Clinical Studies

Cardiac Events in Patients with Silent Myocardial Ischemia

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SUMMARY

The clinical implications of silent myocardial ischemic (SMI) episodes in patients with coronary artery disease were assessed in 253 patients whose angina symptoms were resolved by antianginal drugs. This population included 93 patients without a history of myocardial infarction (angina group) and 160 patients with myocardial infarction (infarction group). These patients were further divided into 2 subgroups according to whether or not SMI was detected by Holter monitoring immediately before discharge. The incidence of cardiac events was 19% for the angina group and 18% for the infarction group. The incidence of cardiac events did not differ between the 2 groups, but the cardiac event profile did. Briefly, 14 angina patients experiencing cardiac events needed coronary revascularization for worsening symptoms, while 18 myocardial infarction patients experiencing cardiac events had another infarction. In both angina and myocardial infarction patients, the cumulative rates of cardiac events were significantly higher in the subgroups with SMI ($p < 0.01$ in either group). The significant prognostic factors as determined in the Cox regression model were multivessel disease, asynergy score, and SMI on Holter monitoring for angina patients, and SMI on Holter monitoring and multivessel disease for myocardial infarction patients. In conclusion, the cardiac event rate is significantly elevated in the subgroups with SMI, regardless of whether the patient had previous myocardial infarction; patients with SMI carry a poor prognosis, especially when they have a history of myocardial infarction.

Key Words:

Silent ischemia Holter monitoring Prognostic predictor Cardiac event

THE favored time zone for the occurrence of myocardial ischemic episodes is known to coincide with that for acute myocardial infarction and sudden cardiac death.^{1),2)} These cardiac events are unpredictable in some patients with heart disease. In light of these findings, silent myocardial is-

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chemic (SMI) episodes have been considered as a possible cause of the absence of signs presaging such cardiac events.³⁾ SMI is presumed to be caused by multiple interactive factors, such as disturbance of the anginal warning system due to advanced age, diabetes mellitus, myocardial infarction, and neuropathies;⁴⁾ mild myocardial ischemia;⁵⁾⁻⁷⁾ an abnormal individual response to pain,⁸⁾ and an elevation in plasma endorphin secretion.^{9),10)} Kohya et al⁶⁾ and others⁷⁾ reported that whereas patients with both angina pectoris and SMI without a previous myocardial infarction have milder myocardial ischemia than those with a previous myocardial infarction, the severity of myocardial ischemia in patients with myocardial infarction poorly correlated with symptoms. These observations suggest that angina pectoris patients without previous myocardial infarction should be distinguished from those with previous myocardial infarction in studies of SMI. The goal of this study was to determine prognostic implications of SMI in patients with coronary artery disease. Accordingly, cardiac event rates and prognostic predictors were determined in patients with coronary artery disease who were divided into a group of patients with angina pectoris and a group of patients with myocardial infarction. Multivariate analysis of prognostic predictors in 2 groups was performed on the basis of the findings obtained in Holter electrocardiographic, exercise electrocardiographic, left ventriculographic, and coronary arteriographic studies.

SUBJECTS AND METHODS

1. Subjects

This study was carried out in 2 groups of patients chosen from among the inpatients at Nippon Medical School Hospital. One group consisted of 93 patients with exertional angina pectoris who did not have a previous myocardial infarction (72 males and 21 females with a mean age of 56 ± 8 years, subsequently designated the angina group). On admission, they were found to have ischemic ST-segment depression during treadmill exercise testing or Holter monitoring. Furthermore, in left ventriculographic and coronary arteriographic studies, they were found to have significant stenosis. Their chest pain was relieved by antianginal drugs.

The other group consisted of 160 patients with acute myocardial infarction (134 males and 26 females with a mean age of 55 ± 9 years, subsequently designated the myocardial infarction group) who were admitted to the coronary care unit of the same hospital around the same time that the angina pectoris patients were hospitalized. None of the myocardial infarction patients had any angina symptoms after treatment with antianginal drugs.

Despite adequate treatment in the hospital, 110 patients (50 in the angina group and 60 in the myocardial infarction group) showed evidence of SMI in Holter monitor records. In both the angina pectoris and myocardial infarction groups, treadmill exercise tests and left ventriculographic and coronary arteriographic studies were performed concurrently with Holter monitoring. Patients who presented with left bundle branch block and Wolff-Parkinson-White syndrome or any conditions that obscure ST-segment changes were excluded from the study.

2. Holter Electrocardiograph

The Holter electrocardiograph used in this study was a Marquette model 8500 with a Marquette model 8000T analyzer. The leads were, in principle, bipolar leads C_5-C_{5R} and a modified lead II, but the ECG leads with Q waves were avoided in myocardial infarction patients. The reciprocal ST-segment depression that followed a transient ST-segment elevation (consistent with the site of infarction) was not considered an ischemic event unless scintigraphic perfusion defects were observed or unless stenosis was revealed in the coronary artery corresponding to the contralateral lead. ST-segment analysis was performed by measuring the ST-segment deviation at 80 msec from the J point on the real-time electrocardiogram, referring to the trend electrocardiogram for information. Episodes of ischemia were defined according to the criteria of Tanabe et al^(11,12) as a change that fulfills three conditions: (1) horizontal or down-sloping ST-segment depression, (2) at least 1 mm of horizontal or down-sloping ST-segment depression lasting at least 1 min and (3) a change sustained for at least 1 min to maximum ST-segment depression.

3. Treadmill Exercise Test

An exercise test was performed on all angina pectoris patients according to the protocol of Bruce et al,⁽¹³⁾ and modified protocols of Bruce et al⁽¹³⁾ or Alpern and Mickle⁽¹⁴⁾ were used for testing myocardial infarction patients. Continuous, 12 lead electrocardiographic tracings were obtained after the commencement of the test and blood pressure measurements were obtained at 1-min intervals. The exercise test was discontinued when subjective symptoms such as angina, fatigue in the lower extremities and shortness of breath, ST-segment depression greater than 2 mm, a decrease of 20 mmHg in blood pressure, an increase of 250 mmHg or more in blood pressure, or serious arrhythmia appeared, or when the protocol was completed. ST-segment deviation was measured at 80 msec from the J point, and ST-segment depression was considered significant when at least a 0.1 mV ischemic ST-segment depression was observed after the termination of exercise or within 3 min of

recovery, compared to the ST-segment change at rest. The patients already taking antianginal drugs were subjected to exercise testing without discontinuing the drugs. Digitalis, which can affect the interpretation of ST-segment changes, was used by 3 myocardial patients (2%), and beta-blockers, which affect heart rate, were used by 10 angina pectoris patients (11%) and 6 myocardial infarction patients (4%).

4. Left Ventriculography and Coronary Arteriography

According to the American Heart Association criteria, coronary artery stenosis was considered significant when the left main coronary artery had 50% or greater stenosis and when 75% or greater stenosis was present at other sites. The left ventricular ejection fraction was determined by the modified area length method from the image obtained by left ventriculography. Left ventricular wall movements were classified according to the American Heart Association criteria and scored (normal=0, reduced=1, none=2, dyskinesia=3, aneurysmal=4), and the sum of the scores for 7 segments was reported as the asynergy score. Coronary arteriographic studies revealed that, in the angina group, 52 patients had 1-vessel coronary arterial disease, 27 had 2-vessel disease, and 14 had 3-vessel disease. In the myocardial infarction group, 79, 49, and 32 patients had 1-, 2-, and 3-vessel diseases, respectively.

5. Method of Prognosis Follow-up

All patients were periodically followed at the outpatient clinic at intervals of 2 to 4 weeks. The period of follow-up began on the day of Holter monitoring prior to discharge; the time of occurrence of cardiac events, such as sudden death, nonfatal myocardial infarction, need for revascularization with nonelective percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG) for new or worsening symptoms, or unstable angina indicating hospitalization was noted for each patient. Elective PTCA, CABG, and deaths from noncardiac diseases were not included in the cardiac events. The mean period of follow-up was 53 ± 45 months for the angina group and 44 ± 32 months for the myocardial infarction group.

6. Statistical Assessment of Data

All data are expressed as mean $\pm$ standard deviation, and were assessed by the chi-square test or Student's t-test for the significance of differences between the angina pectoris and the myocardial infarction groups. Differences were considered significant when $p < 0.05$.

Cardiac event rates were calculated by the Kaplan-Meier method and

assessed statistically by the generalized Wilcoxon method. Multivariate analysis of prognostic factors was done using the Cox proportional hazards regression model.¹⁵⁾ For the angina and the myocardial infarction groups, 7 variables for multivariate analysis were chosen: sex, age, number of coronary risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, hyperuricemia, obesity), number of diseased coronary arteries, left ventricular ejection fraction, SMI on Holter monitoring and ischemic ST-segment depression on treadmill exercise testing.

RESULTS

Clinical Features

The clinical features of patients in the angina pectoris group are summarized in Table I. Anginal attacks on admission were unstable in 18 patients (19%), but the majority of patients had stable angina pectoris. Nitrate and/or nicorandil therapy had been used by 57 patients (61%). Forty-one patients (44%) had multivessel coronary artery disease. ST-segment depression was induced in 79 patients (85%), and exercise-induced angina symptoms occurred in 33 patients (35%).

The patients were also divided according to whether or not SMI was

Table I. Clinical Features of Angina Pectoris Patients

	Total	No SMI	SMI	p Value
Number of cases	93	43	50	—
Male : Female ratio	73 : 20	35 : 9	39 : 11	NS
Age (years)	56 ± 20	55 ± 8	56 ± 8	NS
Unstable angina on admission	18 (19)	5 (12)	13 (26)	
Coronary risk factors*	66 (71)	28 (65)	38 (76)	NS
Medical treatment				
Nitrate & nicorandil therapy	57 (61)	26 (60)	31 (62)	NS
Calcium antagonists therapy	45 (48)	24 (56)	21 (42)	NS
β-blocker therapy	10 (11)	2 (5)	8 (16)	NS
Multivessel disease	41 (44)	17 (39)	24 (48)	NS
LVEF (%)	70.5 ± 10.2	72.9 ± 9.6	68.9 ± 10.5	NS
Asynergy score	0.6 ± 1.4	0.4 ± 1.0	0.8 ± 1.7	NS
Treadmill exercise test				
Occurrence of ST-segment depression	79 (85)	34 (79)	45 (90)	NS
Induced-angina	33 (35)	20 (47)	13 (26)	NS

* Number of cases with more than two coronary risk factors: diabetes mellitus, hypertension, hyperlipidemia, smoking, and obesity.

LVEF = left ventricular ejection fraction. Percentages are shown in parentheses. SMI was determined from Holter monitor records.

Table II. Clinical Features of Myocardial Infarction Patients

	Total	No SMI	SMI	p Value
Number of cases	160	100	60	—
Male : Female ratio	134 : 26	82 : 18	52 : 8	NS
Age (years)	55±9	55±9	57±9	NS
A history of previous angina	89	52 (52)	37 (62)	NS
Coronary risk factors*	117	72 (72)	45 (75)	NS
Medical treatment				
Nitrate & nicorandil therapy	49 (31)	32 (32)	17 (28)	NS
Calcium antagonists therapy	45 (28)	27 (27)	18 (30)	NS
β -blocker therapy	6 (4)	4 (4)	2 (3)	NS
Killip's classification**	10 (6)	8 (9)	2 (3)	NS
Site of infarction				
Anterior	42 (26)	27 (27)	15 (25)	NS
Inferior	65 (41)	33 (33)	32 (53)	p<0.05
Extensive	35 (22)	29 (29)	6 (10)	NS
Others	18 (11)	11 (11)	7 (12)	NS
Multivessel disease	81 (51)	43 (43)	38 (63)	NS
LVEF (%)	55.7±15.2	54.3±15.2	58.4±14.3	NS
Asynergy score	3.7±2.7	3.8±2.8	3.5±2.6	NS
Treadmill exercise test				
Occurrence of ST-segment depression	82 (51)	39 (39)	43 (72)	p<0.05
Induced-angina	16 (10)	7 (7)	9 (15)	NS

* Number of cases with more than two coronary risk factors: diabetes mellitus, hypertension, hyperlipidemia, smoking, and obesity. ** Number of cases with more than class II.

LVEF=left ventricular ejection fraction. Percentages are shown in parentheses. SMI was determined from Holter monitor records.

detected on Holter monitoring. The frequency of exercise-induced angina tended to be higher in the group without SMI, but the reverse was the case with other variables. Left ventricular function tended to be depressed in the group with SMI. However, there was no significant difference in any variable between the 2 subgroups.

Table II shows the clinical features of patients in the myocardial infarction group. Infarction was observed with the highest frequency (65 patients, 41%) in the inferior region. Eighty-one patients (51%) had multivessel disease, and exercise-induced ST-segment depression occurred in 82 patients (51%). The percentage of patients receiving calcium antagonist therapy was significantly higher in the subgroup with SMI ($p<0.001$), and the percentages of patients with infarction in the inferior region and exercise-induced ST-segment depression were also significantly higher in the group with SMI (both $p<0.05$). There was no significant difference in other variables between the 2 groups of myocardial infarction patients.

Table III. Cardiac Events in Patients with Angina Pectoris and Myocardial Infarction

	N	Nonfatal AMI	Cardiac Death	PTCA, CABG	Unstable Angina	No. of Events	% with Events
Angina pectoris	93	2	2	14	0	18	19
No SMI	43	0	1	3	0	4	9
SMI	50	2	1	11	0	14	28
Myocardial infarction	160	18	3	4	3	28	18
No SMI	100	5	2	2	0	9	9
SMI	60	13	1	2	3	19	32
Total	253	20	5	18	3	46	18

AMI=acute myocardial infarction; CABG=coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty. No SMI vs SMI in myocardial infarction patients, $p<0.05$ (chi-square test).

Incidence of Cardiac Events

The cardiac event rate in the whole population was 18% (46/253), as shown in Table III. It was the same in both disease groups, at 19% (18/93) in the angina and 18% (28/160) in the myocardial infarction group (χ^2 test, $p<0.05$). The cardiac events in the angina group consisted of 2 cases each of non-fatal acute myocardial infarction and cardiac death and 14 cases of coronary revascularization with PTCA or CABG, whereas the corresponding numbers of cardiac events in the myocardial infarction group were 18, 3, and 4, respectively, and 3 patients had unstable angina requiring hospitalization.

The cardiac event rate in angina pectoris patients did not differ significantly between the SMI subgroups (14/50 with SMI, 4/43 without SMI). Two patients in the group with SMI had episodes of myocardial infarction, while no episode of myocardial infarction occurred in the group without SMI. There was one cardiac death in each group. Eleven patients in the group with SMI needed coronary revascularization, while 3 in the group without SMI needed it.

The cardiac event rate in myocardial infarction patients was significantly higher in the SMI subgroup (32% (19/60) versus 9% (9/100) in the group without SMI, $p<0.05$). The incidence of reinfarction was higher in the group with SMI, which had 13 reinfarctions, than in the group without SMI, which had 5 reinfarctions. There was 1 cardiac death in the group with SMI and 2 cardiac deaths in the group without SMI.

Cardiac Event Rates and Prognostic Predictors

Figure 1 compares the cumulative cardiac event rates between the angina

Table IV. Multivariate Analysis for Predictors of Cardiac Events in Angina Pectoris and Myocardial Infarction Patients by Cox's Regression Model

	Angina ^a Pectoris		Myocardial Infarction	
	Chi-square	p Value	Chi-square	p Value
Gender	0.32	0.5691	0.09	0.7587
Age	0.19	0.6657	3.06	0.0800
Coronary risk factor*	0.29	0.5928	1.69	0.1935
Multivessel disease	20.73	0.0000	3.92	0.0477
LVEF	1.58	0.2087	1.16	0.2821
Treadmill exercise test				
Occurrence of ST-segment depression	4.19	0.0407	0.98	0.3225
Holter monitoring				
Occurrence of ST-segment depression without anginal symptom	6.96	0.0083	9.61	0.0019

* Number of cases with more than two coronary risk factors: diabetes mellitus, hypertension, smoking, hyperlipidemia, hyperuricemia, and obesity.

LVEF=left ventricular ejection fraction.

Fig. 1. Cumulative cardiac event rates in angina pectoris and myocardial infarction patients using the Kaplan-Meier method.

and the myocardial infarction groups. In the former, the cumulative cardiac event rates at 1, 3, and 5 years of follow-up were 12, 17, and 18%, while in the latter, the corresponding values were 4, 14, and 21%. In both groups the cumulative cardiac event rates increased with the period of follow-up.

Significant prognostic predictors of cardiac events (Table IV) were multivessel disease, SMI on Holter monitoring, and occurrence of ST-segment depression on treadmill exercise testing in the angina group and SMI on

Fig. 2. Cumulative cardiac event rates in angina pectoris and myocardial infarction with and without SMI episodes using the Kaplan-Meier method.

Holter monitoring and multivessel disease in the myocardial infarction group. The common significant prognostic predictors to both groups were, therefore, multivessel disease and SMI.

SMI and Cardiac Events

Figure 2 compares the cumulative cardiac event rates between subgroups with SMI and without SMI in the angina and myocardial infarction groups. The cumulative cardiac event rates at 1, 3, and 5 years of follow-up were significantly higher, at 19, 24, and 29%, respectively, in the angina group with SMI, compared to 5, 8, and 8% in the group without SMI ($p < 0.01$). Similarly, the cumulative cardiac event rates at 1, 3, and 5 years were significantly higher, at 9, 21, and 39%, respectively, in the myocardial infarction group with SMI, compared to 3, 7, and 9% in the group without SMI ($p < 0.01$). Note that the cumulative cardiac event rates appear to be a function of the presence or absence of SMI.

DISCUSSION

It has already been documented that exercise tests^{16),17)} and Holter electrocardiography^{18),19)} provide useful approaches to detect SMI in patients with coronary artery disease. These approaches have already found wide application in studies of pathophysiology of myocardial ischemia^{20),21)} and drug effects²²⁾ in patients with angina pectoris and myocardial infarction. In the

present study as well, Holter electrocardiography was used in the diagnosis of SMI episodes, and the criteria of Tanabe et al^{(11), (12)} were used to differentiate ST-segment depression from nonischemic depression. Considering that there was confirmed stenosis of a coronary artery in all the patients of our series, it seems quite possible that the transient ST-segment depression observed in this study is of an ischemic nature.

On the other hand, because coronary T waves appear in electrocardiograms of many myocardial infarction patients, the lead sites that do not generate Q waves or coronary T waves were used in this study. Furthermore, reciprocal ST-segment depression following a transient ST-segment elevation was not considered an ischemic event unless either scintigraphic perfusion defects were observed on exercise myocardial scintigraphy or stenosis was revealed in the coronary artery corresponding to the contralateral lead.

Exercise testing revealed SMI in 2–5% of adults without previous angina pectoris or myocardial infarction.⁽²³⁾ Fleg et al⁽²⁴⁾ recently reported that 6% of patients gave a positive reaction to both exercise testing and myocardial scintigraphy. Since the incidences of angina pectoris, myocardial infarction, and cardiac death in patients with SMI were more than 5 times higher than those in patients without SMI, the early detection of SMI is important.⁽²³⁾ The present study divided subjects into an angina group and a myocardial infarction group because the pathophysiologies of angina pectoris and myocardial infarction differ. For instance, coronary disease patients with myocardial infarction have more severe impairment of cardiac function and more severe coronary disease than those without myocardial infarction.^{(25)–(27)} Myocardial ischemia is more severe in angina pectoris patients with symptomatic myocardial ischemia than in those with SMI,^{(6), (7)} while in patients with myocardial infarction, the degree of myocardial ischemia is independent of the silent or symptomatic nature of the disease.^{(6), (28)}

In both angina pectoris and myocardial infarction patients, the cardiac event rates were higher in the group with SMI. In the angina group many patients needed coronary revascularization by PTCA or CABG, whereas in the myocardial infarction group there were many patients who had reinfarction. The differences in cardiac event rate between the angina and the myocardial infarction groups cannot be explained solely by the factors described in this study. However, the high frequency of coronary revascularization in the angina group can be partially explained by assuming that the transient ST-segment depression persisted after disappearance of cardiac symptoms. Thus, in cases of advanced ischemia coronary revascularization could be performed aggressively to prevent the development of myocardial infarction.

On the other hand, reinfarction was frequent in the myocardial infarc-

tion group. This may be attributed in small part, to the fact that this group included many patients who did not tolerate coronary revascularization and, in large part, by the fact that they remained asymptomatic. In recent years, it has been revealed^{29),30)} that the coronary artery disease lesion responsible for reinfarction differs from the site of stenosis in the first infarction and that the occurrence of reinfarction is hard to predict in patients with mild coronary artery disease. For example, in 6 of 18 patients of our series, the responsible coronary artery disease lesion did not agree with the site of first infarction. These observations seem to account for different cardiac event rates between the angina and the myocardial infarction groups.

Although the cardiac event rate in patients with SMI did not vary markedly between the angina and the myocardial infarction groups, the former group carried a good prognosis because of early coronary revascularization, while the prognosis of the latter group was poor. This fact suggests³¹⁾ that myocardial infarction patients should undergo early coronary revascularization, whether or not they are symptomatic.

Our results suggest that SMI is the most important risk factor for predicting cardiac events in both the angina and myocardial infarction group. In addition, the occurrence of ST-segment depression during treadmill exercise tests was a predictor in the angina group. In recent years, several studies have indicated^{16),32)–34)} that silent myocardial ischemia is an important predictor of coronary artery disease. It should be noted, however, that those studies included patients with myocardial infarction.

In the present study, Holter electrocardiography proved to be a useful tool for the detection of SMI. There are reports by other investigators^{34)–36)} that Holter electrocardiography is the best test for SMI; other reports state that stress thallium scintigraphy³⁷⁾ and radionuclide ventriculography³¹⁾ are useful for the same purpose. Fleg et al²⁴⁾ found that SMI was detected at a higher rate by both exercise testing and myocardial scintigraphy than by either test alone, and emphasized the utility of performing both tests. The mechanisms of underlying symptomatic myocardial ischemia and SMI have not yet been elucidated to a full extent. Given the fact that SMI is more severe in myocardial infarction patients than in angina pectoris patients without previous myocardial infarction, prevention and treatment of SMI are of particular importance in myocardial infarction patients.

REFERENCES

1. Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E, The MILIS Study Group:

- Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* **313**: 1315, 1985
2. Willich SN, Levy D, Rocco MB, Toffler GH, Stone PH, Muller JE: Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. *Am J Cardiol* **60**: 801, 1987
 3. Fox K, Mulcahy D: Circadian patterns of myocardial ischemia. *Am Heart J* **118**: 1084, 1989
 4. Cohn PF: Silent myocardial ischemia in patients with a defective anginal warning system. *Am J Cardiol* **45**: 697, 1980
 5. Chierchia S, Lazzari M, Freedman B, Brunelli C, Maseri A: Impairment of myocardial perfusion and function during painless myocardial ischemia. *J Am Coll Cardiol* **1**: 924, 1983
 6. Kohya T, Tomita F, Itoh K, Suzuki Y, Kawabata N, Andoh J, Yasuda H: Silent myocardial ischemia during Holter monitoring in ischemia heart disease. *Jpn Circ J* **53**: 1399, 1989
 7. Kishida H, Suzuki T, Saito T, Otsu F, Hata N, Nejima J, Kusama Y, Yasutake H, Inokuchi N: Characteristics of symptomatic and asymptomatic myocardial ischemia during ambulatory electrocardiographic monitoring in patients with angina pectoris. *Jpn Heart J* **30**: 151, 1989
 8. Glazier JJ, Chierchia S, Brown MJ, Maseri A: Importance of generalized defective perception of painful stimuli as a cause of silent myocardial ischemia in chronic stable angina pectoris. *Am J Cardiol* **58**: 667, 1986
 9. Weidinger F, Hammerle A, Sochor H, Smetana R, Frass M, Glogar D: Role of beta-endorphins in silent myocardial ischemia. *Am J Cardiol* **58**: 428, 1986
 10. Sheps DS, Adams KF, Hinderliter A, Price C, Bissette J, Orlando G, Margolis B, Koch G: Endorphins are related to pain reception in coronary disease. *Am J Cardiol* **59**: 523, 1987
 11. Tanabe T, Iga T, Fukushi H, Goto Y: A new device for detection of postural ST-T changes in ambulatory electrocardiography. *Am Heart J* **109**: 187, 1985
 12. Tanabe T, Homma Y, Kanemoto N, Hinohara S, Goto Y: Studies on discrimination between ischemic and postural ST-T changes in ambulatory electrocardiographic monitoring. *J Jpn Soc Intern Med* **73**: 323, 1984 (in Japanese)
 13. Bruce RA, Blackmon JR, Jones JW, Strait G: Exercising testing in adult normal subjects and cardiac patients. *Pediatrics* **32**: 742, 1963
 14. Alpern HL, Mickle EM: Function testing in the cardiac patients. *in Postmyocardial Infarction Management and Rehabilitation*, ed by Vyden JK, Marcel Dekker, New York, p 315, 1983
 15. Kalbfleisch JS, Prentice RL: *The Statistical Analysis of Failure Time Data*, John Wiley, New York, 1980
 16. Bonow RO, Bacharach SL, Green MV, La Freniere RL, Epstein SE: Prognostic implications of symptomatic versus asymptomatic (silent) myocardial ischemia induced by exercise in mildly symptomatic and in asymptomatic patients with angiographically documented coronary artery disease. *Am J Cardiol* **60**: 778, 1987
 17. Rozanski A, Berman DS: Silent myocardial ischemia. I. Pathophysiology, frequency of occurrence, and approaches toward detection. *Am Heart J* **114**: 615, 1987
 18. Stern S, Tzivoni D, Stern Z: Diagnostic accuracy of ambulatory ECG monitoring in ischemic heart disease. *Circulation* **52**: 1045, 1975
 19. Kunkes SH, Pichard A, Meller J, Gorlin R, Herman MV, Kupersmith J: Use of the ambulatory ECG to diagnose coronary artery disease. *J Electrocardiol* **13**: 341, 1980
 20. Deanfield JE, Shea M, Ribiero P, de Landsheere CM, Wilson RA, Horlock P, Selwyn AP: Transient ST-segment depression as a marker of myocardial ischemia during daily life. *Am J Cardiol* **54**: 1195, 1984
 21. Rocco MB, Barry J, Campbell S, Nabel E, Cook EF, Goldman L, Selwyn AP: Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* **75**: 395, 1987

22. Frishman WH, Teicher M: Antianginal drug therapy for silent myocardial ischemia. *Am Heart J* **114**: 140, 1987
23. Rozanski A, Berman DS: Silent myocardial ischemia. II. Prognosis and implications for the clinical assessment of patients with coronary artery disease. *Am Heart J* **114**: 627, 1987
24. Fleg JL, Gerstenblith G, Zonderman AB, Becker LC, Weisfeldt ML, Costa PT Jr, Lakatta EG: Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers. *Circulation* **81**: 428, 1990
25. Killip T, Kimball JI: Treatment of myocardial infarction in a coronary care unit. A two-year experience with 250 patients. *Am J Cardiol* **20**: 457, 1967
26. Schuster EH, Bulkley BH: Ischemia at a distance after acute myocardial infarction: A cause of early postinfarction angina. *Circulation* **62**: 509, 1980
27. Singh AK, Rivera R, Cooper GN Jr, Karlson KE: Early myocardial revascularization for postinfarction angina: Results and long-term follow-up. *J Am Coll Cardiol* **6**: 1121, 1985
28. Ozawa T, Ikeda K, Yamaki M, Kubota I, Tsuiki K, Yasui S: Clinical implications of exercise-induced chest pain: Comparison of patients with and without pathologic Q waves in coronary artery disease. *Am Heart J* **120**: 550, 1990
29. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavey J, Weiss M, Borrico S, Gorlin R, Fuster V: Angiographic progression of coronary artery disease and the development of myocardial infarction. *Am J Coll Cardiol* **12**: 56, 1988
30. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP: Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mid-moderate coronary artery disease. *Circulation* **78**: 1157, 1988
31. Breitenbücher A, Pfisterer M, Hoffmann A, Burckhardt D: Long-term follow-up of patients with silent ischemia during exercise radionuclide angiography. *J Am Coll Cardiol* **15**: 999, 1990
32. Weiner DA, Ryan TJ, McCabe CH, Luk S, Chaitman BR, Sheffield LT, Tristani F, Fisher LD: Significance of silent myocardial ischemia during exercise testing in patients with coronary artery disease. *Am J Cardiol* **59**: 725, 1987
33. Falcone C, deServi S, Poma E, Campana C, Scire A, Montemartini C, Specchia G: Clinical significance of exercise-induced silent myocardial ischemia in patients with coronary artery disease. *J Am Coll Cardiol* **9**: 295, 1987
34. Rocco MB, Nabel EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP: Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* **78**: 877, 1988
35. Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody FV, Singh BN: Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* **10**: 1, 1987
36. Deedwania PC, Carbajal E: Silent ischemia during daily life is an independent predictor of mortality in stable angina. *Circulation* **81**: 748, 1990
37. Bairey CN, Rozanski A, Maddahi J, Resser KJ, Berman DS: Exercise thallium-201 scintigraphy and prognosis in typical angina pectoris and negative exercise electrocardiography. *Am J Cardiol* **64**: 282, 1989