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Clinical Implications of Silent Versus Symptomatic Exercise-Induced Myocardial Ischemia in Patients With Stable Coronary Disease

CRAIG R. NARINS, MD, WOJCIECH ZAREBA, MD, FACC, ARTHUR J. MOSS, MD, FACC, ROBERT E. GOLDSTEIN, MD, FACC,* W. JACKSON HALL, PHD

Rochester, New York and Bethesda, Maryland

Objectives. **This study was undertaken to better understand the functional and prognostic significance of silent relative to symptomatic ischemia.**

Background. **Previous studies have reached conflicting conclusions as to whether painless ischemia identified during noninvasive cardiac testing is related to a lesser extent of myocardial ischemia or a different prognosis than ischemia accompanied by angina, or both.**

Methods. **Nine hundred thirty-six clinically stable patients 1 to 6 months after an acute coronary event, either myocardial infarction or unstable angina, underwent ambulatory monitoring, exercise treadmill testing and stress thallium-201 scintigraphy. They were then followed up prospectively for a mean of 23 months for recurrent cardiac events (cardiac death, nonfatal myocardial infarction or unstable angina).**

Results. **Compared with patients with symptomatic ischemia during testing (n = 125), those with silent ischemia (n = 378) demonstrated less severe and extensive reversible defects on stress thallium scintigraphy (p = 0.0008), less functional impairment during treadmill testing manifested by longer exercise duration (640 ± 173 vs. 529 ± 190 s, p = 0.002) and longer time to ST segment depression (530 ± 215 vs. 419 ± 205 s, p = 0.0001) and less frequent ST segment depression during ambulatory monitoring (9% vs. 19%, p = 0.005). Patients with symptomatic ischemia had a significantly (p = 0.004) increased number of subsequent recurrent cardiac events (28.8%) versus those with silent (18.0%) or no (17.3%) ischemia. Adverse outcomes were especially concentrated in the subgroup with symptomatic ischemia and poor exercise tolerance. The difference in cardiac event rates between patients with silent versus symptomatic ischemia persisted after adjustment for baseline clinical characteristics by Cox regression analysis.**

Conclusions. **Patients with painless ischemia during exercise testing 1 to 6 months after recovery from a coronary event have less jeopardized ischemic myocardium and fewer recurrent cardiac events than patients with symptomatic ischemia.**

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Several important issues regarding the pathophysiologic mechanism and clinical significance of silent ischemia remain unresolved. First, it is unclear why myocardial ischemia tends to be predominantly symptomatic in some patients but silent in others. Proposed explanations have included intraindividual differences in somatic pain tolerance (1,2), differences in psychologic and cultural background (3–5) and differences in central modulation of incoming pain signals (6). Several investigators (7–13), using a variety of techniques to assess myocardial perfusion, have reached conflicting conclusions as to whether silent ischemia differs from symptomatic ischemia as a result of corresponding differences in the severity and extent of the underlying myocardial ischemic insult.

A second unresolved issue relates to the prognostic relevance of silent ischemia detected during noninvasive testing. Again, previous studies have led to contradictory conclusions as to whether future cardiac events are less (14,15), equally (9,11,16–20) or more (21,22) likely in patients who demonstrate silent as opposed to symptomatic ischemia during stress testing. However, despite the myriad of studies that have addressed the issue of prognosis, almost all have been retrospective in design, and many have lacked the statistical power necessary to detect a potential difference in cardiac event rates. With the current analysis of a prospectively designed study, we had the opportunity to investigate the mechanisms, clinical correlates and prognostic significance of silent and symptomatic myocardial ischemia in patients who had recently recovered from a documented coronary event.

Methods

Patient recruitment. The present study involved 936 patients from 12 centers in the United States, Canada and Israel who were participants in the Multicenter Study of Myocardial Ischemia (MSMI). Full details and major results of this study have been published previously (23) (see Appendix). Enroll-

From the Division of Cardiology and Departments of Medicine, Community and Preventative Medicine and Biostatistics, University of Rochester School of Medicine and Dentistry, Rochester, New York; and *Uniformed Services University of the Health Sciences, Bethesda, Maryland. This study was supported by Research Grant HL-38702 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

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Address for correspondence: Dr. Arthur J. Moss, Heart Research Follow-up Program, Box 653, University of Rochester Medical Center, Rochester, New York 14642.

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
MSMI = Multicenter Study of Myocardial Ischemia

ment began on July 1, 1988 and ended on May 31, 1991, with follow-up through November 30, 1991. All patients admitted to the coronary care unit with documented myocardial infarction or unstable angina were considered for enrollment. Confirmation of enzyme level elevation was necessary for the diagnosis of acute myocardial infarction. The diagnosis of unstable angina required an increase in the frequency or duration of typical anginal symptoms plus transient ischemic-type ST or T wave electrocardiographic (ECG) changes without enzyme level elevation indicative of infarction.

Patients were scheduled for enrollment into the study 1 to 6 months (mean [±SD] 2.7 ± 1.4) after their index coronary event, at a time when they were considered to be clinically stable. Patients were ineligible for enrollment for any of the following prespecified reasons: coronary artery bypass graft surgery after the index coronary event, coronary angioplasty performed <1 month before enrollment, major medical comorbidity, musculoskeletal disorders that would prevent the patient from performing the exercise test, use of cardiac glycosides, bundle branch block or atrial fibrillation, implanted pacemaker, participation in other investigational studies, psychological factors, or physician refusal.

Of the 2,096 patients who met the eligibility requirements, informed consent was obtained from 936. Nonenrollment of eligible patients was due to a variety of reasons, including patient or physician refusal, unanticipated interim medical problems, vacation, inability to contact eligible patients within the 6-month time window and miscellaneous logistic problems. At the time of enrollment, a complete medical history was recorded, and baseline noninvasive testing for myocardial ischemia was obtained, consisting of a 12-lead rest ECG, 24-h ambulatory ECG and exercise tolerance test with thallium-201 scintigraphy. Anti-ischemic medications were withheld only on the morning of the exercise test.

Data acquisition. Details for the performance and evaluation of the noninvasive ischemic tests were described in full in the primary publication (23). Treadmill exercise testing was performed using a slightly modified Bruce protocol beginning with a 3-min "stage ½," 1.7-mph at 5% grade. Exercise was terminated when one of the following end points was reached: target heart rate, severe fatigue, severe angina, hypotension or ventricular tachycardia. Patients who experienced angina during the exercise test were identified. At peak exercise, 2.5 mCi of thallium-201 was injected intravenously, and planar myocardial imaging was started within 5 min. Delayed imaging was performed 2.5 to 3 h later. Two-channel ambulatory ECGs were obtained on Marquette model 8500 series cassette tape recorders (Marquette Electronics, Inc.), with positive electrodes placed in the CM_3 and CM_5 positions. Coronary angiography was performed (as a nonprotocol procedure) in 786 patients (84%) before or during the study period. Angiographic results are reported in terms of the 75% coronary artery jeopardy score (24).

Core laboratories. Core laboratories were established to maximize consistency of interpretation and coding of the noninvasive ischemic tests used in the MSMI trial.

An ischemic-type ST segment abnormality on exercise testing was defined as horizontal or downsloping ST segment depression >0.1 mV below the preexercise ST segment position in any lead during or after exercise. Interpretation of each thallium-201 study was based on analysis of quantitative circumferential profiles with visual overreads, as previously described (25). The studies were categorized as normal or as having reversible *(ischemia)* or fixed defects *(scar)*. Four-level ordinal grading reflecting the extent and severity of reversible defects (none, mild, moderate, severe) was also performed (26). ST segment shifts or reversible defects temporally associated with angina were considered to reflect symptomatic ischemia, whereas those occurring without symptoms were deemed to show silent ischemia. An ischemic-type ST segment abnormality on the ambulatory ECG was defined as >0.1-mV ST segment depression below the baseline ST segment position that persisted for at least 1 min.

All 936 patients were subclassified into three groups on the basis of the combined results of the exercise ECG and thallium scintigram: 1) *symptomatic group* = angina during exercise and objective ischemia on either test (n = 125); 2) *silent group* = no angina during exercise but ischemia on one or both tests (n = 378); and 3) *no-ischemia group* = patients without ischemia on either test (n = 433) (Table 1).

Follow-up. Patients were contacted at 4-month intervals throughout the study to determine their clinical status, pharmacologic and interventional therapy and the occurrence of study end points. All patients were followed up for at least 6 months, to a maximum of 43 months. The mean duration of follow-up was 23 months.

Table 1. Results of Baseline Tests

Test	Ischemia [no. (%) of pts]			Total No. of Pts
	None	Silent	Symptomatic	
ETT	650 (71%)	190 (21%)	76 (8%)	916
STS	526 (59%)	270 (30%)	98 (11%)	894
ETT or STS	433 (46%)	378 (40%)	125 (13%)	936

ETT = exercise treadmill test; pts = patients; STS = stress thallium scintigraphy.

Table 2. Baseline Clinical Characteristics

	Ischemia on Noninvasive Testing			
	None (%) (n = 433)	Silent (%) (n = 378)	Symptomatic (%) (n = 125)	3-Tailed p Values*
Mean age (yr)	57.3	58.8	59.5	0.03
Female	31	18	18	< 0.001
Event type				
Q wave MI	42	49	35	0.01
Non-Q wave MI	26	25	26	
Unstable angina	32	26	39	0.01
Thrombolytic therapy for index event	32	34	19	< 0.01
CHF at index event	16	17	15	
Previous MI	14	22	30	< 0.001
Angina in past mo	31	25	54	< 0.001
Diabetes (taking insulin)	5	6	7	
Hypertension	41	40	46	
Smoking at baseline	15	12	12	
PTCA during index hospital period	39	28	27	< 0.01
Beta-blocker therapy	47	54	56	
Calcium channel blocker therapy	60	48	63	0.001

*Only significant p values (<0.05) are shown. CHF = congestive heart failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

End points. The prespecified end points were death due to cardiac cause, nonfatal myocardial infarction and unstable angina occurring on or before November 30, 1991. The criteria for diagnosing nonfatal myocardial infarction were the same as those applied to the index coronary event. The diagnosis of *unstable angina* required hospital admission to a coronary care unit for the increase in the frequency or duration of typical anginal symptoms and either ischemic-type ST segment or T wave ECG changes or an increase in antianginal therapy, or both, but without enzyme level elevation indicative of infarction. *Cardiac events* were enumerated as follows: 1) the primary end point (cardiac death, nonfatal infarction myocardial infarction or unstable angina, whichever occurred first); 2) a restricted secondary end point (myocardial infarction or cardiac death); and 3) cardiac death.

Statistical analysis. Descriptive statistics are expressed in terms of mean value ± SD. All results are reported with the use of two-tailed p values. Sample size calculations for the MSMI trial were previously described (23). Baseline clinical characteristics and ischemic test variables of patients with silent and symptomatic ischemia were compared using chi-square tests (for dichotomous variables) or *t* and F tests (for continuous variables). Multivariate models using type of ischemia (silent or symptomatic) as the outcome variable were created to test for independence of univariate relations between covariates and silent and symptomatic ischemia (SAS statistical software) (27). The first model used the 12 preselected clinical and 2 medication covariates listed in Table 2. A backward selection approach was used by which variables were omitted one at a time until all variables had a p value <0.10. Using the same approach, a second model was created for the exercise and thallium test variables shown in Table 3.

The effects of silent, symptomatic and no ischemia on time to end point were examined graphically by Kaplan-Meier curves (28); the log-rank statistic was used when comparing the two curves. Multivariate end-point analysis was performed using the Cox proportional hazards regression model (29) for cardiac-related end points (SAS statistical software). Patients who died of noncardiac causes were censored at the time of death. A backward selection procedure was used to identify important risk predictors for the time to end point from the 12 preselected clinical covariates shown in Table 2, with geographic region (North America or Israel) entered as a stratification factor. A p value ≥0.10 was used for removing a variable in constructing the basic clinical model. The contribution of type of ischemia (silent or symptomatic) was then evaluated. Only "nominal" confidence levels and p values are reported for further subgroup analysis.

Results

Clinical characteristics. Exercise treadmill testing and thallium scintigraphy were performed at enrollment an average of 2.7 ± 1.4 months after the acute index coronary event. Of the 936 patients who underwent testing, 503 demonstrated objective evidence of ischemia on at least one of these two tests (Table 1). Ischemia was clinically silent in 378 patients (75%) and was accompanied by angina in 125 (25%).

Table 3. Diagnostic Test Results

	Ischemia on Noninvasive Testing			p Value	
	None (n = 433)	Silent (n = 378)	Symptomatic (n = 125)	3-Tailed	Silent vs. Symptomatic
ETT					
Exercise duration (s)	616 ± 198	640 ± 173	529 ± 190	< 0.001	< 0.001
Time to 1-mm ST segment depression (s)	NA	530 ± 215	420 ± 205	NA	< 0.001
STS					
Ischemia				< 0.001	0.04
None (%)	100	30	21		
Mild (%)	0	19	16		
Moderate (%)	0	21	21		
Severe (%)	0	30	42		
Scar (%)	41	55	57	< 0.001	NS*
Ischemia on ambulatory ECG (%)	4	9	19	< 0.001	< 0.005
Mean 75% coronary angiographic jeopardy score	3.1	3.8	4.2	< 0.001	< 0.05

*$p > 0.05$. Data presented are mean value ± SD, unless otherwise indicated. ECG = electrocardiogram; NA = not applicable; other abbreviations as in Table 1.

Clinical characteristics of patients with no ischemia, silent ischemia and symptomatic ischemia are shown in Table 2. Patients in the silent ischemia group were more likely ($p = 0.01$) to have experienced a Q wave myocardial infarction as their index event (49% vs. 35%) and to have received thrombolytic therapy (34% vs. 19%) than patients in the symptomatic ischemia group. Patients in the silent ischemia group were less likely ($p = 0.01$) to have unstable angina as their index event (26% vs. 39%) than the symptomatic patients. At baseline evaluation, patients with silent ischemia were less likely ($p < 0.001$) to have experienced angina in the preceding month (25% vs. 54%) and were less likely ($p < 0.001$) to have been prescribed calcium channel blocking agents (48 vs. 63%). The silent and symptomatic groups were similar with respect to age, gender, diabetes, smoking, hypertension, history of myocardial infarction before the index coronary event or incidence of coronary angioplasty during the index hospital period (Table 2). Multivariate logistic regression modeling confirmed that, independent of other clinical characteristics, patients who experienced silent ischemia during testing were less likely to have experienced clinical angina in the preceding month ($p = 0.001$), less likely to have been prescribed calcium channel blockers ($p = 0.03$) and more likely to have received thrombolytic therapy during the index hospital period than patients with symptomatic ischemia ($p = 0.002$).

Relative to those with no ischemia on exercise testing, patients with silent ischemia were older and more often male, more often had a previous myocardial infarction and less often underwent coronary angioplasty during the index hospital period or recent clinical angina (Table 2).

Extent of myocardial ischemia. In an attempt to assess differences in severity and extent of ischemia between patients with silent and symptomatic ischemia, diagnostic test data were examined in detail (Table 3). Patients who experienced silent ischemia had a longer time to 1-mm ST segment depression during exercise testing (530 ± 215 vs. 420 ± 205 s, $p = 0.001$), greater total exercise duration (640 ± 173 vs. 529 ± 190 s, $p < 0.001$), less extensive reversible defects on thallium scintigraphy (51% vs. 63% with moderate or severe scintigraphic ischemia, $p = 0.04$) and a lower likelihood of demonstrating 1-mm ST segment depression during ambulatory electrocardiography (9% vs. 19%, $p = 0.005$) than patients with symptomatic ischemia. Achievement of target heart rate was the reason for terminating the exercise test more often in patients with silent ischemia (14% vs. 6%, $p = 0.03$).

Multivariate logistic regression analysis was performed utilizing the thallium and exercise test variables shown in Table 3. Silent myocardial ischemia remained independently related to less severe/extensive ischemia on thallium scintigraphy ($p = 0.0008$), longer time to 1-mm ST segment depression ($p = 0.002$) and longer total exercise duration ($p = 0.0001$).

End points. Kaplan-Meier analysis was performed to determine the univariate relation between silent, symptomatic and no exercise-induced ischemia and time to the predefined cardiac end points. Patients who developed symptomatic myocardial ischemia during baseline testing were significantly more likely to experience a primary end point (cardiac death, nonfatal myocardial infarction or unstable angina) during the 23-month follow-up period than patients who developed silent or no ischemia ($p = 0.004$) (Fig. 1). The incidence of primary end points did not differ significantly between patients with silent ischemia and no inducible ischemia.

The incidence of restricted end points (nonfatal infarction or cardiac death) did not differ significantly as a function of symptoms during testing (Fig. 2). However, cardiac death by itself was significantly more common in patients with symptomatic ischemia than those with silent or no ischemia ($p = 0.001$) (Fig. 3). Although revascularization procedures were

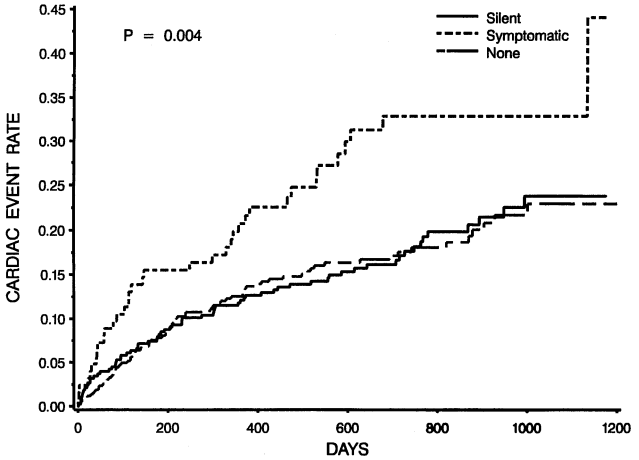

Figure 1. Kaplan-Meier analysis for time to recurrent cardiac event (cardiac death, nonfatal myocardial infarction, unstable angina) according to presence and type of ischemia (symptomatic, silent or none).

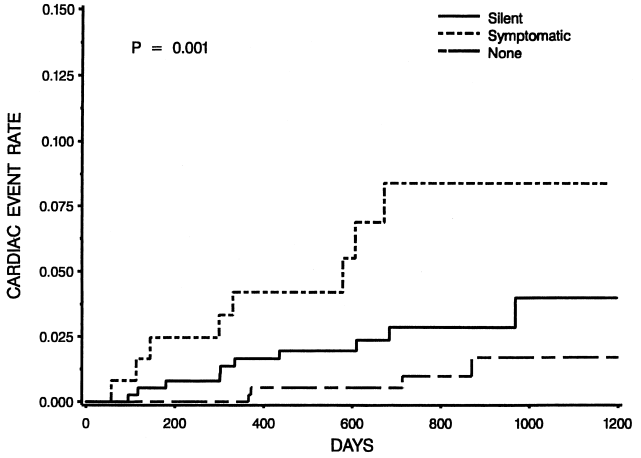

Figure 3. Kaplan-Meier analysis for time to cardiac death according to type of ischemia (symptomatic, silent or none).

not a prespecified study end point, patients in the silent ischemia group were significantly less likely than those in the symptomatic group to undergo coronary angioplasty or bypass surgery during the follow-up period (21% vs. 30%, p = 0.04).

Cox regression analysis was performed to test whether the presence or absence of symptoms during baseline testing served as an independent predictor of prognosis apart from that of other baseline clinical variables listed in Table 1. Clinical variables independently associated ($p < 0.10$) with the occurrence of a primary end-point included angina in the month preceding baseline testing, diabetes, hypertension, previous myocardial infarction and coronary angioplasty performed during the index hospital period but before baseline testing (Table 4). After adjusting for these covariates, the additional presence of silent ischemia during baseline cardiac testing did not make a significant independent contribution to the model (p = 0.82), whereas symptomatic ischemia remained a significant independent predictor of recurrent cardiac events (p = 0.036). Likewise, when Cox analysis was restricted to consider only cardiac death, the presence of symptomatic ischemia during baseline testing emerged as a strong independent predictor of cardiac mortality (Table 4). Further analysis incorporating variables related to exercise time and time to ST segment depression during treadmill testing revealed that the increased risk associated with symptomatic ischemia appeared to be concentrated in the subgroup with a short (<6 min) exercise duration. In patients with symptomatic ischemia and exercise duration <6 min, the hazard ratio was 1.9 ("nominal"

Figure 2. Kaplan-Meier analysis for time to restricted secondary cardiac events (cardiac death or nonfatal myocardial infarction) according to presence and type of ischemia (symptomatic, silent or none).

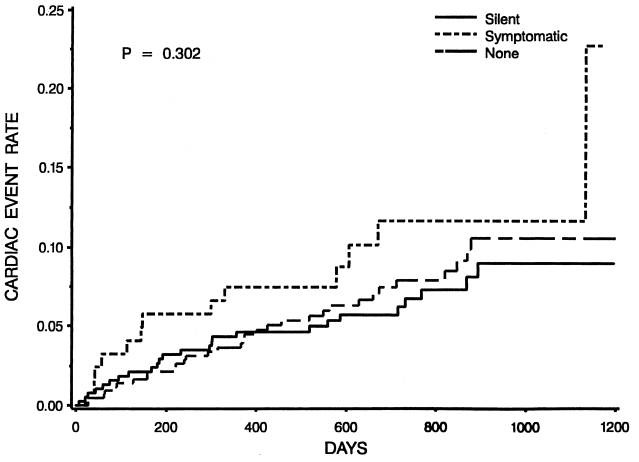

Table 4. Clinical Variables Associated With Cardiac End Points*

End Point	HR (95% CI)	p Value
Primary		
Angina in previous mo	1.76 (1.30–2.40)	< 0.001
Diabetes	2.29 (1.41–3.71)	0.001
Hypertension	1.39 (1.03–1.87)	< 0.03
Previous MI	1.38 (0.98–1.93)	0.06
PTCA during index hospital period	1.39 (1.01–1.91)	0.05
Ischemia		
Silent	1.04 (0.74–1.45)	0.82
Symptomatic	1.55 (1.03–2.33)	0.04
Cardiac death		
Older age†	1.48 (0.95–2.29)	0.08
Prior MI	2.23 (0.94–5.26)	0.07
Ischemia		
Silent	2.35 (0.73–7.55)	0.15
Symptomatic	5.06 (1.49–17.1)	0.009

*Final Cox proportional hazards model, including all significant clinical predictors for the primary end point (cardiac death, nonfatal myocardial infarction [MI], unstable angina) and type of ischemia during testing (silent or symptomatic). †Per decades away from age 60 years; thus, the risk of death is estimated to be 48% higher in patients 70 years old than in those 60 years old. CI = confidence interval; HR = hazard ratio; PTCA = percutaneous transluminal coronary angioplasty.

95% confidence interval [CI] 1.2 to 2.8, "nominal" p = 0.003) for the primary end point and 3.8 (nominal 95% CI 1.5 to 9.4, nominal p = 0.005) for cardiac death, whereas no significant increase in risk remained apparent in other groups regardless of occurrence of symptoms.

Discussion

The purpose of the present study was twofold: 1) to determine whether the presence or absence of exercise-induced ischemic symptoms is related to the severity and extent of the underlying myocardial ischemia; and 2) to determine the prognostic importance of silent myocardial ischemia relative to symptomatic ischemia in a large cohort of prospectively evaluated patients with clinically stable coronary disease. Our results demonstrate that patients who experience silent myocardial ischemia during noninvasive testing have significantly smaller amounts of jeopardized ischemic myocardium, as determined by thallium scintigraphy, than patients who develop symptomatic ischemia. Likewise, ECG signs of ischemia appeared later in the exercise period, and exercise duration was greater, in the silent ischemia group. Patients with silent ischemia were also significantly less likely to experience a recurrent spontaneous cardiac event. Cox regression analysis demonstrated that this difference in cardiac event rates between patients with silent ischemia and symptomatic ischemia persisted even after adjustment for other baseline clinical characteristics associated with poor outcome. The combination of symptomatic ischemia and poor exercise tolerance was a very powerful predictor of adverse events.

Pathophysiologic mechanisms of silent ischemia. From a pathophysiologic standpoint, it remains unclear precisely why some patients experience symptoms in conjunction with objective evidence of ischemia during stress testing, whereas other patients (or the same patient at other times) manifest ischemia that is clinically silent. Previous studies have suggested that patients who develop silent ischemia during diagnostic testing may differ from those who develop symptoms in terms of psychologic and personality traits (3,4), ethnocultural factors (5), general ability to tolerate painful stimuli (1,2) and ability to centrally modulate incoming pain signals (6).

Several investigators (7–13), using exercise ECG, radionuclide angiographic and thallium scintigraphic variables, have attempted to determine whether the development of anginal symptoms is related to the extent of underlying myocardial ischemia. Bonow et al. (16), in a study that included 131 patients with angiographically documented coronary disease, found that patients with silent ischemia during exercise radionuclide angiography were significantly less likely to demonstrate a decrease in left ventricular ejection fraction with exercise than patients who developed angina during testing. Likewise, Travin et al. (11), using a case-control approach, found that patients with silent ischemia on exercise thallium scintigraphy had less frequent and severe ischemic ST depression and less extensive and severe defects on thallium imaging. However, these results are in disagreement with studies reporting no significant differences in severity or extent of thallium scintigraphic changes between patients who experienced silent as opposed to symptomatic ischemia (8–10).

Several potential explanations exist for the discrepant findings of these earlier reports. As elegantly demonstrated by Klein et al. (13), previous studies have been conducted using widely different patient populations, ranging from clinically asymptomatic subjects to only those with evidence of a marked ischemic response to exercise. Previous studies have also used differing definitions of silent ischemia, and few have used multivariate analysis. Within our study cohort, which consisted uniformly of clinically stable patients with known coronary disease, silent myocardial ischemia was independently associated with thallium scintigraphic and exercise ECG findings suggestive of smaller amounts of jeopardized ischemic myocardium. This association supports the concept that the symptomatic appreciation of pain reflects a greater extent and severity of the induced myocardial ischemia than myocardial ischemia that does not yield symptoms.

Silent ischemia and prognosis. The prognostic importance of silent ischemia relative to symptomatic ischemia during noninvasive testing also remains controversial. Cole and Ellestad (14), in a retrospective analysis of 1,402 patients who had ECG evidence of ischemia during treadmill testing, found that coronary events (cardiac death, myocardial infarction or progression of angina) were two times more frequent in patients with symptomatic ischemia as opposed to silent ischemia. Mark et al. (15), in reviewing the 5-year outcome of 842 consecutive patients in the Duke Cardiovascular Database who had angiographically documented coronary disease and an abnormal exercise test result, found that patients with silent ischemia during exercise had significantly better overall survival and infarct-free survival rates. However, several investigators (9,11,16–20) failed to discover any prognostic differences in patients with ischemic responses to exercise on the basis of the presence or absence of coexistent angina. Callahan et al. (19), in the largest of the negative studies, found no mortality difference at 2 years based on development of angina during exercise in a retrospective study of 1,773 veterans referred for treadmill testing. Rounding out the controversy, two retrospective studies (21,22) describe an increased risk of subsequent cardiac events in patients with silent ischemia as opposed to symptomatic ischemia during cardiac stress testing.

These widely discordant findings most likely result from factors related to study design. Most important, few of the previous studies focusing on prognosis have used prospective follow-up. In addition, many of the prognostic studies have lacked adequate statistical power to detect potential differences between patients with silent and symptomatic ischemia. Previous studies have included patient groups at differing risks for cardiac events and have used a variety of end points (e.g., death from any cause; spontaneous cardiac end points only; spontaneous cardiac end points plus revascularization). Definitions of silent ischemia have also varied from study to study. Furthermore, most investigations have not included multivar-

iate or Cox analysis to assess the independence of the observed relation between silent myocardial ischemia and outcome.

With the current study, we had the opportunity to overcome many of these methodologic problems. The study was prospective in design; the cohort studied was large, with well defined entry and exclusion criteria; end point analysis was based on the occurrence of carefully documented spontaneous cardiac events; and multivariate and Cox regression analysis were used.

The primary results of the MSMI trial (23) demonstrated that detection of ischemia by noninvasive testing in a large group of clinically stable patients 1 to 6 months after recovery from an acute coronary event had no significant independent prognostic value in predicting subsequent coronary events. Increased risk for primary cardiac events was evident only in small, selected patient subsets (exercise-induced ST segment depression with limited exercise duration or reversible thallium defect plus increased lung uptake). Although the present substudy serves to identify an association between symptomatic ischemia and recurrent events, it does not alter the general conclusions reached in the primary study regarding the overall utility of noninvasive testing.

The lack of a significant difference in the incidence of recurrent coronary events between patients with silent ischemia and those with no inducible ischemia during noninvasive testing is contrary to the findings of several previous investigations (30,31) performed in the immediate postinfarction period. It should be reemphasized that the current study was carried out in a cohort of patients who had clinically stable coronary disease (low to moderate risk) at the time of enrollment, several months after the acute index coronary event. Our results do not necessarily imply that aggressive therapy to eliminate silent ischemia in higher risk patient populations may not carry some prognostic benefit. However, they do suggest that treatment of silent ischemia in lower risk populations has less potential for benefit (32).

Conclusions. We found that patients with stable coronary disease who experienced silent myocardial ischemia during noninvasive stress testing 1 to 6 months after a coronary event had less severe and extensive myocardial ischemia than those with symptomatic ischemia. Relative to those who experienced symptomatic ischemia, patients who developed silent ischemia also had a significantly decreased risk of subsequent cardiac events and cardiac death. Cox regression analysis demonstrated that the presence or absence of angina during testing was related to outcome in an independent manner. Hence, in clinically stable patients with exercise-induced ischemia, it appears that the additional presence of anginal symptoms during exercise tends to identify those with a greater amount of jeopardized myocardium who are at increased risk for an adverse outcome.

We are indebted to Moonseong Heo, PhD and Patricia Severski for assistance with the statistical analysis.

Appendix

Executive Committee for Substudy of the Multicenter Study of Myocardial Ischemia

A. J. Moss, MD, W. J. Hall, MD, R. Raubertas, MD, M. W. Brown, MD, **University of Rochester, Rochester, New York**; R. E. Goldstein, **Uniformed Services University of the Health Sciences, Bethesda, Maryland**; J. T. Bigger, Jr., MD, J. L. Fleiss, MD, J. Coromilas, MD, **College of Physicians and Surgeons, Columbia University, New York, New York**; H. Greenberg, MD, R. Case, MD, E. M. Dwyer, MD, **Roosevelt-St. Lukes Hospital, New York, New York**; M. Bodenheimer, MD, **Long Island Jewish Hospital, New Hyde Park, New York**; R. J. Krone, MD, R. Kleiger, MD, **Jewish Hospital, Saint Louis, Missouri**; F. I. Marcus, MD, **University of Arizona Health Science Center, Tucson, Arizona**; F. J. Th. Wackers, MD, **Yale University School of Medicine, New Haven, Connecticut**; J. Benhorin, MD, S. Stern, MD, D. Tzivoni, MD, **Bikur Cholim Hospital, Jerusalem, Israel**; J. A. Gillespie, **Highland Hospital, Rochester, New York**; J. J. Gregory, MD, **Overlook Hospital, Summit, New Jersey**; E. Lichstein, MD, **Maimonides Medical Center, Brooklyn, New York**; J. O. Parker, **Kingston General Hospital, Kingston, Ontario, Canada**; L. Van Voorhees, MD, **Washington Hospital Center, Washington D.C.**

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