The Daily Profile of Ventricular Premature Beats in the Patients with Ischemic Heart Disease

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To clarify factors affecting the prevalence of ventricular premature contraction (VPC) in patients with stable ischemic heart disease, daily profiles of VPC prevalence were studied in 92 patients using continuous 24-hour electrocardiographic recordings. VPCs in patient groups with effort angina and inferior infarction showed similar daily profiles. However, a significant relationship between VPC prevalence and heart rate was observed in inferior infarction group, while patients with resting angina exhibited another relationship between the two parameters. Higher prevalence rate of VPCs in the early morning in patients with resting angina suggested the contribution of cardiac autonomic nerve activity to the increased frequency of VPCs, while constant frequency of VPCs during the day in anterior infarction group provided no influences on heart rate, effort, and autonomic nerve activity on the VPC prevalence. Age, sex, left ventricular ejection fraction, and nitrates and diltiazem used for the treatment of angina pectoris did not affect the daily profile of VPC prevalence in any patient groups. These results indicated that the clinical and pathophysiological differences of ischemic heart disease, even in stable patients, showed the different distribution of VPC prevalence within a day which is due, in part, to the varied activities of cardiac autonomic nerves.

MANY studies have demonstrated the relationship between frequency and complexity of ventricular premature contraction (VPC) and risk of subsequent sudden death in patients with ischemic heart disease.¹⁻⁴ Mortality from coronary heart diseases is closely related to the site and extent of coronary artery involvement and the degree of deranged myocardial function.⁵ It has been proposed that VPCs are graded on the basis of frequency, multiform configuration, repetitive pattern and degree of prematurity and, that the risk predictive element of such beats is related to the occurrence of certain

advanced grades.⁶⁻⁸ However, recent studies did not support this proposal^{9,10} because of marked differences in duration of ECG monitoring and in the subjects studied. Almost all investigations previously reported analyzed ECG recordings of angina pectoris and myocardial infarction as one group regardless of the pathophysiological differences, and each study included a variable ratio of ischemic heart disease subgroups, effort or resting angina and anterior or inferior myocardial infarction. It is supposed that the prevalence pattern of VPCs at a particular time of the day would affect the risk and that the site of coronary involvement and myocardial lesions would account for the individual prevalence pattern of VPCs.

The purpose of the present investigation was to study factors affecting VPC prevalence within a day in patients with stable ischemic heart dis-

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TABLE I BACKGROUND OF DISEASE GROUPS

	Case	Sex	Age	EF (%)	VPC type	
Anterior infarction	27	M 26	59 + 10.4	45.2 + 11.9	MF	12
		F 1			paired	3
					VT	2
Inferior infarction	24	M 17	65 + 8.1	51.2 + 12.2	MF	4
		F 7			paired	7
					VT	3
Effort angina	26	M 18	64 + 7.4	59.4 + 9.4	MF	4
		F 8			paired	5
					VT	2
Resting angina	15	M 13	60 + 8.6	62.7 + 10.1	MF	5
		F 2			paired	2
					VT	1
Total	92	M 74	62 + 8.9	53.9 + 12.7	MF	25
		F 18			paired	17
					VT	8

EF = left ventricular ejection fraction, MF = multiform, VT = ventricular tachycardia

TABLE II CAG FINDINGS AND ANTIANGINAL DRUGS

	CAG studied	CAG finding	Calcium blocker	Nitrates
Anterior infarction	14	LAD 13	10	12
		LAD + LCx 1		
Inferior infarction	10	RCA 7	9	16
		RCA + LAD 2		
		normal 1		
Effort angina	8	LAD 5	11	16
		LAD + LCx 1		
		LAD + RCA 1		
		3 vessels 1		
Resting angina	5	LAD 3	10	8
		LAD + LCx 1		
		normal 1		
Total	37		40	52

CAG = coronary arteriogram, LAD = left anterior descending coronary artery, LCx = circumflex coronary artery, RCA = right coronary artery.

ease who were ambulatory in a limited schedule. We intended to clarify the individual pattern of VPC frequency in a day in patient groups with angina effort, effort or resting, and myocardial infarction, anterior or inferior, separately.

MATERIALS AND METHODS

Study Population

The study population consisted of 246 pa-

tients admitted to the First Department of Internal Medicine, Okayama University Hospital and its branch hospitals with diagnoses of angina pectoris or myocardial infarction 3 months or more after the onset. A complete medical history and physical examination were obtained on all patients. Angina pectoris was diagnosed by a combination of typical attacks of precordial pain with no changes in myocardial enzymes and ischemic changes in 12-lead ECGs during the attack

Fig.1. Frequency of ventricular premature contractions. The frequency was expressed by a ratio of the total ventricular ectopic contractions to the total heart rate for 24 hours. AI = anterior myocardial infarction, II = inferior myocardial infarction, EA = effort angina, RA = resting angina, EF = left ventricular ejection fraction.

Fig.2. Daily profile of VPC prevalence in four patient-groups. VPC prevalence (%) was calculated the total VPCs during each time interval divided by the total VPCs for 24 hours times 100. AI = anterior myocardial infarction, II = inferior myocardial infarction, EA = effort angina, RA = resting angina.

which provided significant ischemic ST-segment depression. All patients with myocardial infarction had histories of typical coronary type chest pain, serial acute myocardial enzyme changes and evolving Q wave abnormality with acute ST and T wave changes on ECG before 3 months or more. 92 of the 246 patients who had 2 or more average VPCs per hour were used for data analysis in this study. The 92 patients consisted of 26 patients with effort angina, 15 with resting angina, 27 with anterior myocardial in-

fraction and 24 patients with inferior myocardial infarction. The mean age of the patients was 62 ± 8.9 (SD), and 74 were males and 18 were females. Biplane coronary angiography and left ventriculography were performed in 37 of the 92 patients, 14 in anterior infarction, 10 in inferior infarction, 8 in effort angina and 5 in resting angina, and all patients received 99m-Tc radio-angiography for measuring left ventricular ejection fraction within two weeks after a 24-hour electrocardiographic recording. Significant coro-

STATISTICAL ANALYSIS BY ROGERS' METHOD

	every 6hrs	every 3hrs
Anterior Infarction	0.7651	1.3500
Inferior Infarction	11.4455**	12.6778**
Effort Angina	7.6435*	7.6346*
Resting Angina	6.2071*	2.3798

**P<0.01, *P<0.05

Fig.3. Prevalence rate of ventricular premature contractions plotted on four time-axis.

nary artery involvement was defined as 75% or greater stenosis of a major coronary artery.

Data Analysis

Continuous 24-hour electrocardiographic recordings were obtained with a 2-channel Model 447 Avionics Holter recorder. Bipolar chest leads, CM5 and NASA, were recorded. During the monitoring period, all patients were ambulatory in the hospital environment. An Avionics Model 9020 Arrhythmia Computer was employed for analysis of the recordings. The arrhythmia computer was set for each recording to identify prematurity and differing QRS width and amplitude to count automatically the frequency of VPCs. Patients who experienced chest pain of angina attack and/or provided ischemic ST changes in the Holter ECG recordings during the examination, were excluded from analysis so as to avoid direct effects of myocardial ischemia on the frequency of VPCs. For normalizing the VPC prevalence rate recorded, an average frequency of VPCs every 6 hours, at 0-6, 6-12, 12-18

and 18-24 o'clock, was obtained in each patient, since a wide patient-to-patient variation was observed in the frequency of VPCs during a 24-hour recording between the patients. The normalized frequency of VPCs was calculated as a quotient of total VPCs of each 6 hours divided by total VPCs for 24 hours.

Statistical analysis between the groups and within the group was made by analysis variance. Individual data comparisons were performed by use of Dunnett's procedure. Group data were expressed by mean $\pm$ standard deviation.

RESULTS

Table I summarizes the background data and types of VPCs greater than grade 2 of Lown's VPC criteria⁶ recorded in the Holter ECG in the patient groups. The age and left ventricular ejection fraction (EF) were not significantly different among the groups, though anterior infarction group tended to have lower EF than the remaining groups. Coronary angiogram obtained

Fig.4. Daily profile of heart rate in the patient-groups.

Fig.5. Relationship between heart rate and vpc prevalence. A significant relationship was observed between two indices in inferior infarction group, but not in effort angina group.

in 37 patients revealed that all patients with anterior infarction and angina pectoris except one had significant lesions in the anterior descending coronary artery, and 9 of the 10 patients

with inferior infarction showed significant right coronary involvements (Table II). Fifty-two out of 92 patients had been treated with long-acting nitrates, and a calcium antagonist (diltiazem) had

Fig.6. Comparison of the daily profile of ventricular premature contraction between age groups.

also been administered to 40 of the 52. The remaining 40 patients had no medications. Frequency of VPCs to the total heart rate for 24 hours was significantly higher in infarction groups than in the angina patients, in elderly patients, and in the patients with low EF than those with normal EF (Fig. 1). Figure 2 which represents normalized frequency of VPCs in the four groups exhibits similar daily profiles of VPC frequency in the inferior infarction and effort angina groups: lowest from the midnight to the early morning and highest during the period from noon to evening. In contrast, anterior infarction showed almost constant VPC frequency throughout a day. In the resting angina group, the frequency pattern characterized by the low ratio of VPC in the period from evening till midnight was different from other groups. Plotting the prevalence rate on the four axis of time intervals and statistical analysis by Rogers methods manifested clearly the difference of the VPC frequency during a day among the disease groups (Fig. 3). Heart rate was higher in the infarction groups

than the angina groups in any time intervals, while the daily profile of heart rate showed a similar pattern among all groups (Fig. 4). To estimate the contribution of heart rate on the daily profile of VPC frequency, we plotted the normalized frequency (%) against mean heart rate and heart rate ratio (%) during the identical period. The heart rate ratio was calculated as a percentage of the total heart rate in each time interval to the heart rate for 24 hours. Patients with inferior infarction demonstrated a significant positive relationship between the two parameters, while other three groups did not show demonstrable relationship (Fig. 5). All 92 patients were divided into three age groups for testing the influence of age on the daily profile of VPC frequency; 50–59, 60–69 and 70 years or elder. Each age group consisted of similar ratio of myocardial infarction, and no significant difference of left ventricular ejection fraction was observed among the three age groups. No difference in the daily profile of the VPC frequency were observed in the three age groups (Fig. 6). Left ventricular ejection

Fig. 7. Difference of the daily profile of ventricular premature contraction between groups with normal and deteriorated left ventricular function.

fraction did not affect the pattern as shown in Fig. 7. The findings described above suggested that multifactorial not unifactorial mechanisms account for the different patterns of normalized VPC frequency in the four groups of ischemic heart disease; as a result a multivariate analysis was used to evaluate the effects of sex, age, ejection fraction, heart rate and drugs for treatment (nitrates or diltiazem) on the VPC frequency pattern of each disease group. Sex, age, ejection fraction and drugs used for the patients did not significantly correlate with the VPC frequency. Heart rate positively correlated with the frequency in groups of myocardial infarction and resting angina group. However, the correlation coefficients were quite low (less than 0.3), so that these five factors were unlikely to influence substantially the daily profile of the VPC frequency.

DISCUSSION

Many previous investigators¹⁻⁴ reported that

high frequency and repetitive VPCs were strongly associated with mortality in patients with ischemic heart disease. Frequency and pattern of ventricular premature contraction (VPC) in patients with ischemic heart disease would be affected by various factors such as extent of ischemia, hemodynamic deterioration, effort, emotional changes, age, and others. The prevalence and grade of VPCs were higher in the patients with multivessel disease compared with values in the patients with one vessel disease, and the presence of elevated left ventricular end-diastolic pressure (LVEDP) or asynerhy was associated with increased ventricular ectopy.¹¹ Furthermore, findings that objective psychologic tests precipitated ventricular arrhythmia strongly suggested the facilitating role of autonomic nerve system changes in the provocation of ventricular arrhythmias.¹² These led us to the hypothesis that different clinical and pathophysiological states of the ischemic heart disease would exhibit variable prevalence rate and daily patterns of

VPC frequency. Lown et al.¹³ and Tanabe and his coworkers¹⁴ reported higher prevalence rate during awake periods and a marked reduction of the arrhythmia during sleep, while other investigators¹⁵ found no significant differences in the distribution of VPCs in either wake or sleep. On the contrary, Yanaga et al.¹⁶ observed increased prevalence of VPCs during sleep in the patients with ischemic heart disease. Thus, the daily profile of VPC prevalence was still unclear. The discrepancy between these studies can be, attributed, in part, to the following reasons: the studies were conducted mainly among outpatients with ischemic heart disease who had different activities including physical and mental work. In addition patients with various pathophysiological conditions were analyzed as one group regardless of angina pectoris or myocardial infarction, and whether they were stable or unstable. In the present study, therefore, we selected in-patients with stable ischemic heart disease for study-subjects. The patients were ambulatory on the limited schedule, so that each patient showed similar physical activity during the ECG monitoring. The patients who complained of ischemic chest pain or showed ischemic ST-T changes during Holter recordings were not included in this study. This enabled us to compare daily profiles of VPC prevalence among the patients groups with ischemic heart disease; effort angina, resting angina, anterior myocardial infarction and inferior myocardial infarction.

The present study revealed that each disease group had the characteristic distribution of VPCs within a day. The prevalence pattern of each group was primarily free of age, sex, calcium antagonists administered for the treatment of angina pectoris, and cardiac function estimated by left ventricular ejection fraction. The fact that coronary angiography exhibited similar sites of coronary lesions elucidated no participation of stenotic coronary lesions in the daily patterns of VPC prevalence. The effort angina group and the group with inferior myocardial infarction a similar pattern of daily VPC profile. VPCs appeared more frequently in the afternoon and less frequently in the period between midnight and early morning. However, VPC frequency of the inferior infarction group correlated positively with heart rate, while no significant relationship was observed between VPC frequency and heart rate in patients with effort angina. It is unlikely that myocardial ischemia itself accounts for the

difference between two disease groups, because neither significant ST segment changes nor subjective symptoms suggesting facilitated myocardial ischemia were observed during Holter's ECG recordings. Significant relationship between VPC frequency and heart rate in the inferior infarction suggested the influence increased sympathetic nerve activity on frequent VPCs. A dense distribution of the vagus nerve was observed in the left ventricular inferior wall¹⁷ and inferior myocardial infarction involved the nerve,¹⁸ resulting in relative increase in the activity of the sympathetic nerve system. A previous report¹⁹ indicated that stimulation of the stellate ganglion significantly decreased the ventricular fibrillation threshold and stellectomy increased the threshold by 11% of control in the anesthetized dog. Vagal stimulation also reduced the incidence of spontaneous ventricular fibrillation in experimental coronary occlusion.²⁰ Therefore, it is reasonable to assume that the daily pattern of VPC prevalence in the inferior infarction was, at least in part, due to changes in cardiac nerve activities. This study revealed that in the resting angina group the highest prevalence rate was in the early morning. During this period of the day, many investigators observed frequent episodes of resting angina pain and increased coronary artery tone.^{21,22} It is known that autonomic nerve activity is varied and unstable in the early morning, which sometimes provokes coronary spasm.^{23,24} However, no ischemic ST segment changes in the recordings were analyzed, provided that aggravated myocardial ischemia did not occur in the daily profile of VPCs of this group. Therefore, although we could not clarify apparent reasons for the characteristic prevalence pattern of ventricular ectopy in this group, it is possible that the instability of the cardiac nerves would participate in increased ventricular ectopies even when the nerve imbalance was not strong enough to cause myocardial ischemia due to coronary spasm. A constant appearance of VPCs in a day in the patients with anterior infarction suggested that VPCs of this group were free of effort, cardiac nerve tone, and sleep or wake.

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