Silent Myocardial Ischemia in Patients with Variant Angina

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Twenty-four hour ambulatory electrocardiographic recording was performed in 56 patients with variant angina admitted to the coronary care unit in order to evaluate the incidence and pathophysiology of silent episodes of ST elevation. Of 696 episodes of ST elevation of more than 0.1 mV identified during a recording period of 141 days, 531 (76%) episodes were completely silent. The incidence of silent episodes increased as the number of total ischemic episodes per day increased. Silent ST elevation revealed a significantly shorter duration and a lower intensity than symptomatic ST elevation. However, there were wide overlaps in the duration and intensity of ST elevation between silent and symptomatic episodes. In some patients, silent and symptomatic episodes of similar duration and intensity were observed. Arrhythmias during ischemic episodes such as premature ventricular contractions, ventricular tachycardia, high grade atrioventricular block, and sinus arrest were observed in 32 of 56 patients, 57% of cases and 9% of the total episodes. Arrhythmias were more common during symptomatic episodes (29%) than during silent ones (9%, $p < 0.01$), but serious arrhythmias such as ventricular tachycardia, high grade atrioventricular block and sinus arrest occurred even during silent episodes. In both silent and symptomatic episodes, the duration and intensity of ST elevation were significantly lower in ischemic episodes with arrhythmias than in those without arrhythmias. These results suggest that 1) the majority of ischemic events are silent in patients with variant angina; 2) the severity of ischemia seems to be an important factor as the cause of anginal pain, but additional factors may be involved; 3) arrhythmias were more common during symptomatic than silent episodes.

WITH the use of recent technology including ambulatory ECG recording and radio-nuclide imaging, silent myocardial ischemia has been recognized as objective evidence for myocardial ischemia in the absence of related subjective symptoms in patients with coronary artery disease.¹⁻³ However, there has been little

integration of the data regarding the cause, incidence and pathophysiology of the silent myocardial ischemia. In patients with variant angina, it has been established that myocardial ischemia is caused by coronary spasm and that transient episodes of ST elevation representing an acceptably reliable, easily identifiable marker of acute transmural ischemia occur during rest angina.⁴⁻⁶ In addition, it appears to be the form of spasm-induced myocardial ischemia in which serious arrhythmias are frequent.⁷⁻⁸ Accordingly, the study of variant angina using ambulatory ECG

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recording may provide important information for the evaluation of silent myocardial ischemia and related arrhythmias. In the present study, 24-hour ambulatory recordings were used to study the incidence and pathophysiology of silent myocardial ischemia in 56 patients with variant angina admitted to the coronary care unit.

METHODS

Study patients

Retrospective analysis of analog tape recordings obtained during ambulatory electrocardiographic monitoring of 56 patients with variant angina who were admitted to the coronary care unit from January 1979 to June 1987 were performed. Forty-six were male and 10 female, ages ranged from 38 to 72 years. The diagnosis of variant angina was made by the following criteria: 1) episodes of angina at rest associated with transient ST elevation in a standard 12 lead ECG; 2) relief of angina as well as ST elevation spontaneously or after sublingual nitroglycerin; 3) no subsequent evidence of acute myocardial infarction. Anterior or anterolateral myocardial ischemia demonstrating ST elevation in precordial leads was observed in 30 patients and inferior ischemia demonstrating ST elevation in leads II III aVF in 22 patients. Four patients showed ST elevation in both anterior and inferior leads at different episodes. Coronary arteriography was performed in 55 patients. Percent luminal stenosis of the coronary artery was evaluated by angiograms taken after intravenous infusion of nitroglycerin in a dose of 0.1 to 0.2 mg. Twenty-six patients had no or mild coronary stenosis of less than 50%. Sixteen patients had a stenosis of 50 to 75% in the major coronary arteries. Thirteen had a significant stenosis more than 75%. Five of the 13 patients had a multi-vessel disease. Twenty-eight patients had episodes of angina on effort. None of these patients had evidence of old myocardial infarction.

Recording and analysis of the ambulatory ECG

During the first day of admission, the 24-hour ambulatory ECG was recorded. Cardiovascular medications including calcium channel blockers and nitrates were withdrawn 24 hours prior to ECG recording, but sublingual nitroglycerin was allowed for anginal pain.

Recording and analysis were as described previously in detail⁸. Briefly, a precordial bipolar

ECG was continuously recorded on a calibrated analog tape system (Avionics). One of the two leads was selected to mimic the lead that showed the highest ST elevation in a 12 lead ECG during angina. Analysis of the recorded tape was done using Avionics Electrocardioscanner (Model 9000A). ST elevation was detected by both trendgrams of the mean level of the ST segment (averaging 20 beats, 0.08 sec from the nadir of the S wave) and visual analysis of an oscilloscopic ECG display. All episodes showing ST elevation were displayed in real time to evaluate the duration and intensity of ST elevation and the presence of arrhythmias. Transient episodes of ST elevation of 0.1 mV or more lasting more than 30 sec were considered to be ischemic. The duration and maximal level of ST elevation during ischemic events were measured and those values were used as an indicator of severity of myocardial ischemia. ST elevation associated with an abrupt change in QRS complex and postural ST changes were excluded. Arrhythmias associated with ischemic ST elevation were premature ventricular contractions (PVCs), ventricular tachycardia (VT), advanced or complete atrioventricular block (AVB) and sinus arrest or block (SA).

Statistical analysis

All data were expressed as mean $\pm$ SEM. Chi-square test and Student's t test were used for statistical analysis. Probability values (p) of less than 1% were considered statistically significant.

RESULTS

Characters of ambulatory ECG recordings

Of 141 tapes (2–6 tapes per person), 89 showed at least one episode of ischemic ST elevation. Some patients had only one ST elevation per day whereas others had as many as 68 episodes per day. Ambulatory tapes showing a few episodes of ST elevation were most common. The number of tapes showing 1 to 5, 6 to 10, 11 to 20 and 21 or more episodes of ST elevation were 55, 12, 17 and 5, respectively.

ST elevation exclusively occurred at rest and was not associated with physical activity. Episodes of ST elevation irrespective of accompanying anginal pain occurred predominantly at midnight and early in the morning as described previously⁸. In most cases, ST elevation was not preceded by changes in heart rate.

Incidence of Silent Ischemia

Fig.1. Total number of symptomatic (open column) and silent (shaded column) episodes of transient ST elevations in 24 hour ambulatory ECG recording showing 1 to 5, 6 to 10, 11 to 20, and 21 or more episodes. The proportion of silent ischemic events to total number of ischemic events increased as the numbers of total ischemic events per day were increased.

Incidence of silent ischemic episodes

Of a total of 696 episodes of ST elevation, 531 (76%) were silent (completely asymptomatic). The incidence of silent ischemia observed during 24 hours of ambulatory recording was increased markedly depending on the total numbers of the ischemic events (Fig. 1). The proportion of silent episodes to the total was 45, 69, 75 and 97% ($p < 0.01$) in the tapes showing 1 to 5, 6 to 10, 11 to 20 and 21 or more ischemic episodes per day, respectively. In addition, the mean duration and intensity of ST elevation tended to be less in tapes in which total numbers of ischemic episodes were high. This trend was observed in individual patients.

The mean duration and intensity of transient ST elevation were compared during silent and symptomatic ischemic events (Fig. 2). Silent ST elevation revealed a significantly shorter duration (3.1 ± 1.1 versus 7.9 ± 2.0 min, $p < 0.001$) and a lower intensity (0.4 ± 0.3 versus 1.6 ± 0.3 min $\times$ mV, $p < 0.001$) as compared to symptomatic elevation. Additionally, 99% of the ST elevations were less than 1 min in duration and were not accompanied by subjective symptoms.

Eleven of 56 patients (20%) had only symptomatic ST elevation and 45 had both symptomatic

Relationship between Symptom and Ischemia

Fig.2. Mean duration (min) and intensity (min $\times$ mV) of ST elevation were presented.

TABLE I THE DURATION OF ST ELEVATION (min) WITH AND WITHOUT ARRHYTHMIAS

	With arrhythmias	Without arrhythmias
Symptomatic ST elevation	$9.2 \pm 1.2^*$	5.8 ± 2.0
Silent ST elevation	$4.7 \pm 1.0^*$	2.4 ± 1.0

*: $p < 0.01$ versus without arrhythmias.

and silent episodes of ST elevation in variable proportions.

Incidence of arrhythmias

Arrhythmias such as PVCs, VT, AVB and SA were observed during 9% of the total ischemic episodes and in 32 of the 56 patients. The frequency of arrhythmias was significantly higher during symptomatic episodes (29%: 48/165) than during silent ones (6%: 13/531, $p < 0.01$). However, serious arrhythmias including VT, AVB and SA were also recorded during silent episodes. In both symptomatic and silent episodes, the duration of ST elevation was lower in events without arrhythmias than in events with arrhythmias (Table I).

DISCUSSION

Presence of silent ischemia in variant angina

In the Framingham study⁹ 23% of myocardial infarction occurred in the absence of symptoms. In addition, it is known that some patients with severe coronary artery disease reveal strongly ischemic ECG changes on exercise testing without cardiac pain.¹⁻³ However, the mechanisms responsible for cardiac pain in patients with ischemic heart disease are still poorly understood.¹⁰⁻¹¹ In patients with variant angina, silent myocardial ischemia was first described by Guazzi et al.¹²⁻¹³ Maseri et al.¹⁴⁻¹⁵ subsequently used observations with ambulatory hemodynamic monitoring to demonstrate that silent ST elevation might be associated with severe impairment of left ventricular function, that it clearly preceded the onset of ST elevation and that an obvious impairment of left ventricular function clearly preceded the onset of ST elevation and chest pain occurred late after the onset of ST elevation. Accordingly, it has been assumed that silent ST elevation in patients with variant angina indicates myocardial ischemia. However, the clinical characteristics of silent ischemia in variant angina with regard to its incidence and pathophysiology have not yet been reported in detail.

Incidence of silent ischemia in variant angina

It has been shown that transient silent ECG change representing myocardial ischemia is commonly seen in patients with unstable angina¹⁶⁻¹⁷ and stable effort angina¹⁸⁻¹⁹ when continuous ECG recordings are performed. The incidence of silent ischemia in our patients was

76% of the total. This value is comparable to the findings in a number of studies on ambulatory patients with unstable angina¹⁶⁻¹⁷ and stable effort angina.¹⁸⁻¹⁹ These results suggest that patients with angina pectoris have transient ischemia more often than the frequency of subjective symptoms would suggest. Therefore, ambulatory ECG recording may be a valuable tool to assess the incidence of ischemia.

Our results also suggest that the frequency of silent ischemia increased as the total numbers of ischemic incidents increased, although the cause of the phenomena could not be clarified in this study. Experimental studies have demonstrated that repeated transient myocardial ischemia was able to induce coronary collateral development.²²⁻²³ Clinical observations indicated immediate appearance of coronary collaterals during coronary artery occlusion due to spasm in some patients with variant angina.²⁴⁻²⁵ In the present study, the average severity of ischemic events tended to decrease with increased daily frequency of total ischemic events. These lines of evidence may suggest that coronary collaterals developed after spasm-induced repetitive myocardial ischemia and could have contributed to the less severe level of myocardial ischemia and to the increase in the incidence of silent ischemia in our patients. However, this hypothesis requires further clinical studies.

Severity of myocardial ischemia and arrhythmias during silent ST elevation

In the present study, the severity of myocardial ischemia was indicated by the duration and intensity of ST elevation. Silent ST elevation was shorter and less profound in intensity than symptomatic ST elevation (Fig. 2). These results, therefore, suggest that silent ischemic episodes in variant angina represent a lesser degree of myocardial ischemia, as had been suggested in unstable angina²⁰ and stable effort angina.¹⁹ Our finding of a brief duration of ST elevation (< 1 min) exclusively occurring in the absence of subjective symptoms might suggest that a brief period of ischemia is not an adequate stimulus to cause cardiac pain. However, the wide overlap in severity of ischemia between silent and symptomatic episodes suggests that the severity of ischemia is not the sole factor that determines symptomatic or silent myocardial ischemia. Arrhythmias were observed in 9% of the total 696 episodes of ST elevation. Arrhythmias were found more fre-

quently in symptomatic episodes (29%) than in silent ones (6%). In both symptomatic and silent ST elevation, the duration of ST elevation associated with arrhythmias was greater than that without arrhythmias. These results suggest that the occurrence of arrhythmias during ST elevation relates to the severity of myocardial ischemia. However, serious arrhythmias including VT, AVB and SA were also observed during silent episodes. These findings may indicate that silent ischemia is a potential cause of sudden death.⁷⁻⁸

Implications

This study is retrospective and uncontrolled, 24 hour ambulatory ECG recording was performed in 56 patients with variant angina and our results may provide a precise picture of ischemic events in such circumstances. Ambulatory ECG monitoring may be an important tool not only to detect silent ischemic events but to determine the frequency of total ischemic episodes in order to make a prognosis and evaluate response to therapy. Recent reports suggest that silent ischemia after medical treatment is the most important determinant of prognosis in unstable angina pectoris.¹⁶⁻¹⁷ We previously reported a case of variant angina in which angina was abolished after oral diltiazem therapy but the presence of silent ischemia resulted in the occurrence of acute myocardial infarction.²¹ However, available data with respect to the cause of silent ischemia and its prognostic significance in patients with variant angina are quite limited, therefore further studies need to be performed.

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