween, during routine daily activity (cf. Fig. 2, bottom). The present results seem to be consistent with the observations of Lie et al. on the heart rate changes before the occurrence of ventricular fibrillation.

In our study, the VPC-HP and VT-HP relations were identical in most patients with frequent VTs (14 of 16 patients). This finding is in agreement with the notion that the mechanisms of VPCs and VT may be the same. However, there are some reports that do not support this idea. Indeed, in our present study, 2 patients classified as having a "non-positive" VPC-HP relationship had a "positive" VT-HP correlation, thereby indicating different mechanisms for the genesis of VPCs and VT in these patients.

The increase of VPC frequency, the development of couplets or multiform VPCs, and the occurrence of VPCs with short or long CI have been considered as warning signs for VT evolution. Here, we add another characteristic of VPCs which may predict the occurrence of VT, that is, a "positive VPC-HP relationship", since the VT episodes were significantly more frequent in the P group than in the NP group (Table 1).

**Mechanisms of VPCs and VT in the P group**

Our present and previous studies suggest that triggered activity arising from DADs plays a prime role in the genesis of VPCs and VT in the patients of the P group. Animal experiments have shown that rapid pacing increases the amplitude of DADs and produces the runs of triggered activity. The present study showed that the occurrence of both VPCs and VT in the P group in-
creased with increasing heart rates. DADs are readily suppressed by calcium channel blockers or beta blockers. Diltiazem and atenolol indeed suppressed the VPCs in patients of the P group, but not the VPCs in patients of the NP group.

Another characteristic of DADs reported in animal experiments is that the CI shortens when paced at high rates. A negative CI-HR relation seen in patients of the P group is compatible with this important characteristic of DADs. In the programmed electrical stimulation study, the prolongation of CI with a decreasing cycle length of the preceding extra stimulus has been used as a most reliable criterion for the diagnosis of reentry. However, the present study disclosed a distinct negative CI-HR relation in most NP group patients. Previous studies using 24h ECG recordings also reported a shorter CI under higher heart rates in the majority of patients with various cardiac diseases. Their and our data suggest that, when ECGs are examined during routine daily activity, the CI generally shortens with increased heart rates, regardless of the mechanisms of VPCs. Reasons for this finding remain to be found. Nau et al reported that the CI of VPCs, as compared in identical heart rate, was shorter when the heart rate was increased by exercise than by atrial pacing. It is possible that sympathetic tone inevitably associated with the exercise contributed to the greater shortening of the CI, because increased sympathetic activity tends to improve conduction, particularly under abnormal conditions. Thus increased heart rates secondary to enhanced sympathetic tone might have shortened CI of VPCs, though a heart rate increase, per se, tends to lengthen the CI by decreasing the safety factor of conduction. With respect to VPCs of the P group, a positive VPC-HR relation and a negative CI-HR relation are more reasonably understood, because the heart rate increase and enhanced sympathetic activity might both lead to a greater loading of intracellular Ca^{2+}, that subsequently increases the DAD amplitude and shortens the CI.

**Implications**

Evaluation of VPC-HR relation as reported here seems to be useful in predicting frequent VT episodes, since the incidence of frequent VTs (10 or more episodes over 24h) was greater in the P (21%) than in the NP group (8%). Recently, we reported that the spontaneous day-to-day variation of VPC frequency strongly depends on the variation of the underlying heart rate. In this context, we here emphasize that the variation of heart rate is also crucial for the initiation of VT. Marked day-to-day variation of the incidence of VT has been reported previously. This could have been secondary to the day-to-day variation of the heart rate. Since diltiazem and atenolol suppressed VPCs in patients of the P group, but not in patients of the NP group, it is intriguing to speculate that calcium channel blockers or beta blockers may be more effective for the suppression of VTs in patients with positive rather than non-positive VT-HR relationship.

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