Suppression of Ventricular Premature Contractions Possibly Related to Triggered Activity by Oral Diltiazem and Atenolol

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The clinical importance of triggered activity as a cause of arrhythmias is uncertain. We assumed that ventricular premature contractions (VPCs) caused by triggered activity could be increased at higher heart rates and be suppressed by calcium channel blockers and beta-adrenoceptor blockers. Thus, we evaluated VPC frequency as a function of underlying heart rate and examined the efficacy of diltiazem and atenolol on VPCs, using 24 hour ECG recording. Plots of VPC frequency vs. heart rate were made at 1-beat/min intervals for all heart rates recorded for at least 5 min during 24 hours. Diltiazem (90–180 mg/day) and atenolol (50 mg/day) were given orally for 4 weeks, respectively in 36 and 16 patients with VPCs of more than 2000/day. Patterns of relationship between VPC frequency and heart rate observed before diltiazem therapy included: 1) an increase of VPCs at higher heart rates (positive correlation) in 16 patients, 2) an increase at low heart rates and a decrease at high heart rates (bidirectional correlation) in 13 patients, 3) an increase at low heart rates and flat curve at high heart rates (positive-flat correlation) in 5 patients, 4) a linear decrease (negative correlation) in 1 patient, and 5) flat curve (flat correlation) in 1 patient. The patterns of correlation in patients treated with atenolol were positive in 6, bidirectional in 7, positive-flat in 2 and negative in 1. Both drugs significantly reduced the VPC frequency per 24 hours for patients with a positive correlation (P group), but induced no significant change for those with the other patterns of correlation (NP group). At the 70% VPC suppression level, diltiazem was effective in 9 of 16 patients of P group and only 1 of 20 patients of NP group ($p < 0.01$); atenolol was effective in 5 of 6 patients of P group and only 1 of 10 patients of NP group ($p < 0.05$). Both drugs reduced the slope of a positive correlation. These results suggest that: 1) VPCs which increase at higher heart rates may be related to triggered activity, and 2) an evaluation of VPC frequency as a function of heart rate predicts the response of VPCs to diltiazem and atenolol, and probably to other calcium antagonists and beta blockers.

Key words:

Triggered activity
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UNTIL recently, clinical arrhythmias were thought to result from reentrant excitation or enhanced automaticity or both. However,

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Fig. 1. Relationship between the frequency of ventricular premature contractions (VPCs) and heart rate in a 76-year-old man (A) and a 65-year-old man (B). Open circles represent the data obtained before, triangles 2 weeks, and closed circles 4 weeks after diltiazem therapy. In A and B, there was a positive correlation between VPC frequency and heart rate. Diltiazem reduced VPC frequency per 24 hours by 99% in A and 65% in B. Note the decline of the slope of relationship between VPC frequency and heart rate during diltiazem therapy.

recent studies indicate another mechanism for clinical arrhythmias, that is, triggered activity occurring from delayed after-depolarization.^{1,2} Such activity reportedly occurs in vitro in most cardiac tissues,¹ including human atrial³ and Purkinje fibers,⁴ by exposing them to an environment similar to that expected to exist in the clinical setting. Circumstantial evidence supports the possibility that triggered activity might cause arrhythmias in some patients.⁵⁻⁷ However, proof of triggered activity as a cause of clinical ventricular arrhythmias is still lacking.^{1,2}

Characteristics of triggered activity that may be an aid to its identification in the clinic include response to pacing and to antiarrhythmic drugs. As stimulus rates are increased, the amplitude of after-depolarization is increased and eventually attains the threshold for initiation of propagated response, i.e., triggered activity.^{1,8,9} Delayed after-depolarization is calcium channel-dependent phenomenon and thus suppressed by calcium channel blockers.¹ Beta-adrenoceptor stimulation enhances slow inward Ca^{++} current by increasing intracellular cyclic AMP and potentiates the development of triggered activity.^{10,11} These findings suggest that, if the ventricular premature contractions (VPCs) were indeed due to triggered activity, the VPCs should be increased with the increase in underlying heart rates and be sup-

pressed by calcium channel blockers and beta adrenergic receptor blocking agents. Therefore, in the present study, we analysed the relationship between VPC frequency and underlying heart rate during routine daily activity in patients with frequent VPCs using 24-hour ECG recording, and then examined whether the effects of diltiazem and atenolol on VPCs are the same or different depending on the relationship between VPC frequency and heart rate.

METHODS

The effects of diltiazem and atenolol on VPCs were studied respectively in 36 patients (23 men and 13 women) aged 12–76 years (mean $\pm$ SEM: 50.9 ± 3.1 years) and 16 patients (11 men and 5 women) aged 20–69 years (mean $\pm$ SEM: 46.3 ± 3.8 years). Patients gave informed consent. This study included only patients with VPCs of more than 2000 per 24 hours, before the initiation of diltiazem or atenolol therapy. Patients with the following were excluded: resting systolic blood pressure < 100 mmHg, severe hypertension, marked bradycardia, heart failure, acute myocardial infarction, AV block and intra-ventricular conduction disturbance. Patients with asthma, pulmonary emphysema and obstructive pulmonary disease were also excluded.

Fig.2. Relationship between the frequency of ventricular premature contractions (VPCs) and heart rate in a 47-year-old woman (A), a 49-year-old woman (B), a 13-year-old girl (C) and a 70-year-old man (D). Open and closed circles represent respectively the data obtained before and 4 weeks after diltiazem therapy. A: a bidirectional correlation before and after diltiazem; B: a negative correlation before diltiazem and a bidirectional correlation after diltiazem; C: a positive-flat correlation before and after diltiazem; D: a flat correlation before diltiazem and a positive-flat correlation after diltiazem. Diltiazem produced no significant reduction in VPC frequency per 24 hours in any of these patients: percent changes of VPC frequency at 4 weeks after diltiazem were 8% in A, -4% in B, 42% in C and -11% in D. In A and C, open circle indicated by arrow represents the median heart rate for a bidirectional (A) and a positive-flat correlation (C) (cf. Fig. 8).

All antiarrhythmic drugs were discontinued for at least 1 week before the initiation of therapy. Diltiazem was given orally three times daily in a dose of 90 mg to 2 patients or 180 mg to 33 patients. The remaining patient received a daily dose of 90 mg for the initial 2 weeks which was then increased to 180 mg for the next 2 weeks. Twenty-four hour ECG recordings were made before and 4 weeks after the initiation of diltiazem therapy in all 36 patients. In 34 of these patients, recordings were also made at the 2 week period of treatment. Atenolol was given orally once daily in a dose of 50 mg. In all 16 patients, the 24-hour ECG monitorings were made before, and 2 and 4 weeks after the initiation of atenolol

therapy.

A 24-hour ECG was recorded with a two-channel Avionics recorder and was analysed with the Avionics computer system (DCG 7 Dynamic Electroscanner). This system determined the total number of VPCs per hour and the mean daily heart rate (total number of heart beats during 24 hours/1440). A second computer system (M-343, Sord Computer Systems, Inc.) used in conjunction with the Avionics system obtained tabular and graphic information concerning the relationship between VPC frequency and heart rate. Methods were fundamentally the same as those reported by Winkle¹² and Ito et al.¹³ In brief, the heart rate and VPC frequency were

Fig.3. Effects of diltiazem on the frequency of ventricular premature contractions (VPCs) (upper panels) and the mean daily heart rate (lower panels). Data are expressed as mean $\pm$ SEM. A: patients with a positive correlation. $n = 16$ patients for 0 and 4 weeks, and 15 patients for 2 weeks. B: patients with a non-positive correlation. $n = 20$ patients for 0 and 4 weeks and 19 patients for 2 weeks. Diltiazem significantly decreased VPC frequency and heart rate in patients with a positive correlation (A), but not for those with a non-positive correlation (B).

tabulated for each minute during 24 hours. The number of minutes at each heart rate (in 1-beat/min increments) and the 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. VPC frequency per minute was plotted vs. heart rate. In this study, only heart rates recorded for at least 5 min during 24 hours were used for analysis. The accuracy of this system was reported previously.¹³

In order to characterize the changes in the relationship between VPC frequency and heart rate during diltiazem or atenolol treatment, three representative heart rates were selected for analy-

sis from all heart rates recorded: maximum, minimum and median heart rates. Definition of median heart rate is given in the Results section. The VPC frequency at each of the 3 heart rates was averaged for the group of patients with the same category of VPC frequency-heart rate relationship and the averaged VPC frequency was plotted against the average of the corresponding heart rate (cf. Fig. 8).

All measured parameters were expressed as mean $\pm$ SEM unless otherwise specified. Statistical analyses were made by Student's *t* test and chi square test. *P* values less than 0.05 were considered statistically significant.

RESULTS

1. Correlation between VPC Frequency and Heart Rate and the Effects of Diltiazem on VPCs

All 36 patients showed distinct relationship between VPC frequency and heart rate. The patterns of relationship could be classified into several categories: 1) an increase in VPC frequency at higher heart rates (positive correlation) in 16 patients (Fig. 1, open circles), 2) an increase at relatively low heart rates and a decrease at high heart rates (bidirectional correlation) in 13 patients (Fig. 2A, open circles), 3) a linear decrease at higher heart rates (negative correlation) in 1 patient (Fig. 2B, open circles), 4) an increase at low heart rates and almost no change at high heart rates (positive-flat correlation) in 5 patients (Fig. 2C, open circles), and 5) almost constant VPC frequency over the entire range of heart rates (flat correlation) in 1 patient (Fig. 2D, open circles). Some of these patients had a step or notch on their relationship (Fig. 1 and 2). For the sake of simplicity, we hereafter classify the patients into 2 groups depending on their relationship between VPC frequency and heart rate, i.e., those with a positive correlation (P group, Fig. 1) and those with the other correlation (non-positive correlation) (NP group, Fig. 2).

The age and sex ratio were similar between the P (12 men and 4 women; age: 56.9 ± 4.1 years) and the NP groups (11 men and 9 women; age: 46.2 ± 4.6 years). Cardiac diseases were noted in 5 of 16 cases in P group (ischemic heart disease in 2, hypertension in 2 and mitral valve prolapse syndrome in 1), and in 4 of 20 cases in NP group (ischemic heart disease in 1 and hypertension in 3). There was no significant difference in the incidence of cardiac disease between these

Fig.4. Percent changes in the frequency of ventricular premature contractions (VPCs) on diltiazem therapy. A, 16 patients with a positive correlation, and B, 20 patients with a non-positive correlation.

Fig.5. Relationship between the frequency of ventricular premature contractions (VPCs) and heart rate in a 20-year-old man (A) and a 37-year-old man (B). Open circles represent the data obtained before, triangles 2 weeks, and closed circles 4 weeks after atenolol. In A, there was a positive correlation between VPC frequency and heart rate. Atenolol decreased VPC frequency per 24 hours by 51% at the 2 week period of therapy and by 88% at the 4 week period. Note that the slope of correlation between VPC frequency and heart rate remained unchanged at the 2 week period, but decreased definitely at the 4 week period. In B, there was a bidirectional correlation. Atenolol produced only a slight change (i.e., 36% reduction) in VPC frequency per 24 hours.

Fig. 6. Effects of atenolol on the frequency of ventricular premature contractions (VPCs) (upper panels) and the mean daily heart rate (lower panels). Data are expressed as mean $\pm$ SEM. A, data for 6 patients with a positive correlation, and B, for 10 patients with a non-positive correlation. Atenolol decreased significantly the VPC frequency and the heart rate for patients with a positive correlation (A). For patients with a non-positive correlation (B), heart rate decreased significantly with no significant change in VPC frequency.

2 groups.

For all 36 patients, diltiazem decreased significantly the total number of VPCs from 621 ± 69 /hr at the pretreatment period to 498 ± 67 /hr ($p < 0.05$) and 423 ± 65 /hr ($p < 0.01$) at the 2 and 4 week periods of treatment, respectively. Mean daily heart rate was also reduced significantly after diltiazem therapy (74.5 ± 1.3 beats/min at pretreatment vs. 70.6 ± 1.4 beats/min and 70.1 ± 1.5 beats/min at 2 and 4 weeks, respectively; $p < 0.001$). There was no significant difference in either VPC frequency or mean daily heart rate between the 2 and 4 week periods of therapy. The effects of diltiazem differed depending on the VPC frequency-heart rate relationship. In the P group (Fig. 3A), diltiazem decreased the total number of VPCs from 687 ± 122 /hr at the

pretreatment period to 397 ± 96 /hr and 263 ± 89 /hr at the 2 and 4 week periods of treatment, respectively ($p < 0.001$). Mean daily heart rate was also reduced with treatment (75.5 ± 2.2 beats/min at pretreatment vs. 69.7 ± 2.2 beats/min and 68.0 ± 2.2 beats/min at 2 and 4 weeks, respectively; $p < 0.001$). In contrast, in the NP group (Fig. 3B), diltiazem produced no significant change in both VPC frequency and mean daily heart rate (568 ± 76 /hr and 73.7 ± 1.5 beats/min at pretreatment; 577 ± 90 /hr and 71.2 ± 1.9 beats/min at 2 weeks; and 552 ± 85 /hr and 71.2 ± 2.0 beats/min at 4 weeks). Before diltiazem therapy, there was no significant difference in either total number of VPCs or mean daily heart rate between the P and NP groups.

Figure 4 illustrates the percent changes of total number of VPCs during diltiazem therapy. In the P group (Fig. 4A), the change of VPC frequency ranged from -98 to 3% (mean: $-46.9 \pm 9.3\%$) at the 2 week period of treatment and from -100 to 21% (mean: $-63.3 \pm 10.0\%$) at the 4 week period; in the NP group (Fig. 4B), -71 to 92% (mean: $4.1 \pm 10.7\%$) at the 2 week period and -98 to 141% (mean: $-4.4 \pm 11.6\%$) at the 4 week period. At the 4 week period of diltiazem therapy, 11 of 16 cases (69%) of the P group achieved a 65% or more reduction of VPC frequency, but only 2 of 20 cases (10%) of the NP group attained this level of VPC reduction ($p < 0.005$). At the 90% VPC suppression level, diltiazem was effective in 6 of 16 cases (38%) in the P group as compared with the effectiveness in only 1 of 20 cases (5%) in the NP group ($p < 0.05$).

In two patients of P group (a 76-year-old woman and a 67-year-old man), there was an intermittent Mobitz I AV block on the 24-hour ECG record at the 4 week period of diltiazem therapy. No other adverse effects were noted.

2. Effects of Atenolol

The patterns of relationship between VPC frequency and heart rate observed before atenolol therapy in 16 patients included a positive correlation in 6 (Fig. 5A, open circles), a bidirectional correlation in 7 (Fig. 5B, open circles), a positive-flat correlation in 2 and a negative correlation in 1. The age and sex ratio were similar between the P (3 men and 3 women; age: 42.3 ± 6.6 years) and the NP groups (8 men and 2 women; age: 48.6 ± 4.8 years). Two patients of NP group had hypertension, and the remaining 14 patients had no definite cardiac disease other

Fig.7. Percent changes in the frequency of ventricular premature contractions (VPCs) during atenolol therapy. A: 6 patients with a positive correlation, and B: 10 patients with a non-positive correlation.

than frequent VPCs.

For all 16 patients, atenolol reduced significantly the total number of VPCs from 529 ± 110 /hr at the pretreatment period to 282 ± 44 /hr and 225 ± 38 /hr at the 2 and 4 week periods of treatment, respectively ($p < 0.05$). Mean daily heart rate was also decreased significantly during atenolol therapy (75.1 ± 1.8 beats/min at pretreatment vs. 62.0 ± 1.7 beats/min and 63.2 ± 1.6 beats/min at 2 and 4 weeks, respectively; $p < 0.001$). Both VPC frequency and mean daily heart rate at 2 and 4 week periods of therapy were statistically similar. Figure 6 shows the changes in VPC frequency and mean daily heart rate during atenolol treatment for the P and NP groups. In the P group (Fig. 6A), atenolol reduced significantly both VPC frequency and heart rate (487 ± 114 /hr and 74.3 ± 2.0 beats/min at pretreatment; 209 ± 65 /hr ($p < 0.02$) and 59.8 ± 1.9 beats/min ($p < 0.01$) at 2 weeks; 98 ± 50 /hr ($p < 0.02$) and 63.8 ± 2.7 beats/min ($p < 0.02$) at 4 weeks). During the 2 to 4 week periods of atenolol therapy, VPC frequency was decreased significantly, but mean daily heart rate was increased significantly. In the NP group (Fig. 6B), mean daily heart rate was significantly reduced (75.7 ± 2.6 beats/min at pretreatment vs. 63.3 ± 2.4 beats/min and 62.8 ± 2.2 beats/min at 2 and 4 weeks, respectively; $p < 0.001$), but the total number of VPCs did not change significantly

(555 ± 167 /hr at pretreatment vs. 326 ± 57 /hr and 301 ± 35 /hr at 2 and 4 weeks, respectively). There was no significant difference in either VPC frequency and mean daily heart rate at the pretreatment period between the P and NP groups.

Figure 7 demonstrates the percent changes in the total number of VPCs during atenolol therapy. The change in the P group ranged from -37 to -76% (mean: $-57.2 \pm 6.1\%$) at the 2 week period of atenolol therapy and from -55 to -96% (mean: $-80.4 \pm 6.2\%$) at the 4 week period (Fig. 7A); in the NP group, the change ranged from -85 to 26% (mean: $-23.4 \pm 9.8\%$) at the 2 week period and from -92 to 95% (mean: $-8.9 \pm 21.0\%$) at the 4 week period (Fig. 7B). At the 4 week period of atenolol therapy, 5 of 6 patients (83%) of the P group achieved a 70% or more reduction of VPC frequency, whereas only 1 of 10 patients (10%) in the NP group achieved this level of VPC reduction ($p < 0.05$). There were no adverse effects attributable to atenolol.

3. Changes in the Relationship between VPC Frequency and Heart Rate during Diltiazem and Atenolol Therapy

During diltiazem or atenolol therapy, most patients in either P (Fig. 1 and 5A) or NP group (Fig. 2A and C, Fig. 5B) showed the same patterns of relationship between VPC frequency and

Fig.8. Summarized results of the changes in the relationship between the frequency of ventricular premature contractions (VPCs) and heart rate on diltiazem (A and B) and atenolol therapy (C and D). Open, dotted and closed symbols stand respectively for the averaged data obtained before, and 2 and 4 weeks after therapy. Circles represent the minimum heart rates, triangles, the median heart rates, and squares, the maximum heart rates. A and C: 16 and 6 patients with a positive correlation. B and D: 20 and 10 patients with a non-positive correlation. Note that diltiazem decreased the slope of positive correlation at the 2 week period of therapy and this decrease was enhanced at the 4 week period (A), while, during atenolol therapy, the decline of slope became evident only at the 4 week period of therapy (C). See text for further explanations.

heart rate as were observed before treatment, though in some patients the patterns changed from one to another (Fig. 2B and D). Even when the pattern of relationship was reproducible, the relationship curves shifted upward or downward or to the right or left during the treatment with diltiazem and atenolol. Figure 8 summarizes such shifts of the relationship between VPC frequency and heart rate induced by diltiazem (A and B) and atenolol (C and D). In this figure, the averaged VPC frequencies at the minimum (circles), median (triangles) and maximum heart rates (squares) were plotted versus the corresponding averaged heart rates. Here the median heart rate was defined as follows. For a positive, negative or flat correlation, the median heart rate was obtained by the formula: (minimum heart rate + maximum heart rate)/2. For a bidirectional correlation, the median heart rate was defined as the

heart rate at the maximum VPC frequency (cf. Fig. 2A, arrow). For a positive-flat correlation, the median heart rate was defined as the heart rate at which the up-going VPC frequency reached a plateau (cf. Fig. 2C, arrow).

Figure 8A and B show the effects of diltiazem. In the P group, the minimum, median and maximum heart rates at pretreatment were 58.3 ± 1.9 beats/min, 78.4 ± 1.9 beats/min and 98.4 ± 2.7 beats/min, respectively, and VPC frequencies at these heart rates were 3.3 ± 0.9 /min, 11.3 ± 2.1 /min and 23.7 ± 3.3 /min (Fig. 8A, open symbols). At the 2 week period of diltiazem therapy (Fig. 8A, dotted symbols), the 3 heart rates and VPC frequency at the maximum heart rate were decreased significantly; at 4 weeks (Fig. 8A, closed symbols), all the 3 heart rates and VPC frequencies at these heart rates were reduced significantly. Diltiazem depressed the slope of posi-

tive correlation at the 2 week period of therapy, and this depression increased at 4 weeks (Fig. 1 and 8A). In the NP group, the minimum, median and maximum heart rates at pretreatment were 55.0 ± 1.5 beats/min, 76.6 ± 2.3 beats/min and 98.0 ± 2.0 beats/min, respectively; the VPC frequencies at these heart rates were 4.8 ± 1.4 /min, 14.1 ± 1.6 /min and 8.8 ± 1.6 /min (Fig. 8B, open symbols). The 3 heart rates at pretreatment were statistically similar for the P and NP groups. Diltiazem produced no significant changes in any parameters for the NP group. Thus, the VPC frequency-heart rate relationship curves obtained before, and 2 and 4 weeks after therapy were superimposed on each other with almost no shift (Fig. 8B).

Figure 8C and D illustrate the changes during atenolol treatment. In the P group, the minimum, median and maximum heart rates at pretreatment were 50.0 ± 1.2 beats/min, 76.7 ± 2.6 beats/min and 103.2 ± 5.3 beats/min, respectively; VPCs at these heart rates were 2.2 ± 1.8 /min, 8.5 ± 1.7 /min and 20.5 ± 6.8 /min (Fig. 8C, open symbols). At the 2 week period of therapy, the median and maximum heart rates and VPCs at the median heart rate were decreased significantly (Fig. 8C, dotted symbols); at 4 weeks, all the heart rates and VPC frequencies were reduced significantly (Fig. 8C, closed symbols). The slope of positive correlation remained almost unchanged at the 2 week period of therapy, but did decrease at 4 weeks (Fig. 5A and 8C). In the NP group, the minimum, median and maximum heart rates were 58.9 ± 2.9 beats/min, 74.2 ± 2.0 beats/min and 97.6 ± 1.2 beats/min, respectively; VPCs at these heart rates were 2.9 ± 0.8 /min, 12.6 ± 2.9 /min and 7.5 ± 2.4 /min (Fig. 8D, open symbols). The 3 heart rates at pretreatment did not differ significantly for the P and NP groups. Atenolol reduced significantly both the minimum and maximum heart rates at the 2 and 4 week periods of therapy with no significant change in the median heart rate and VPC frequencies at the 3 heart rates (Fig. 8D).

DISCUSSION

This study assumed that, if triggered activity occurring from delayed after-depolarization is the cause of VPCs, such VPCs should be increased at higher heart rates and suppressed by calcium channel blockers and beta adrenoceptor blockers. This assumption comes from the findings that: 1) as pacing rates increase, the amplitude of after-

depolarizations increases and eventually the propagated action potential, triggered activity, is induced^{1,2}; and 2) such cellular electrophysiologic events are related to an increase in intracellular calcium concentrations, $[Ca^{++}]_i$, and thus can be suppressed by calcium channel blockers or beta blockers^{1,10,11}. Accordingly, we evaluated VPC frequency as a function of underlying heart rate in patients with frequent VPCs using the computer analysis of 24-hour electrocardiographic strips, and compared the response of VPCs to a calcium channel blocker (diltiazem) and a beta blocker (atenolol) among patients with different relationship between VPC frequency and heart rate.

1. Relationship between VPC Frequency and Heart Rate

We showed that patients with frequent VPCs had various patterns of the relationship between VPC frequency and heart rate; these results were consistent with those reported previously by Winkle¹² and Ito et al.¹³ In the present study, the majority of patients had VPCs which increased with rate increase at the relatively low heart rate range (below 70–80 beats/min). At higher heart rate range, VPC frequency was further increased in some patients (positive correlation), but either suppressed (bidirectional correlation) or remained almost unchanged (positive-flat correlation) in others. A few patients showed a linear decrease of VPCs with increasing heart rates (negative correlation) or almost equal VPC frequency over the entire range of heart rate (flat correlation). The highest heart rates recorded during these 24-hour ECG monitorings (about 90–130 beats/min) may be much below those achieved during routine treadmill exercise test. Therefore, in some patients the patterns of correlation between VPC frequency and heart rate could be changed to different ones if they achieved heart rates during 24-hour ECG recordings similar to those during exercise testing. In the present study, we grouped patients with frequent VPCs into two broad categories depending on whether they had a positive (P group) or non-positive correlation (NP group), and the effects of diltiazem and atenolol on VPCs of the 2 patient groups were compared.

2. Effects of Diltiazem and Atenolol on VPCs of Different Domains

Evaluation of the antiarrhythmic drug efficacy on VPCs can be a difficult problem because

of the well-documented spontaneous variability of VPC frequency in individual patients.¹⁴⁻¹⁷ However, it has been reported that average VPC frequency for a group of patients was similar when two control periods were compared.^{12,15-17} Accordingly, evaluation of drug efficacy using group response rather than individual response minimizes the effects of spontaneous VPC variation. Regarding the assessment of antiarrhythmic agents in individual patients, previous studies claimed that, if two 24-hour ECG monitoring periods are compared, either a 65 or 83% reduction is required to establish VPC reduction attributable to true drug efficacy rather than spontaneous VPC variation.^{14,16} In the present study, both diltiazem and atenolol reduced the averaged VPC frequency for P group, but induced no significant change in NP group. The suppressive effects of these drugs on VPCs were also analysed as a percent reduction of VPC frequency in individual patients. At the 65 or 83% VPC suppression level, diltiazem was effective in 11 or 7 out of 16 cases in P group, but only in 2 ($p < 0.005$) or 1 of 20 cases of NP group ($p < 0.05$). During atenolol therapy, 5 of 6 patients of P group achieved a 70% or more VPC reduction as compared with the effectiveness in only 1 of 10 patients of NP group ($p < 0.05$). These results suggest that both diltiazem and atenolol are more effective in suppressing VPCs in patients with a positive correlation than those with a non-positive correlation.

There are only a few clinical reports on the effects of calcium channel blockers on VPCs.^{5,18-20} A previous study using verapamil showed that this drug is less effective in cases of ventricular arrhythmias than in cases of supraventricular arrhythmias.¹⁸ Previously, we reported that oral diltiazem selectively suppressed VPCs which increased with increasing heart rates (tachycardia-accelerated VPCs)¹³; these findings are consistent with those of the present study. The efficacy of beta blockers on ventricular arrhythmias has been well documented.^{15,21-24} Atenolol is a new cardioselective beta-blocker with no local anesthetic effects and a long plasma half life. The number of studies on the effects of atenolol on ventricular arrhythmias is small.^{25,26} Most previous studies on beta blockers, including atenolol, showed that these drugs could suppress VPCs to a significant level (i.e., 70 or 75% reduction) in approximately 50% of patients with frequent VPCs.^{15,21-25} This finding would be explained by our new finding, that is, about 50%

of patients with frequent VPCs had a positive correlation and atenolol suppressed only the VPCs in this category of patients. To the best of our knowledge, this is the first clinical report that examined the effects of beta blocker on the relationship between VPC frequency and heart rate.

3. Mechanisms for Tachycardia-Accelerated VPCs

Several can be considered to explain the mechanisms of tachycardia-accelerated VPCs and their suppression by diltiazem and atenolol. One possible explanation for the tachycardia-accelerated VPCs is increased myocardial ischemia at higher heart rates. Calcium channel blockers and beta blockers may suppress such ischemia-induced VPCs by improving coronary perfusion or decreasing myocardial oxygen consumption. However, the majority of our patients did not have clinical signs suggestive of ischemic heart disease. Winkle also found that a positive correlation was not confined to patients with coronary artery disease.¹²

The direct antiarrhythmic effects of diltiazem and atenolol would be expected if slow channel-dependent activity underlies the genesis of VPCs. Slow channel-dependent activity may play a role in either reentry, enhanced automaticity or triggered activity.²⁷ However, since intracellular potentials cannot be recorded from the intact human heart, discussion on the cellular electrophysiologic mechanisms for the genesis of clinical arrhythmias is purely speculative. An increase in heart rate may be associated with initiation or acceleration of VPCs, regardless of mechanisms. For example, increased sympathetic activity increases heart rate and enhances the ectopic automaticity in Purkinje fibers. However, pacing at high rates usually suppresses the automaticity of Purkinje fibers (overdrive suppression).^{28,29} The automaticity in the partially depolarized Purkinje fibers may be slow channel dependent.³⁰ The overdrive of such fibers for a relatively short period fails to suppress the automaticity, but a long period of overdrive causes marked suppression.³¹ Thus, the tachycardia-accelerated VPCs may not be due to enhanced automaticity.

Heart rate increase may produce conduction disturbance due to a deficient time for full repolarization and cause reentrant VPCs. Reentrant ventricular tachycardia might be initiated by premature ventricular stimulation or rapid pacing.^{32,33} However, the overdrive can also interrupt reentrant excitation by changing re-

fractory period in the tissue forming reentrant circuit?² Furthermore, we previously found that high levels of local catecholamine concentrations are prerequisite for the maintenance of reentry circuit carried by slow channel-dependent conduction.³⁴ Such an excess in catecholamines is unlikely in our patients. These findings argue against a reentry mechanism for tachycardia-accelerated VPCs.

The findings of an increase in VPCs at higher heart rates and suppression of such VPCs by diltiazem and atenolol seem most consistent with the cellular electrophysiologic events of triggered activity occurring from delayed afterdepolarizations. All available evidence indicates that the amplitude of both afterdepolarization and underlying transient inward current increases under the conditions where $[Ca^{++}]_i$ is elevated.^{1,9} At higher heart rates, an enhanced entry of Ca^{++} through the slow channel per unit time would lead to greater loading of intracellular Ca^{++} stores and hence increase the amplitude of afterdepolarization with eventual evolution of triggered activity.^{1,2,9} Calcium channel blockers can readily suppress afterdepolarization by the direct blockade of slow Ca^{++} channel.^{1,2,9,10} Beta-adrenergic receptor stimulation increases slow inward Ca^{++} current via increasing intracellular cyclic AMP and thus can potentiate triggered activity.^{10,11} Under the conditions at which the slow inward Ca^{++} current is dependent on beta-adrenergic receptor stimulation, beta-receptor blocking agents will reduce the slow inward Ca^{++} current.^{10,11} All these considerations indicate that the characteristics of tachycardia-accelerated VPCs are more consistent with those of triggered activity than with enhanced automaticity or reentrant excitation.

In the present study, a reduction in the total number of tachycardia-accelerated VPCs by diltiazem and atenolol was accompanied by a reduction in both the heart rate and the slope of positive correlation (Fig. 8A and C). One can speculate that the decline of the slope of positive correlation is an indication of decrease of $[Ca^{++}]_i$ in the ventricular cells, since both calcium channel blockers and beta blockers inhibit slow inward Ca^{++} current,^{1,10,11} and may eventually decrease $[Ca^{++}]_i$. Decrease in $[Ca^{++}]_i$ should reduce the amplitude of afterdepolarization and thus cause the decreasing likelihood of evolution of triggered activity.^{1,9} If the tachycardia-accelerated VPCs are caused by triggered activity, decrease of $[Ca^{++}]_i$ would be expected to result in

the decline of the slope of positive correlation. On the other hand, regardless of the drug used (diltiazem or atenolol), the drug-induced reduction of heart rate in itself may decrease $[Ca^{++}]_i$ by either decreasing Ca^{++} influx in the unit of time or giving enough diastolic intervals for the cell membrane to pump out (or for the intracellular Ca^{++} store sites to re-uptake) the excess Ca^{++} from the cytosol or both. During diltiazem therapy, the decrease in the slope of positive correlation occurred at the 2 week period of treatment and this decrease was enhanced at the 4 week period (Fig. 1 and 8A). However, in case of atenolol, there was no remarkable change in the slope of positive correlation at the 2 week period of therapy, and the slope reduction became evident only at the 4 week period (Fig. 5A and 8C). Alternatively, an evolution of the slope reduction lagged well behind the heart rate reduction during atenolol therapy, while in case of diltiazem, both evolved simultaneously. Diltiazem seemed to decrease $[Ca^{++}]_i$ rather directly by blocking the slow Ca^{++} channels, while atenolol would do so mostly via the heart rate reduction, especially in the relatively early period of the treatment.

4. Implications

Most of previous studies on the antiarrhythmic drug efficacy have been concerned with the number of VPCs. An evaluation of VPC frequency as a function of heart rate, as described in this report, is expected to offer new and important information for understanding the mechanisms of ventricular arrhythmias and the effects of antiarrhythmic drugs. The present study suggests that the tachycardia-accelerated VPCs are related to triggered activity. The finding that more than 40% of patients with frequent VPCs had such tachycardia-accelerated VPCs suggests the clinical importance of triggered activity as a cause of ventricular arrhythmias. In addition, since diltiazem and atenolol suppressed selectively the tachycardia-accelerated VPCs, an evaluation of VPC frequency as a function of heart rate can be used as non-invasive clinical tool to predict the response of ventricular arrhythmias to these drugs, and probably to other calcium channel blockers and beta adrenergic receptor blocking agents.

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