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Increased Plasma Epinephrine But Not Reduced Heart Rate Variability Leads to Ventricular Arrhythmias in Patients With Acute Myocardial Infarction

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Abstract

Ventricular arrhythmia observed in the acute stage of myocardial infarction is profoundly related to the autonomic balance. To investigate prediction of ventricular arrhythmia, heart rate variability and plasma catecholamine concentration were simultaneously measured for a week in 17 consecutive patients with first anterior or anteroseptal Q wave infarction treated without specific coronary intervention.

The cross-sectional plot of coefficient of variance (= standard deviation of N-N interval/mean N-N interval × 100; %) as a function of plasma epinephrine on the day of admission remained lower than the standard average. Ventricular premature contractions increased in proportion to the plasma epinephrine concentration. In the first week of hospitalization, plasma epinephrine concentration and frequency of premature contraction decreased exponentially, whereas the coefficient of variance showed a modest decline. Ventricular tachycardia refractory to xylocaine with rate accelerating with persistence was observed only in patients with the peak epinephrine concentration > 375 pg/ml.

Plasma epinephrine concentration rather than coefficient of variance during sleep after the first acute episode is more closely related to the following triggered ventricular arrhythmia.

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Key Words

■ **Ambulatory electrocardiography** ■ **Epinephrine** ■ **Myocardial infarction**
■ **Pathophysiology** ■ **Ventricular arrhythmia**

INTRODUCTION

Heart rate variability is widely used to evaluate the physiological autonomic nervous function in healthy subjects[1–3]. Many investigations concerning autonomic nervous changes in patients with acute myocardial infarction have found sympathovagal imbalance at the onset of the episode[4–8]; decreased heart rate variability immediately after the onset was closely correlated with increased

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mortality during long-term follow-up. Moreover, sympathetic blockade given in these patients was found to improve the long-term prognosis, suggesting that increased sympathetic activity immediately after the onset of infarction is related to increased mortality including sudden cardiac death[9,10]. However, the heart rate variability evaluated in these reports was the average of autonomic nervous functions including day and night, and may be contaminated with various emotional and physical influences[11,12]. Although reduced variability and elevated plasma catecholamine concentration are the 2 representative parameters indicating accelerated sympathetic nervous function, it is not certain which is more related to the ventricular arrhythmias observed during the hospital stay after the onset of infarction.

The cofficient of variance (CV) of N-N (= R-R) intervals during sinus rhythm is widely used as a simple measure of heart rate variability, and has a chronological meaning similar to the standard deviation (SD) of the N-N intervals histogram (SDNN) according to the following equation,

$CV = SDNN / \text{mean N-N interval} \times 100(\%)$

In contrast to SDNN, which is dependent on the basic heart rate, coefficient of variance is rate-corrected by dividing SDNN by the mean N-N interval. This study was designed to correlate the coefficient of variance during sleep, obtained by ambulatory electrocardiography (ECG) monitored throughout the week after the onset of the first acute myocardial infarction, to the ventricular arrhythmias observed in this period. Comparatively, the plasma catecholamine concentration assessed in this period was also correlated to the arrhythmias. Therefore, the final goal of this investigation was to compare the relative importance of heart rate variability and plasma catecholamine in the occurrence of arrhythmia after the onset of infarction.

METHODS

Patients

This study included 17 consecutive Japanese patients with the first onset of myocardial infarction at an anterior or anteroseptal location, 4 women and 13 men (mean age 66.0 ± 10.3 years), hospitalized at the Ishihara Cardiovascular Hospital from 1985 to 1989. This period was partly before the introduction of thrombolytic therapy. Criteria for patient selection included admission to The Ishihara Cardiovascular Hospital within 6 hours after the onset of typical chest pain consistent with acute myocardial infarction, standard ECG findings of ordinary sinus rhythm and ST segment elevation by >0.1 mV in 2 or more leads, and an increase in serum creatine phosphokinase (CK) activity by >400 IU/l. Patients were excluded with signs or symptoms of congestive heart failure, cardiogenic shock and arrhythmias such as atrial fibrillation and conduction disturbances including atrioventricular and bundle branch block detected by ambulatory or 12-lead ECG. No patients were treated by percutaneous transluminal coronary angioplasty or other interventional thrombolytic therapies, as such coronary intervention techniques were not available when this investigation was started. Beta-blockers, digitalis, or other drugs known to influence the autonomic nervous activity were not administered during the investigation. Only xylocaine was administered (1 to 2 mg/min) when necessary. Oral informed consent concerning the conservative therapy for acute infarction was obtained for all patients.

Selected abbreviations and acronyms

CK = creatine phosphokinase
CV = coefficient of variance
ECG = electrocardiogram
SDNN = standard deviation of N-N (= R-R) interval

Electrocardiogram monitoring

Ambulatory ECG monitoring was performed continuously for a week immediately after admission using a conventional portable cassette tape recorder (Fukuda SM24, Fukuda Electronic, Tokyo, Japan). The tapes were retrieved with a high-speed processor (Fukuda SCM240, Fukuda Electronic, Tokyo, Japan) after the monitoring. The acquisition and digital conversion rate of the unit was 256 samples per sec (temporal resolution of 4 msec). The processor was controlled by a personal computer (NEC 9801, NEC, Tokyo, Japan). Contamination by premature beats and artifacts was checked by visual inspection for accurate evaluation of heart rate variability. The coefficient of variance of N-N intervals for 100 consecutive heart beats during sinus rhythm was determined by the formula 1. The mean coefficient of variance was calculated for each patient by averaging coefficient variances obtained every hour from 0 to 5 o'clock during sleep as a measure of "pure" autonomic function, to

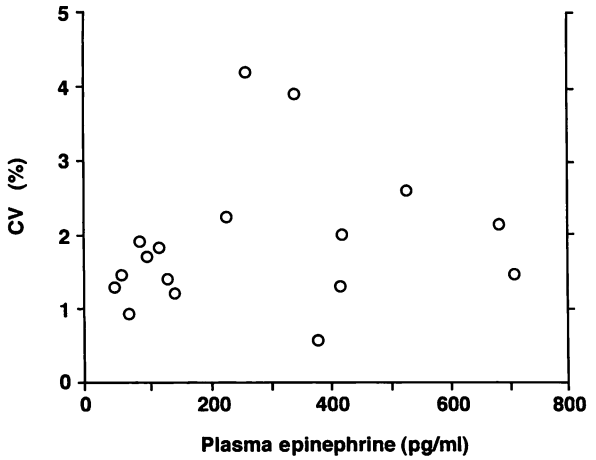

Fig. 1 Relationship of the coefficient of variance (CV) of the N-N intervals obtained by electrocardiographic monitoring to plasma epinephrine level in 17 patients with first acute myocardial infarction during sleep on the day of admission
CV is plotted as a function of the peak plasma epinephrine concentration evaluated on the same day, indicating the scattered distribution of CV as plasma epimephrine concentration is altered.

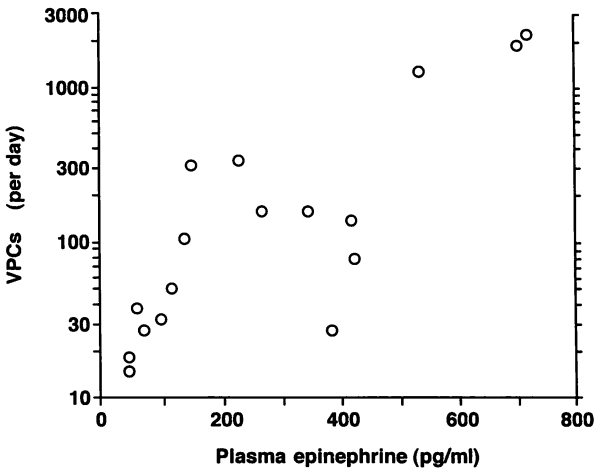

Fig. 2 Correlation between the frequency of ventricular premature contractions (VPCs) observed on the day of admission and the peak plasma epinephrine concentration on the same day
A tendency toward an exponential increase in the frequency of VPCs with elevation of the peak plasma epinephrine concentration is observed. Note the semilogarithmic scale in the ordinate.

avoid the influence of physical activity or emotional stress during the awake period. The number of ventricular premature contractions was counted visually by an experienced cardiologist, who was unaware of the protocol of this investigation.

Biochemical analysis

Plasma was separated immediately after venous blood sampling and stored at 0°C in a refrigerator. Plasma epinephrine and norepinephrine were assayed by conventional high performance liquid chromatography. Serum CK was evaluated by a commercially available assay kit (Wako Chemical, Tokyo, Japan). These biochemical parameters were measured every 4 to 6 hours on the day of admission and once a day thereafter in the early morning for a week.

Statistical analysis

Data are presented as mean ± SD. Statistical analysis was performed by one-way analysis of variance (ANOVA) for comparison of data on different days of hospitalization. Chi-square test in combination with Yetes' correction was used to determine the significance of the differences between numbers of patients in 2 different groups. A level of $p < 0.05$ was accepted as statistically significant.

RESULTS

Coefficient of variance, epinephrine and arrhythmia on admission

Routine ECG examination was compatible with the findings of infarction with abnormal Q wave formation. Contamination of artifacts in ECG monitoring was trivial at least during sleep. Therefore, the algorithm of the coefficient of variance plotted every hour at night was completely continuous in all patients. The mean coefficient of variance of N-N intervals during sleep was plotted against the peak plasma epinephrine concentration in corresponding patients. As in **Fig. 1** this cross-sectional correlation between the coefficient of variance and plasma epinephrine concentration on the day of admission in all 17 patients showed no significant relationship. Irrespective of the change in the plasma epinephrine concentration, coefficient of variance remained low value relative to the normal value (< 2.0%). All patients presented with various frequencies of ventricular premature contractions detected by ECG monitoring on the day of admission. However, semilogarithmic plotting of the number of premature contractions on the day of admission as a function of peak plasma epinephrine concentration evaluated on the same day showed a trend toward an exponential increase (**Fig. 2**). The mean heart rate of all patients during sleep varied

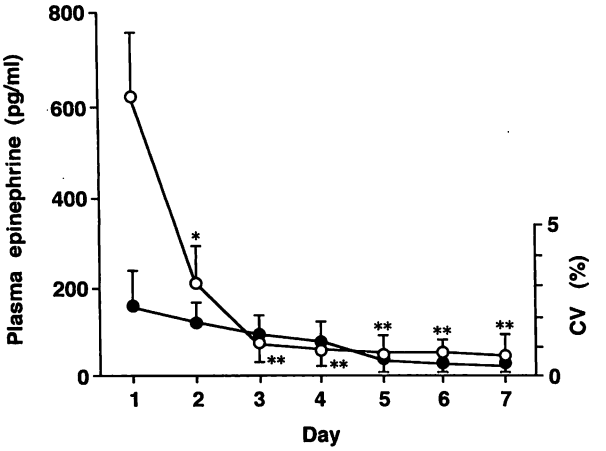

Fig. 3 Serial changes of peak plasma epinephrine concentration (*open circles*) and the CV of the N-N intervals (*closed circles*) through the first week of hospitalization

Peak plasma epinephrine concentration decayed exponentially, whereas the CV showed a modest decline. Vertical bars show SD.

$*p < 0.05$ and $**p < 0.01$ compared with the data on the day of admission.

Abbreviation as in Fig. 1.

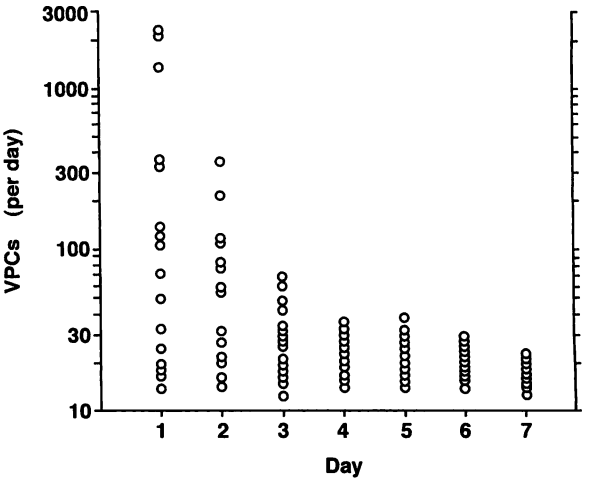

Fig. 4 Frequency of VPCs during the first week after admission

A gradually convergent distribution and an exponential decay of the most frequent VPCs is observed on each day. Note the semilogarithmic scale in the ordinate.

Abbreviation as in Fig. 2.

from 55.0±1.4 to 100.5±21.3 beat/min with an overall average of 78.9±7.6 beat/min. This also tended to correlate with plasma epinephrine concentration. Continuous intravenous administration of xylocaine at 1 to 2 mg/min was conducted on the day of admission in 11 patients who showed frequent (> 30 beat/hour) or malignant (Lown's classification > class Ⅲ) premature contractions.

However, this treatment was not effective in 9 of 11 patients and all 9 patients presented with subsequent ventricular tachycardia. Intravenous bolus (50 mg) administration of xylocaine was undertaken, but ventricular tachycardia remained in 6 of these 9 patients on the day of admission. The rate of sustained ventricular tachycardia increased gradually in these 6 patients. The mean coefficient of variance in patients treated with continuous intravenous infusion of xylocaine ($2.1 \pm 0.2\%$, $n = 11$) was not significantly different from that in those without treatment ($1.1 \pm 0.3\%$, $n = 6$, $p = 0.28$). All the above-mentioned 6 patients had an elevated peak plasma epinephrine concentration (> 375 pg/ml) on the day of admission. The percentage of patients with a positive correlation between the preceding N-N interval and the coupling interval of premature contractions tended to be greater in these 6 patients than the remaining 11 patients (67% vs 18%, $p = 0.085$).

Coefficient of variance, epinephrine and ventricular premature contractions in the following week

Plasma epinephrine concentration showed an exponential decay, whereas the mean coefficient of variance of N-N intervals showed a modest decline throughout the week after admission as shown in **Fig. 3**. The maximum values of these parameters associated with the greatest SD were noted on the day of admission. The SD of these variables showed a gradual decrease throughout the week of hospitalization. Statistically, plasma epinephrine concentration showed a significant fall during the week of hospitalization, whereas the fall in the mean coefficient of variance of N-N intervals was not significant, due in part to the relatively large SD. Plasma norepinephrine concentration showed a great SD on any given day of the investigation and daily changes in plasma norepinephrine concentration showed an apparent slow decline during this week. The frequency of premature contractions was greatly scattered on the day of admission and showed a tendency toward rapid decline with time as shown in **Fig. 4**.

DISCUSSION

The main observation of this investigation is that the ventricular arrhythmias observed after the onset of the first episode of myocardial infarction and refractory to conventional administration of contin-

uous intravenous xylocaine were related to the elevated peak plasma epinephrine concentration rather than to the reduced heart rate variability. Moreover, this type of ventricular arrhythmia seemed to be based on triggered activity according to circumstantial evidence.

Heart rate variability of healthy subjects shows a nocturnal increase indicating vagal dominance and relative sympathetic quiescence during sleep[2,3]. Many investigators have found that this variability in patients with acute infarction is blunted or absent even at night[7,13,14]. However, their studies included various healing stages and infarcted areas. Therefore, the present study was confined to patients with first acute infarction manifesting abnormal Q waves in the same location (anterior or anteroseptal area), admitted with the same time delay after the onset (< 6 hours) and were observed in the same period (the first week of observation after admission) and treated in the same manner (without specific coronary intervention).

Originally, N-N interval variation was defined as SDNN distribution for each subject[15]. Coefficient of variance of N-N interval is a simple time-domain measure of the heart rate variability and is superior to SDNN in terms of the heart rate correction. Kageyama *et al.*[16] investigated the age-dependent alterations of coefficient of variance in the Japanese population using atropine sulfate. Their results show that coefficient of variance of less 2.0% indicates reduced efferent vagal output. In this sense, vagal tone in many patients with acute infarction in our study was attenuated and showed no tendency to recovery in the first week of hospitalization. It is evident that the relationship between the coefficient of variance and the plasma epinephrine concentration is complex as indicated by their cross-sectional relationship on the day of admission (**Fig. 1**), whereas the longitudinal relationship between these 2 parameters tended to be parallel (**Fig. 3**). At present, we conclude that the sympathovagal interaction is complicated and interdependent as indicated by the coefficient of variance and the plasma epinephrine concentration measured during sleep.

The frequency of ventricular premature contractions after the onset of infarction was dependent on the plasma epinephrine concentration (**Fig. 2**). Ventricular premature contractions and ventricular tachycardia observed in this study were refractory to the conventional administration of xylocaine. This antiarrhythmic agent was thought not to affect the autonomic nervous function in terms of the trivial difference of the coefficient of variance of the N-N interval. Much evidence has been accumulated linking sympathetic acceleration to an increased risk for ventricular arrhythmias observed after infarction[17-19]. Ischemia-induced conduction delay and dispersed refractoriness underlies the reentrant arrhythmia, whereas partial depolarization caused by ischemia predisposes abnormal automaticity. The role of triggered activity in the ventricular arrhythmias encountered in our study has drawn attention[20, 21]. Experimentally, most ventricular arrhythmias observed several hours after coronary artery ligation have been ascribed to the triggered activity originating in the surviving conduction system and myocardium[21]. Ito *et al.*[22] and Inoue *et al.*[23] used ambulatory ECG monitoring to observe a positive correlation between the preceding N-N interval and the coupling interval of premature contractions which tended to be sensitive to calcium-channel blocking or β-adrenoceptor blocking drugs. They postulated the role of triggered activity in the genesis of ventricular arrhythmias observed in subjects without organic heart diseases. In the present study, we observed an increase in premature contractions with an elevation of plasma epinephrine concentration. The patients with ventricular tachycardia refractory to conventional intravenous administration of xylocaine had an elevated peak plasma epinephrine concentration (> 375 pg/ml) and tended to show a positive correlation between the preceding N-N interval and the coupling interval of premature contractions prior to the development of ventricular tachycardia. Moreover, the rate of this tachycardia gradually increased as it persisted. Although the sensitivity of the ventricular arrhythmias observed in this study to calcium-channel blockers was not confirmed, this is supposed to be a triggering activity causing the ventricular arrhythmias observed in the acute stage of infarction. Thus, estimation of the extent of sympathetic acceleration after infarction is essential in predicting the following ventricular arrhythmogenesis. The most reliable parameter was the peak plasma concentration of epinephrine but not that of norepinephrine in our study. Norepinephrine has a direct and important role as a neurotransmitter of the cardiac sympathetic nerve terminals. However, the biological clearance of norepinephrine is far greater than that of epinephrine[24]. This accounts for the fact that epinephrine is a more stable and hence

reliable parameter of the sympathoadrenal function relative to norepinephrine.

The present study included a limited number of patients with first Q wave infarction, and did not include normal controls or control patients with other cardiovascular diseases. Such control subjects may have a comparable sympathovagal response in the week after hospitalization. Although coefficient of variance during sleep is thought to represent "pure" autonomic function, heart rate variability is reportedly influenced by specific sleep stages in healthy subjects and in patients with infarction[14]. Moreover, it is uncertain whether the infarcted coronary arteries are recanalized spontaneously and hence whether observed ventricular arrhythmias were reperfusion-induced in our study. Sympathovagal balance is influenced profoundly by the subsequent patency of the infarcted artery[25]. Therefore, identification of the infarcted artery and its patency is the fundamental problem. In spite of these potential limitations, the present study indicates that the peak plasma epinephrine concentration is more useful than the heart rate variability estimated by coefficient of variance of N-N intervals during sleep for predicting subsequent ventricular arrhythmias observed after the onset of the first acute myocardial infarction.

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要　約

心筋梗塞急性期における心拍変動係数と血漿Epinephrine濃度：心室性不整脈との因果関係

江島　準一　金子　武生　丸山　徹　加治　良一　津田　泰夫
金谷　庄蔵　藤野　武彦　仁保　喜之　石原　保之

心室性期外収縮や心室頻拍など，心筋梗塞急性期における心室性不整脈の発生を予知し，その対策を講じる上では，自律神経の機能評価が不可欠であるが，その点で睡眠時の心拍変動と血漿epinephrine濃度のいずれが有用な指標となりうるかを検討した．

発症6時間以内の前壁ないし前壁中隔Q波梗塞17例に対し，保存的治療下に心電図モニターと採血を1週間施行した．全例，入院日の睡眠中の心拍変動係数(CV＝N-N間隔の標準偏差/平均N-N間隔×100；%)は同日の血漿epinephrine濃度と特定の関係はなかったが，後者の濃度が上昇する例ほど期外収縮は指数関数的な増加傾向を示し，血漿epinephrine濃度が375 pg/ml以上の例では全例心室頻拍が出現した．1週間の観察では期外収縮と血漿epinephrine濃度はいずれも指数関数的に減少し，変動係数も減少傾向を示した．心室頻拍はxylocaine抵抗性であり，持続するにつれてその心拍数が増加し，また心室性期外収縮もその連結期が先行N-N間隔と正相関したので，これらの心室性不整脈がcatecholamine依存性であることと併せ，その発生機序として撃発活動の関与が示唆された．

以上より，心筋梗塞発症後数時間以降，1週間程度における心室性不整脈発生の予測因子としては，睡眠中の心拍変動係数よりも，むしろ入院当初の血漿epinephrine濃度のほうが勝っているものと推察された．

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