

## Silent Myocardial Ischemia During Ambulatory Electrocardiographic Monitoring in Patients With Effort Angina

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The frequency and characteristics of asymptomatic ischemic attacks were investigated in 39 patients with effort angina. During 24 hour Holter monitoring, 32 of the 39 patients displayed one or more episodes of ischemic ST depression. Eight patients had attacks ( $n = 25$ ) always accompanied by pain; 9 patients had only asymptomatic ischemic episodes ( $n = 40$ ) and 15 patients had both symptomatic ( $n = 29$ ) and asymptomatic attacks ( $n = 76$ ). In the 15 patients exhibiting both symptomatic and asymptomatic attacks, mean duration of symptomatic episodes was longer (probability [ $p$ ]  $< 0.001$ ) and mean maximal ST depression was greater ( $p < 0.001$ ). When patients exhibiting only symptomatic episodes were compared with those exhibiting only asymptomatic attacks, differences were not significant. All symptomatic and asymptomatic attacks during Holter monitoring were

correlated with the results of stress testing: patients experiencing a delayed response to pain after the onset of ST ischemic depression during stress testing had a higher ratio of asymptomatic to symptomatic attacks during Holter monitoring compared with those patients reporting pain before or at the moment of the appearance of ischemic electrocardiographic features during stress testing.

It is concluded that: 1) asymptomatic episodes of ischemia are more frequent than symptomatic episodes in patients with effort angina; 2) in the same patient, the severity of ischemia is generally a fundamental factor in determining the presence or absence of pain during an ischemic attack; and 3) differences among patients with respect to predominance of symptomatic or asymptomatic attacks probably depend on individual factors.

Anginal chest pain is the main symptom of episodes of acute myocardial ischemia. However, episodes of ischemia have been reported without pain, even without any other subjective symptoms, in patients with spontaneous angina (1-5) and, more recently, in patients with effort angina (6-11). Electrocardiography is the most readily available method to detect these attacks because it demonstrates transitory ST changes that, in the absence of pain or any other subjective symptom, can be considered objective manifestations of ischemia. This has been demonstrated by the presence of temporally related coronary spasm (12-16), reduced thallium-201 uptake (17,18), reduction of coronary sinus oxygen saturation (19) and impairment of ventricular function (20-22). These ST changes, therefore, can be viewed as an objective manifestation of ischemic attacks. Using Holter monitoring, we tested a group of patients with effort angina in order to investigate the frequency and characteristics of

asymptomatic ischemia and consider possible explanations for the absence of symptoms during these attacks.

### Methods

**Criteria for admission to the study.** Admission criteria to the study were as follows: 1) a history of chest pain provoked by exercise or other factors that are known to increase myocardial metabolic demand; 2) an exercise stress test definitely positive for ischemia, performed at least twice during the 3 months preceding the study period; 3) a normal rest electrocardiogram or a tracing that was abnormal only for findings of prior myocardial infarction; 4) absence of conduction disturbances, ventricular hypertrophy, valvular lesions, cardiomyopathy or electrolyte disorders; and 5) absence of any pharmacologic treatment known to influence patient response to exercise stress testing during the week before the study period. Only nitrates were allowed until 12 hours before the study began.

**Study patients.** After obtaining informed consent, we studied 39 patients (35 men, 4 women) selected according to the preceding criteria. Average age was 55 years (range 32 to 68). The onset of angina varied from 2 months to 6 years before the study; 16 patients had had a prior myocardial infarction and 3 were diabetic. Cor-

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onary arteriography had been performed on 31 patients during the 6 months before the study with the following results: 6 patients had greater than 75% stenosis of at least one vessel, 11 patients of two vessels and 14 patients of three vessels.

**Procedure.** Patients underwent 24 hour Holter monitoring. A bicycle stress test was performed the day after monitoring. The criterion of ischemia in both investigations was at least 1.5 mm ST segment dislocation persisting for 0.08 second (23,24).

**Holter monitoring.** After appropriate skin preparation, pre-gelled disposable electrodes were applied utilizing a bipolar lead system. A precordial lead (modified V<sub>5</sub>) and a diaphragmatic lead (modified lead III) were recorded utilizing a two channel 24 hour tape recorder (Del Mar Avionics model, 445). ST changes induced by position (prone, supine, left side, right side, sitting and standing) or hyperventilation were investigated. Patients were instructed to perform their usual daily activities during monitoring. They were asked to keep a detailed diary of all activities and symptoms and were repeatedly told of the importance of entering the exact time of their activities.

Ambulatory electrocardiographic tapes were evaluated by a dynamic electrocardioscanner (Del Mar Avionics model, 660). Electrocardiographic strips showing episodes of ST segment dislocation were printed on standard electrocardiographic paper. Strips recorded immediately before and after such episodes, and when patients noted symptoms or activity changes in their diaries, were also printed. All episodes of ischemic ST segment dislocation were noted and the magnitude and duration of maximal dislocation were then tabulated. These episodes were considered evidence of symptomatic ischemia in patients who had noted related symptoms in their diaries; the episodes were considered asymptomatic when no such correlation existed.

**Stress testing.** During a fasting state, a graded bicycle exercise test (initial load 30 watts increased by 20 watts every 2 minutes) was performed. The same bipolar leads used during Holter monitoring were employed. Termination criteria of exercise testing were those established by the International Society of Cardiology (25) with one exception: stress testing was not discontinued with the appearance of ST segment dislocation indicative of ischemia when it occurred without pain. The patient continued the test with the same load until occurrence of pain. However, exercise was always discontinued 3 minutes after the appearance of electrocardiographic features of ischemia or when ST segment dislocation reached 3 mm. Patient observation was prolonged from the end of exercise until the end of the recovery period. However, observation from the end of exercise testing was never shorter than 10 minutes.

The following data gathered from stress testing were then considered: 1) heart rate at the moment that electrocardiographic patterns of ischemia appeared and at the moment of pain onset; and 2) temporal relation between appearance of electrocardiographic patterns of ischemia and appearance of pain.

**Data analysis.** Results of Holter monitoring and stress testing were correlated. The results of stress testing were also correlated with some factors previously hypothesized to influence anginal pain, that is, age of patients, presence or absence of diabetes and anatomic conditions as demonstrated by selective coronary arteriograms. Data were expressed as the mean  $\pm$  standard deviation. Statistical significance of differences between groups of patients

were examined by analysis of variance. Elaboration of data expressed as percents was performed using the chi-square method.

## Results

**Twenty-four hour Holter monitoring.** Thirty-two of the 39 patients displayed one or more episodes of ischemic ST depression for a total of 170 episodes (Table 1). No ST segment elevation episodes were detected. Eight patients had attacks always accompanied by angina ( $n = 25$ ); 9 patients had only ischemic asymptomatic episodes ( $n = 40$ ) and 15 patients had both symptomatic ( $n = 29$ ) and asymptomatic attacks ( $n = 76$ ). In all, of 170 ischemic registered episodes, 54 were symptomatic and 116 were asymptomatic; the ratio between symptomatic and asymptomatic episodes was 1:2.15.

Forty-nine of 54 symptomatic attacks occurred during physical activities that the patient had learned to be angina-evoking; the remaining 5 occurred during physical activities that the patient had considered well tolerated. Twelve of 116 asymptomatic attacks occurred at rest, 11 during sleep and 93 during some daily physical activity (Fig. 1).

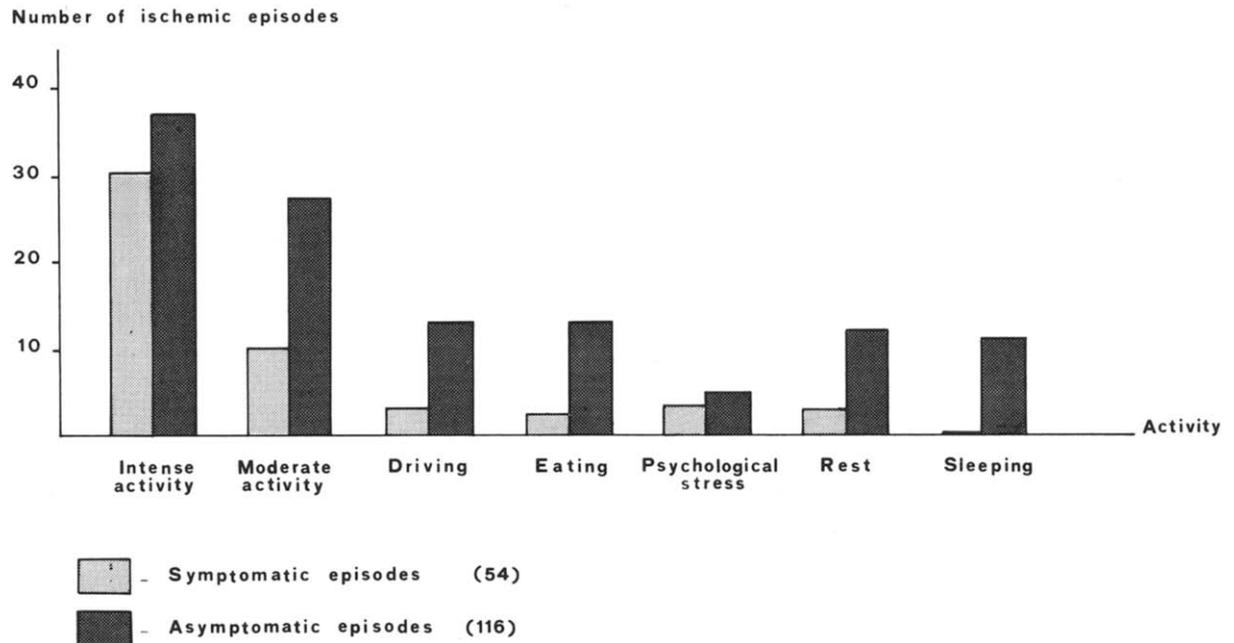
**Mean heart rate** at the moment of the electrocardiographic appearance of ischemia was  $91.4 \pm 14.3$  beats/min and at the moment of the appearance of angina was  $100 \pm 17.7$  beats/min.

**The mean duration of all 54 symptomatic episodes** was  $7 \pm 5$  minutes and 42 seconds and that of all 116 asymptomatic episodes was 4 minutes and 12 seconds  $\pm 2$  minutes and 30 seconds (probability [ $p$ ]  $< 0.001$ ). The mean duration in patients exhibiting only symptomatic episodes was 5 minutes and 12 seconds  $\pm 3$  minutes and 50 seconds; in patients exhibiting only asymptomatic attacks it was 4 minutes and 33 seconds  $\pm 3$  minutes and 0 second. The difference is not significant. In the 15 patients exhibiting both symptomatic and asymptomatic episodes during monitoring, the mean duration of symptomatic episodes was 8 minutes and 36 seconds  $\pm 6$  minutes and 35 seconds and the mean duration of asymptomatic attacks was 4 minutes and 0.06 second  $\pm 2$  minutes and 15 seconds ( $p < 0.001$ ) (Table 2).

**The mean maximal ST depression** was  $3.3 \pm 1.7$  mm in all 54 symptomatic attacks and  $2.5 \pm 1$  mm in all 116

**Table 1.** Ischemic Episodes During Holter Monitoring (39 patients)

Patients (no.)	Total	Episodes (no.)	
		Symptomatic	Asymptomatic
7	0	—	—
8	25	25	—
15	105	29	76
9	40	—	40
Total	170	54	116



asymptomatic episodes ( $p < 0.001$ ). The mean magnitude of symptomatic episodes among those patients exhibiting only such episodes was  $2.3 \pm 0.9$  mm; it was  $2.7 \pm 1.2$  mm among those patients exhibiting only asymptomatic attacks. This difference is also not significant. In the 15 patients exhibiting both symptomatic and asymptomatic episodes during Holter monitoring, the mean maximal ST depression of symptomatic episodes was  $4.3 \pm 1.7$  mm and the mean maximal ST depression of asymptomatic attacks was  $2.4 \pm 1.0$  mm ( $p < 0.001$ ) (Table 2).

**Stress testing.** Stress testing was positive for ischemia in all patients. The mean heart rate at the moment of the appearance of ST ischemic alterations was  $113 \pm 14$  beats/min; it was  $123 \pm 12$  beats/min at the moment that pain appeared. On the basis of the temporal relation between the onset of angina and the appearance of electrocardiographic changes during stress testing, we identified three different situations and grouped the patients accordingly: 1) prece-

**Figure 1.** Activity at the onset of ischemic attacks. Intense physical activity—jogging, playing tennis, bicycling, walking upstairs and sexual activity. Moderate physical activity—slow walking, light housework and light hand labor.

dence of pain or simultaneous appearance of pain and ST segment ischemic alterations (11 patients, group 1); 2) onset of pain with a delay varying from 10 to 60 seconds after the appearance of ischemic alterations (10 patients, group 2); and 3) onset of pain with a delay of more than 60 seconds after the appearance of ischemic alterations (18 patients, group 3).

**Comparison between results of Holter monitoring and stress testing.** The mean heart rate at the moment of the appearance of ST ischemic alterations was lower during Holter monitoring than during stress testing ( $p < 0.001$ ) (Table 3). The same was observed for the mean heart rate at the moment of the onset of angina ( $p < 0.001$ ).

**Table 2.** 24 Hour Holter Monitoring: Duration of Ischemic Attacks and Magnitude of Maximal ST Depression

	Patients (no.)	Episodes (no.)	Type of Episodes	Duration of Episodes	Mean Magnitude of Maximal ST Depression
All patients	32	54	Symptomatic	$7' \pm 5'42''$	$3.3 \pm 1.7$ mm
		116	Asymptomatic	$4'12'' \pm 2'30''$	$2.5 \pm 1$ mm
		Total 170		( $p < 0.001$ )	( $p < 0.001$ )
Patients who experienced only symptomatic or asymptomatic episodes	8 9	25	Symptomatic	$5'12'' \pm 3'50''$	$2.3 \pm 0.9$ mm
		40	Asymptomatic	$4'33'' \pm 3'$	$2.7 \pm 1.2$ mm
		Total 65		( $p > 0.05$ )	( $p > 0.05$ )
Patients who exhibited both symptomatic and asymptomatic episodes	15	29	Symptomatic	$8'36'' \pm 6'35''$	$4.3 \pm 1.7$ mm
		76	Asymptomatic	$4'06'' \pm 2'15''$	$2.4 \pm 1.0$ mm
		Total 105		( $p < 0.001$ )	( $p < 0.001$ )

**Table 3.** Heart Rate (beats/min) at Onset of Ischemic Events\*

	Holter Monitoring	Stress Testing
ST depression onset	91.4 ± 14.3	112.8 ± 14
Pain onset	100 ± 17.8	123.1 ± 12.5

\*p < 0.001.  
Data are mean ± standard deviation.

The ratio between asymptomatic and symptomatic episodes of ischemia as detected by Holter monitoring was not the same in the three groups of patients identified during stress testing (Table 4): 1) 11 patients in group 1 had 44 ischemic episodes during Holter monitoring; 27 of these episodes were symptomatic and 17 asymptomatic (ratio 1:0.62); 2) 8 of 10 patients in group 2 experienced 23 ischemic episodes during Holter monitoring; 11 of these were symptomatic and 12 asymptomatic (ratio 1:1.09); and 3) 13 of 18 patients in group 3 had 103 ischemic attacks during ambulatory monitoring; 16 symptomatic and 87 asymptomatic episodes (ratio 1:5.43).

Correlations between results of stress testing and conditions that might influence the presence or absence of anginal pain were also sought; thus, patients with the largest interval between the appearance of ST ischemic alterations and the onset of angina had a significantly greater incidence of prior myocardial infarction (p < 0.05). There were no statistical correlations between delay of angina onset and the age of patients, or between the delay of onset of pain and anatomic condition of the coronary arteries (Fig. 2). The limited number of diabetic patients did not allow statistical elaboration.

### Discussion

This study shows that the majority of patients with effort angina exhibit asymptomatic episodes of ischemia that are

more frequent than symptomatic ones. Therefore, angina, a symptom on which epidemiologic and clinical studies have been based for the last two centuries, can no longer be considered a valuable criterion for the evaluation of patients with ischemic heart disease (7-9). Almost all symptomatic ischemic episodes occurred during physical activities that the patient had learned were able to provoke pain. In contrast, a considerable number of asymptomatic attacks occurred at rest or during sleep or during physical activities that the patient considered well tolerated.

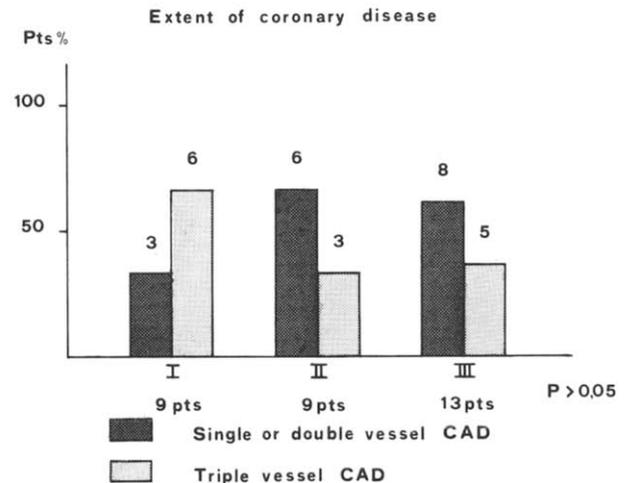
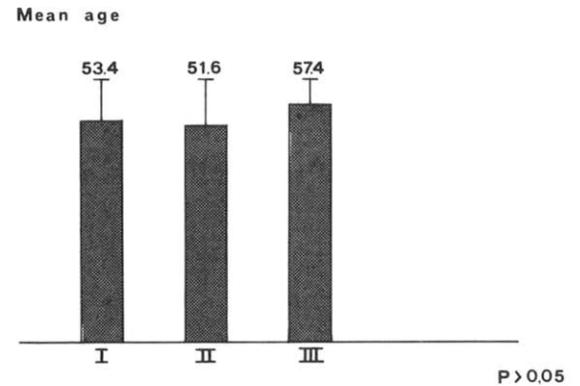
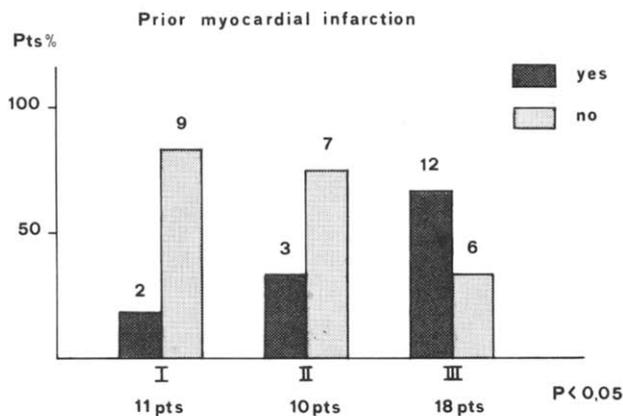
These findings suggest that ischemic attacks are not always evoked by factors that increase myocardial oxygen consumption (MVO<sub>2</sub>); other factors such as a primary reduction of blood flow may be at work. In the same patients, heart rate (a regulator of MVO<sub>2</sub>) was significantly lower in the course of ischemic episodes that occurred during normal daily activities than at the moment of appearance of ischemia at stress testing, a fact that may support this hypothesis. Unfortunately, during Holter monitoring, the systemic blood pressure, (another MVO<sub>2</sub> regulator) was not investigated.

In subjects exhibiting both symptomatic and asymptomatic attacks during Holter monitoring, the duration and magnitude of ST dislocation were greater in symptomatic than in asymptomatic attacks. Although precise correlations between duration and magnitude of ST dislocation and severity of ischemia are not possible, these findings suggest that in the same patient the extent of myocardial ischemia is generally a fundamental factor in determining the presence or absence of pain during an ischemic attack. On the contrary, there were no statistical differences in mean duration and magnitude of ST dislocation during ischemic attacks between the group of patients experiencing only symptomatic episodes on Holter monitoring and the group exhibiting only asymptomatic attacks. Therefore, differences among patients in predominance of symptomatic or asymptomatic attacks probably depend on individual factors as suggested by the relation between results from Holter monitoring and those from stress testing. Asymptomatic ischemic attacks,

**Table 4.** Results of Stress Testing and Holter Monitoring

Stress Testing		Holter Monitoring			
Patients (no.)	Finding	Patients (no.)	Episodes (no.)		Ratio Between Symptomatic and Asymptomatic Episodes
			Symptomatic	Asymptomatic	
11	Angina precedes or coincides with ST depression	11	27	17	1 : 0.62
10	ST depression precedes angina by 10 to 60 seconds	8	11	12	1 : 1.09
18	ST depression precedes angina by more than 60 seconds	13	16	87	1 : 5.43

- I Angina precedes or coincides with ST depression  
 II ST depression precedes angina from 10 to 60 sec.  
 III ST depression precedes angina > 60 sec.



as detected by ambulatory electrocardiographic monitoring, predominate in those patients who do not have pain or exhibit pain with more delay in relation to electrocardiographic features of ischemia during stress testing. This suggests the presence of a defective anginal warning system in these patients (26-29). The causes of this defect are not clear. We found no correlations among those factors previously hypothesized as damaging the anginal warning system (age, prior myocardial infarction, diabetes and extent of vessel disease) and the frequency of asymptomatic episodes of ischemia except in those subjects with prior myocardial infarction.

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