Clinical and Prognostic Significance of Silent Myocardial Ischemia in Survivors after Acute Myocardial Infarction

KENICHI FUKAMI, M.D., KAZUO HAZE, M.D., KENJI UESHIMA, M.D.
FUMIYOSHI KASAGI, Ph.D*, AND KATSUHIKO HIRAMORI, M.D.

To clarify the clinical and prognostic significance of silent myocardial ischemia (SMI) after acute myocardial infarction (MI), the clinical characteristics and long-term prognosis after discharge in 525 medically treated survivors after acute MI were investigated. According to the presence of post-infarction angina and results of all exercise tests during hospitalization, 309 patients without ischemic episodes were classified into control group, 59 patients with SMI into SMI group and 157 patients with post-infarction angina into AP group.

Previous MI (29%, 24%, 11%, respectively), non-Q wave MI (34%, 34%, 15%) and multivessel disease (69%, 61%, 33%) were more frequent in the SMI and AP groups than in the control group. These indicated clinical characteristics in patients with SMI were similar to those in patients with angina pectoris. The incidence of angina prior to MI onset in patients with SMI was lower than in patients with post-infarction angina. This may suggest that there is some common mechanism keeping them silent in the pre- and post-MI period.

During the mean follow-up period of 5.5 years, 93 patients died and 78 had a recurrent MI. Cumulative total and cardiac mortality, and incidence of recurrent MI by actuarial method were higher in the SMI as well as AP group than in the control group. There was no statistically significant difference in prognosis between SMI and AP group.

We conclude total ischemic burden, not only symptomatic but SMI, should be treated using currently available therapeutic modalities for further improvement of long-term prognosis in survivors after acute MI.

POST-INFARCTION angina is well known as an important prognostic predictor in survivors after acute myocardial infarction (MI).¹⁻³ On the other hand, myocardial ischemia may occur in the absence of symptoms in these patients.⁴⁻⁶ Although there are some reports regarding clinical and prognostic significance of silent myocardial ischemia (SMI) after acute MI, the results remain controversial. In Japan, there

are few reports and it is not known whether the clinical and prognostic significance of SMI in Japanese patients is the same as that in western patients. It is very important to clarify the clinical characteristics and long-term prognosis of SMI in considering the management of ischemic heart disease. The purpose of this study was to investigate the clinical and prognostic significance of SMI in survivors after acute MI.

Key words:

Silent myocardial ischemia
Acute myocardial infarction
Long-term prognosis
Actuarial method

SUBJECTS AND METHODS

Subjects: The subjects comprised a total of 525 survivors out of 684 consecutive patients

*Cardiac Division, Department of Internal Medicine, *Department of Epidemiology National Cardiovascular Center*
Mailing address: Kenichi Fukami, M.D., Cardiac Division, Department of Internal Medicine, National Cardiovascular Center, Fujishirodai 5-7-1, Suita, Osaka 565, Japan

TABLE I BASELINE CHARACTERISTICS IN 525 SURVIVORS AFTER ACUTE MYOCARDIAL INFARCTION: COMPARISON AMONG 3 GROUPS

Cases	Control group 309 (59%)		SMI group 59 (11%)		AP group 157 (30%)	
Age	61 ± 12		64 ± 9		65 ± 11	
Male/female	250 / 59 pts		49 / 10		116 / 41	
Previous MI	34 pts	(11%)	17 pts	(29%)*	38 pts	(24%)*
Angina prior to MI	179	(59%)*	35	(60%)*	130	(83%)*
Non-Q wave MI	46	(15%)	20	(34%)*	54	(34%)*
Pump failure	76	(25%)	21	(36%)	44	(28%)
Ejection fraction	48 ± 12%		50 ± 13%		50 ± 12%	
Multivessel disease	53 / 157	(33%)	18 / 26	(69%)*	42 / 69	(61%)*
Diabetes mellitus	87	(30%)	19	(36%)	41	(30%)
CVA	34	(11%)	9	(15%)	17	(11%)

SMI: Silent Myocardial Ischemia; AP: Angina Pectoris; CVA: cerebrovascular accident

*: $p < 0.05$; ** $p < 0.001$ (Significant difference compared with control group)

*: $p < 0.01$ (Significant difference compared with AP group)

with acute MI admitted to coronary care unit of the National Cardiovascular Center between October 1977 and December 1983. Patients excluded were 115 who died, 38 who had undergone coronary artery bypass surgery (CABS) before hospital discharge, and 6 who were lost to follow-up. That is, 99% of the survivors were followed until March 1987. The mean follow-up period was 5.5 years. There were 415 men and 110 women, and the mean age was 62.1 years (range 23–89). The diagnosis of acute MI was based on two or more of the following findings: 1) episodes of chest pain, 2) ST-T abnormalities and/or pathologic Q waves with evolutionary changes in the ECG, 3) a rise in serum creatine phosphokinase to double more the upper range of normal value.

Definition of SMI: SMI was defined as an episode of ischemic ST-segment depression of 1 mm or more, or ST-segment elevation of 2 mm or more at the point of 80 msec after the J point compared with the resting ST-segment level in the absence of chest pain or the usual anginal equivalents. ST-segment elevation in the infarct-related leads was excluded from SMI. ST-segment depression in noninfarct-related leads was also excluded, if there was no significant fixed coronary stenosis of more than 70%, or negative exercise T1-201 scintigram.

Procedure: All exercise stress tests, including rehabilitation practice, treadmill exercise test and/or exercise T1-201 scintigraphy during hospitalization of about four weeks, were reviewed. Treadmill exercise tests and exercise T1-201

scintigraphy were performed in 274 and 90 patients, respectively. Left ventriculography and coronary angiography were undergone by 254 patients before discharge.

The subjects were classified into three groups by the presence of post-infarction angina and the results of exercise tests. The 1st was a control group and consisted of patients with neither angina nor SMI. The 2nd was an SMI group of patients with SMI and without angina. The 3rd was an AP group of patients with post-infarction angina. On March 1987, the patients' status was fully reviewed by outpatient medical records and/or telephone interview. Each patient's survival or cause of death, presence of recurrent MI and readmission from angina or congestive heart failure were investigated. Clinical features and long-term prognosis were compared among the three groups.

Statistical analysis: Survival rate and incidence of cardiac death and recurrent MI after hospital discharge were assessed by the actuarial method,⁷ with a median follow-up of 5.5 years (range 1–9 years). Differences between the three groups were studied using Chi-square test and generalized Wilcoxon test.⁸ Statistical significance referred to a probability (p) value of less than 0.05. These statistical analyses were performed by means of an SPSS statistical package.⁹

RESULTS

SMI was observed in 95 (18%) of all patients

TABLE II LONG-TERM PROGNOSIS IN SURVIVORS AFTER ACUTE MYOCARDIAL INFARCTION: COMPARISON AMONG 3 GROUPS

Events	Control group		SMI group		AP group	
CABS after discharge	7 cases	(2.3%)	4	(6.8%)	2	(1.3%)
death	33	(10.7)	17	(28.8)**	43	(27.4)**
cardiac death	14		13**		30**	
MI	7		7**		8	
sudden death	5		5*		15**	
CHF	1		0		6	
others	1		1		1	
non-cardiac death	18		4		13	
unknown cases	1		0		0	
Readmission						
MI	25	(8.1)	10	(16.9)*	21	(13.4)
angina pectoris	28	(9.1)	6	(10.2)	22	(14.0)
CHF	12	(3.9)	3	(5.3)	10	(6.4)

SMI: Silent Myocardial Ischemia; AP: Angina Pectoris; CABS: coronary artery bypass surgery

MI: myocardial infarction; CHF: congestive heart failure

*: $p < 0.05$; ** $p < 0.001$ (Significant difference compared with control group)

during low grade exercise tests during rehabilitation practice, 52 (19%) of 274 patients during treadmill exercise test and 26 (29%) of 90 patients during exercise Tl-201 scintigraphy. In total, 128 patients (24%) had SMI during at least one of the three kinds of exercise tests during their hospitalization. However, 69 of these 128 patients also had post-infarction angina. A total of 59 (11%) of all patients had SMI only (SMI group); 28 of them had SMI in infarct-related leads and 31 in noninfarct-related leads. One hundred and fifty-seven (30%) patients had post-infarction angina (AP group). Three hundred and nine (59%) patients had neither post-infarction angina nor SMI (control group). Thus, we considered patients with definite SMI but no angina as in the SMI group, according to a thorough review of all kinds of exercise tests.

The clinical features in these three groups are compared in Table I. Previous MI was present in 11% (34 of 309) of the control group, 29% (17 of 59) of the SMI group and 24% (38 of 157) in the AP group. Episodes of angina prior to MI onset were found in 59% of the control group, 60% of the SMI group and 83% in the AP group. Non-Q wave MI was documented in 15%, 34% and 34% of each group. Multivessel coronary artery disease was found in 33% (53 of 159), 69% (18 of 26) and 61% (42 of 69) of each group, respectively. Previous MI, non-Q wave MI and multivessel coronary artery disease were

significantly more frequent in the SMI and AP groups than in the control group ($p < 0.001$). No significant differences were found in age, gender, incidence of patients with pump failure in acute phase, left ventricular ejection fraction examined before discharge or incidence of patients complicated with diabetes mellitus and/or cerebrovascular accidents.

Table II shows the results of a prognostic survey in the three groups. During the mean follow-up period of 5.5 years, 93 patients died; 57 (61%) died from cardiac events such as sudden death, recurrent MI, and congestive heart failure; 35 (38%) died from noncardiac events and one died from an unknown cause. Fifty-six patients had recurrent MI, and 22 died. Fifty-six patients were readmitted to hospital because of severe angina pectoris, and 25 were readmitted because of congestive heart failure. Cardiac death as well as total death was more frequent in the SMI and AP groups than in the control group ($p < 0.001$). Recurrent MI was more frequent in the SMI group than in the control group ($p < 0.05$). Seven patients (2.3%) in the control group, 4 (6.8%) in the SMI group and 2 (1.3%) in the AP group had CABS after hospital discharge for angina pectoris refractory to medical treatment. In the three groups, there were no significant differences in incidence of CABS and readmission because of angina pectoris or congestive heart failure after discharge.

TABLE III LONG-TERM PROGNOSIS IN SURVIVORS AFTER ACUTE MYOCARDIAL INFARCTION: CUMULATIVE MORTALITY AND MORBIDITY IN 3 GROUPS

	Years	1	3	5	7	9
Survival rate	control group	0.954	0.918	0.888	0.880	0.880
	SMI group	0.883	0.783	0.726	0.637	0.637
	AP group	0.891	0.769	0.729	0.729	0.729
Cardiac mortality	control group	0.013	0.027	0.058	0.058	0.058
	SMI group	0.101	0.172	0.233	0.297	0.297
	AP group	0.078	0.167	0.195	0.195	0.195
Recurrence rate of MI	control group	0.020	0.062	0.062	0.090	0.090
	SMI group	0.067	0.013	0.177	0.177	0.177
	AP group	0.078	0.118	0.127	0.127	0.127

SMI: Silent Myocardial Ischemia; AP: Angina Pectoris

(n = 525)

Table III shows the cumulative survival rate, cardiac mortality and incidence of recurrent MI by actuarial method in each of the three groups.

Fig.1. Comparison of cumulative survival, cardiac mortality and MI recurrence curve in the 3 groups.

The survival curves, the curves of cumulative cardiac mortality and cumulative recurrence rate of MI in the three groups are shown in Fig. 1. A generalized Wilcoxon test for the statistical differences between the three groups confirmed that in the SMI and AP groups, survival rate was significantly lower, and cardiac mortality and incidence of recurrent MI were significantly higher than in the control group, and also that there was no statistically significant difference between the SMI and AP groups. Annual cardiac mortality and incidence of recurrent MI was 0.6% and 1% in the control group, 2.2% and 2% in the SMI group, and 3.3% and 1.4% in the AP group, respectively.

DISCUSSION

Patients who have ischemic findings without chest pain after recovery from acute MI are often observed in clinical practice. However, the exact prevalence and clinical significance of SMI in survivors after acute MI have not been clarified. The long-term prognoses of patients with SMI are also unclear. Although some studies have been reported, the results remain controversial. We concentrated on patients with SMI but no angina.

Prevalence: The prevalence of SMI in survivors after acute MI may be variable according to the definition of SMI and the methods used to detect it. Most reports concerning the prevalence of SMI after acute MI are based on a single exercise stress test or 24–48 hour ambulatory Holter recording. Gibson et al¹⁰ reported that silent ST-segment depression at exercise stress

test after acute MI was found in 43 of 190 patients (23%), but that only 47% of them were associated with Tl-201 redistribution. Opasich et al¹¹ studied 353 patients with acute MI using a bicycle ergometer and reported that 24% of them had silent ischemic ECG changes. We reviewed all exercise stress tests including rehabilitation practice during hospitalization, and diagnosed that SMI was present only when significant ischemic ST-segment changes were documented without symptoms, excluding ST-segment elevation in infarct-related leads and ST-segment depression in noninfarct-related leads without Tl-201 redistribution or significant coronary artery stenosis. According to our definition, SMI was found in 28% of all survivors after acute MI. However, 54% of them also had symptomatic ischemic episodes. Therefore, 11% of all survivors after acute MI had only silent ischemic episodes during their hospitalization of about 4 weeks.

Clinical features: Ouyang et al¹² evaluated 60 patients who had a positive response to treadmill exercise test. They reported that no significant difference was noted between patients with SMI and those with symptomatic ischemia with regard to multivessel coronary artery disease (74% vs. 73%) and totally occluded infarct-related artery (66% vs. 55%), and in the total exercise duration and rate-pressure product. The angiographic characteristics and exercise performance of patients with silent treadmill ischemia were similar to those with symptomatic ischemia. In our study, too, clinical features in patients with SMI were similar to those in patients with post-infarction angina; previous MI, non-Q wave MI and multivessel disease were more frequent in patients with SMI as well as in patients with post-infarction angina than in those without ischemic episodes. The incidence of angina prior to MI in patients with SMI was lower than that of patients with post-infarction angina.

Mechanism of SMI: The mechanism of SMI is still unclear. One possible mechanism is an alteration of pain perception,¹³⁻¹⁴ and another is a reduced extent of myocardial ischemia.¹⁵⁻¹⁶ If less myocardium is at jeopardy during SMI, it is difficult to understand the absence of differences in cardiac mortality and the incidence of cardiac events between patients with SMI and those with post-infarction angina. In our study, the incidence of angina pectoris prior to MI in patients with SMI was lower than that of patients with

post-infarction angina. A strongly stimulated "endogenous pain modulating system" such as might be produced by endogenous opiates might be a possible mechanism.¹⁷ However, further investigation is required.

Prognostic significance: The results of a number of studies into the prognostic significance of SMI in survivors after acute MI are still controversial. In a study from the Duke-Harvard Collaborative Coronary Artery Disease Data Bank,¹⁸ follow-up data indicated that 44 patients with SMI had a significantly better prognosis over a 7 year period than did 127 matched patients with symptomatic ischemia; annual mortality in the former was 2.7% compared with 5.4% in the latter ($p < 0.05$). Gibson et al¹⁹ evaluated 241 survivors after acute MI under 65 years of age using Tl-201 stress scintigraphy, and classified them into three groups; 99 patients without ischemic episodes, 99 patients with SMI and 43 patients with angina pectoris. Compared to patients without ischemic episodes, those with SMI or angina pectoris had more cardiac events during 27 months of follow-up. However, they reported that more patients with angina pectoris suffered from cardiac events than those with SMI ($p = .0036$). From these limited studies, it would appear that asymptomatic patients have a better prognosis than symptomatic ones. However, Theroux et al²⁰ performed treadmill exercise tests before hospital discharge in 210 patients who had been free of chest pain for at least four days and followed them for 1 year. Twenty-eight (65%) of 43 patients who had chest pain during the test reported angina, as compared with 60 of 167 (36%) who had no chest pain during the test ($p < 0.001$). The 1-year mortality was 2.1% in patients without ischemic ST changes during exercise and 27% in those with such changes ($p < 0.001$). The authors reported that angina in the presence of ST segment depression had no effect on these statistics. In a study by Opasich and his associates,¹¹ mortality and cardiac events during 29 months of follow-up in 85 patients with SMI were no different from those in 26 patients with symptomatic ischemia (3.8% vs. 5.9%), while the incidence of effort angina (81% vs. 25%) or unstable angina (35% vs. 12%) was greater in symptomatic patients than in patients with SMI. Thus, the investigators concluded that the occurrence of anginal pain associated with ST-segment depression during exercise test does not increase the prognostic risk.

In our study, cardiac mortality and incidence of recurrent MI in patients with SMI or post-infarction angina were significantly higher than in patients without ischemic episodes ($p < 0.0001$, $p < 0.05$). Furthermore, no statistically significant differences in the prognosis between patients with SMI and those with post-infarction angina were found. Annual cardiac mortality and incidence of MI recurrence were 0.6% and 1% in patients without ischemic episodes, 3.3% and 2% in patients with SMI, and 2.2% and 1.4% in patients with post-infarction angina, respectively. These results indicate that although overall prognosis in survivors after acute MI is good,²¹ long-term prognosis of patients with SMI is poor, as is as that of patients with post-infarction angina. These differing results among studies may be due in the main to uniformity of study populations and methods used for detecting patients with SMI. In some studies, totally asymptomatic patients, partially symptomatic patients or those who had not previously had MI were included in the study populations. Populations were selected by age in some studies. In addition, most studies used a single exercise test or 24–48 hours ambulatory Holter recording as a method for detecting patients with SMI. In our study, all patients underwent at least three exercise tests. Only patients with no cardiac symptoms during positive exercise tests wide hospitalized were considered as SMI. Further, we excluded patients who had received coronary artery bypass surgery before discharge and selected only medically treated patients to maintain uniformity of study population. As a result, there were no differences between patients with SMI and those with post-infarction angina in terms of clinical features and long-term prognosis after discharge.

We conclude that the incidence of cardiac events after discharge in medically treated survivors of acute MI was equally common in asymptomatic and symptomatic patients. To further improve long-term prognosis in survivors of acute MI, total ischemic burden, not only angina pectoris but also SMI, should be treated using currently available therapeutic modalities, including percutaneous transluminal coronary angioplasty and coronary artery bypass surgery.

REFERENCES

- HAZE K, HIRAMORI K: Post-infarction angina. *Kokyu to Junkan* 32: 913, 1984 (in Japanese)
- TAYLOR GJ, HUMPHRIES JO, MELLITS ED, PITT B, SCHULZE RA, GRIFFITH LSC, ACHUFF SC: Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. *Circulation* 62: 960, 1980
- SCHULTER EH, BULKEY BH: Early post-infarction angina. Ischemia at a distance and ischemia in the infarct zone. *N Engl J Med* 305: 1101, 1981
- COHN PF: The role of noninvasive cardiac testing after an uncomplicated myocardial infarction. *N Engl J Med* 309: 90, 1983
- COHN PF, BROWN EJ, COHN JK: Detection and management of coronary artery disease in the asymptomatic population. *Am Heart J* 108: 1064, 1984
- GIBSON RS, WATSON DD: Clinical applications of myocardial perfusion scintigraphy with thallium-201. In *Progress in cardiology*, ed by YU PN, GOODWIN JF, Lea and Febiger, Philadelphia, 1983, p 67
- CUTLER SJ, EDERER F: Maximum utilization of the life table method in analyzing survival. *J Chron Dis* 8: 699, 1958
- GEHAN E: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrika* 52: 203, 1958
- MIYAKE I, YAMAMOTO K: SPSS statistical package. Tokyo, Toyokeizaishinpo Co., 1984
- GIBSON RS, BELLER GA: Prevalence and clinical significance of exercise-induced painless ST segment depression two week post infarction. *Circulation* 70 (Suppl): II-60, 1984
- OPASICH C, COBELLI F, ASSANDRI J, CALSAMIGLIA G, FEBBO O, LAZOVERE MT, POZZOLI M, TRAMARIN R, TRAVERSI E, ARDISSINO D, SPECCHIA G: Incidence and prognostic significance of symptomatic and asymptomatic exercise-induced ischemia in patients with recent myocardial infarction. *Cardiology* 71: 284, 1984
- OUYANG P, SHAPIRO EP, CHANDRA NC, GOTTLIEB SH, CHEW PH, GOTTLIEB SO: An angiographic and functional comparison of patients with silent and symptomatic treadmill ischemia early after myocardial infarction. *Am J Cardiol* 59: 730, 1987
- DROSTE C, ROSKAMM H: Experimental pain measurement in patients with asymptomatic myocardial ischemia. *J Am Coll Cardiol* 1: 940, 1983
- MANNHEIMER C, CARLSSON CA, EMANUELSSON H, VEDIN A, WAAGSTEIN AF, WILHELMSSON C: The effects of transcutaneous electrical nerve stimulation in patients with severe angina pectoris. *Circulation* 71: 308, 1985
- 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
- RIGHETTI A, RATIB O, EI-HARAKE B, RUTISHAUSER W: Thallium-201 myocardial scintigraphy and electrographic findings in asymptomatic coronary patients during exercise testing. In *Silent Myocardial Ischemia*, ed by RUTISHAUSER W and ROSKAMM H, Springer-Verlag, Berlin, 1984, pp 79–83

17. DROSTE C, ROSKAMM H: Pain measurement and pain modification by naloxane in patients with asymptomatic myocardial ischemia. *In* Silent Myocardial Ischemia, ed by RUTISHAUSER W and ROSKAMM H, Springer-Verlag, Berlin, 1984, pp 14-23
18. COHN PF, HARRIS P, BARRY WH, ROSATI RA, ROSENBAUM P, WATERNAUX C: Prognostic importance of anginal symptoms in angiographically defined coronary artery disease. *Am J Cardiol* 47: 233, 1981
19. GIBSON RS, SAYRE SL, KAISER DL: The prevalence and prognostic significance of silent post-infarction ischemia. *Circulation* 74 (Suppl): II-58, 1986
20. THEROUX P, WATERS DD, HALPHEN C, DEBAISIEUX JC, MIZGALA HF: Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 301: 341, 1979
21. SAITO M, FUKAMI K, HAZE K, SUMIYOSHI T, HIRAMORI K, KASAGI F, HORIBE H: Long-term prognoses of patients with acute myocardial infarction: Is mortality and morbidity as low as the incidence of ischemic heart disease in Japan? *Am Heart J* 113: 891, 1987