Silent Ischemia During Daily Life Is an Independent Predictor of Mortality in Stable Angina

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We prospectively examined the prognostic significance of silent myocardial ischemia detected by ambulatory electrocardiogram (ECG) monitoring during daily life in 107 patients with long-term stable angina who were symptomatically controlled on conventional antianginal agents. Forty-six patients (group 1) demonstrated one or more episodes (87% silent) of myocardial ischemia; the remaining 61 patients (group 2) had no ischemic ST segment changes. During the mean follow-up period of 23±8 months, 11 cardiac deaths (five sudden and six nonsudden) occurred in group 1, and five cardiac deaths (all nonsudden) occurred in group 2. Kaplan-Meier survival analysis between the groups confirmed that patients with silent ischemia (group 1) had worse prognoses during the follow-up period (p=0.023). Although the higher incidence of hypertension, smoking, hypercholesterolemia, and diabetes in our patients might reflect a more sickly population of stable angina patients, the multivariate Cox's hazard function analysis of these and other variables including Q waves on ECG, exercise parameters, and ambulatory ECG findings revealed presence of silent ischemia during daily life as the most powerful and independent predictor of cardiac mortality (p=0.01). These data indicate that, in such patients with stable angina, silent myocardial ischemia occurs frequently during treatment with conventional antianginal drugs and identifies a subset of patients who are at high risk of cardiac death. (Circulation 1990;81:748–756)

Although exertional chest pain is the typical clinical manifestation of stable angina, numerous recent studies have demonstrated that, in such patients, frequent episodes of silent myocardial ischemia can be detected during continuous ambulatory electrocardiogram (ECG) monitoring.¹⁻³ The silent ischemic events considerably outnumber the symptomatic ones; 70–80% of the transient ischemic episodes recorded during routine daily life are asymptomatic.²⁻⁵ Particularly important, these silent ischemic events persist despite medical therapy that is considered adequate in controlling anginal symptoms.⁶ Silent ischemia in patients with either unstable angina or myocardial infarction is associated with adverse prognoses.⁷⁻¹⁰ The prognostic significance of silent ischemia in stable angina, however, is less clearly defined.¹¹ We prospectively studied the frequency and duration of silent ischemic events in patients with stable angina receiving antianginal therapy to determine whether the presence of residual silent ischemia documented during ambulatory ECG monitoring during daily life constitutes an independent predictor of cardiac death.

Methods

Patient Selection

One hundred eighteen consecutive male patients with long-term stable angina and clinical evidence of coronary artery disease, whose symptoms were controlled on stable doses of antianginal drugs, were enrolled from October 1985 to July 1987. Before enrollment, these patients were being followed in the medicine or cardiology clinics. All patients gave their informed consent for participation in the study, which was approved by the hospital's human study and research committees. Eleven consenting patients were excluded because of baseline electrocardiographic abnormalities. For at least 6 months' duration, all patients had angina, which was defined as chest pain occurring during exertion, producing mild to moderate limitation of ordinary activity and usually relieved by rest, administration of sublingual nitroglycerin, or both. The diagnosis of coronary...
artery disease was confirmed by one or more of the following: coronary angiography showing significant (≥70%) luminal diameter narrowing of one or more major coronary arteries, redistribution myocardial perfusion defect on exercise thallium 201 scintigraphy, or a history of well-documented myocardial infarction at least 6 months before participation in the study. All patients were receiving one or more of the conventional antianginal drugs (i.e., nitrates, β-blockers, calcium channel blockers) as prescribed by their primary physician. Patients were excluded if they had conditions that affected the evaluation of ischemic changes on the ECG, such as severe left ventricular hypertrophy, left bundle branch block, preexcitation syndromes, pacemaker rhythms, atrial arrhythmias, and other baseline ST segment changes. Patients with uncorrected hypokalemia and those receiving digitalis or tricyclic antidepressants were also excluded.

Study Design

All patients initially underwent two-channel ambulatory ECG monitoring for 24 hours while receiving antianginal drugs prescribed by their primary physicians. The ambulatory ECG monitoring tapes were coded to mask the patients’ identities, and analysis of the tapes was performed at a later date in a blinded manner. The results of the ambulatory ECG recordings were not made available to the primary physicians to avoid any deviation from the usual care provided. All patients were followed at regular 3–4-month intervals throughout the duration of the study.

Ambulatory Electrocardiogram Monitoring

Continuous 24-hour two-channel ambulatory ECG recordings were obtained with validated and calibrated frequency-modulated tape-recorders (Oxford Medilog MR 20, Oxford, UK) with a frequency-response range of 0.05–100 Hz, which meets the American Heart Association standards for evaluation of the ST segment. Modified bipolar left precordial and an inferior or anterior lead were selected and corresponded to the location of maximum ST segment depression in the 92 patients with a positive exercise test. The electrocardiographic leads with Q waves or baseline ST segment depression were avoided. Baseline electrocardiographic recordings were made on each patient before and after hyperventilation, and in the supine, prone, sitting, and standing positions to ensure that the ST segment was not affected by posture. Patients were instructed to press an event button on the recorder if they experienced an episode of angina during their usual activities, and to record the number and duration of episodes in angina diaries. The ambulatory ECG monitoring tapes were scanned at 60–120 times real-time on a playback analyzer unit (Oxford Medilog MA 20) by an experienced technician for the presence, frequency, and duration of ischemic episodes. An ischemic episode was defined as horizontal or downsloping ST segment depression of 1 mm or more from baseline, 0.08 second from the J-point, and lasting 1 minute or more. An interval of at least 2 minutes during which ST segment returned to the baseline level was required before another discrete episode was counted. The technician scanning the monitoring tapes identified all potential ischemic episodes meeting these criteria and recorded the time of onset, peak ST depression, and termination of the events. The electrocardiographic tracings of these episodes were obtained at 25 mm/sec speed for review. Additionally, hourly examples of baseline measurements without ST changes were recorded on paper. For each patient, the total number of episodes and the total duration of episodes in minutes were determined every 24 hours. All episodes of ST segment depression were identified as being either symptomatic or silent, based on the details obtained from patient diaries. The ambulatory ECG recordings were blindly and independently reviewed by at least two experienced investigators who performed visual, trend-plotting printout, and real-time printout analysis of the monitoring periods showing ST segment abnormalities. In case of a discrepancy between the two observers, the tapes were reanalyzed. Only those tapes with interpretable signals for at least 18 hours throughout the 24-hour recording period were analyzed.

Exercise Testing

Maximal, symptom-limited, exercise treadmill testing was performed using the Bruce protocol. More than 50% of the patients had performed the exercise test within 6 months, and the majority remaining performed the exercise test within 1 year of enrollment, so that by the end of 1 year, 86% had performed the test. The test was terminated at the point of physical exhaustion, severe angina, ST segment depression greater than 2 mm, a decline in systolic blood pressure greater than 20 mm Hg, complex ventricular arrhythmia, severe dyspnea, or claudication. The total exercise time, time to ischemia, heart rate, and blood pressure at the onset of 1-mm ST depression and peak exercise, maximal ST segment depression, and development of angina during exercise were recorded.

Patient Follow-up

All patients were followed at 3–4-month intervals from the time of entry into the study. At each visit, detailed clinical information was obtained and evaluations were made to document the occurrence of any clinical event since enrollment. The specific events evaluated during the follow-up included occurrence of death from any cause, myocardial infarction, hospitalization for unstable angina, and need for coronary revascularization because of worsening symptoms. Deaths were classified as cardiac (sudden and nonsudden) or noncardiac. Sudden death was defined as death occurring within 1 hour of the onset of symptoms. The details of death were obtained from the relatives, primary physicians, hospital records, obituaries, and coroner’s report. For hospitalized patients, medical records were reviewed.
in detail to confirm the nature of the event and subsequent clinical outcome. The decision to recommend revascularization procedure was made by the clinician providing care for the patient and was based on increasing symptoms refractory to medical therapy, or angiographic findings suggestive of left main disease or three-vessel disease with left ventricular ejection fraction less than 40%. All patients were followed throughout the duration of the study. During the follow-up period, the results of the ambulatory ECG recordings were not made available to the primary physicians and did not contribute to the decision concerning revascularization or modification of the prescribed medical treatment.

Data Analysis

Comparisons of subgroups with and without silent ischemia on ambulatory ECG monitoring were made with unpaired t test of significance for continuous variables, and χ2 analysis was performed for categorical variables. The data are expressed as frequency or mean (± SD) for normally distributed and continuous variables, respectively; otherwise they are reported as median and range. Statistical significance is defined by a p value of 0.05 or less.

Kaplan-Meier actuarial methods13 were used to examine the time-dependent cumulative probabilities of death and occurrence of nonfatal cardiac events, and differences were tested by the method of Mantel-Haenszel.14 Deaths from noncardiac causes were excluded from the final analysis. Multivariate Cox's proportional hazard function analyses were used to evaluate the relative importance of a number of clinical variables, exercise parameters, and ambulatory ECG monitoring findings, and to ensure that our results were not because of any of these confounding variables.15 The clinical variables included in the analyses were age, hypertension, diabetes, current cigarette smoking, clinical history of myocardial infarction, and presence of Q waves on 12-lead ECG. Because the majority of patients had total exercise time data available, this exercise parameter was used for the initial Cox's regression analysis. The ambulatory ECG monitoring variables used were presence or absence of silent myocardial ischemia. Because exercise testing is known to provide reliable prognostic information in patients with coronary artery disease, we repeated a similar stepwise multivariate Cox's regression analysis in the group of 92 patients who had an ischemic response during the exercise test. The variables used in the repeat analysis included age, hypertension, diabetes, current cigarette smoking, clinical history of myocardial infarction and presence of Q waves on 12-lead ECG, as well as the total exercise time, time to ischemia, peak heart rate, and peak blood pressure during exercise, and the presence or absence of silent myocardial ischemia.

Results

Patient Population and Clinical Characteristics

One hundred seven patients with evidence suggesting coronary artery disease and stable angina participated in this study. All had analyzable ambulatory ECG monitoring tapes. The mean age of the study group was 63±6 years (range, 45–79 years), and the average duration of angina was 9.4±7 years (range, 2–42 years). The mean follow-up period was 23±8 months (range, 12–31 months), with 77% of the patients having at least an 18-month follow-up (minimum follow-up, 12 months). The study population was divided into two groups; group 1 (n=46) consisted of patients demonstrating evidence of silent ischemia during the ambulatory ECG monitoring, and group 2 (n=61) was comprised of patients without evidence of ischemia. The baseline clinical characteristics of the groups are shown in Table 1. There were no significant differences in the clinical variables with respect to age, angina duration, previous myocardial infarction, hypertension, active smoking, diabetes, serum cholesterol, or presence of Q waves on the 12-lead ECG. The comparison between the two groups regarding the use of antianginal drugs, given alone or in combination, and aspirin did not reveal any statistical difference (Table 1). Although the total exercise time during symptom-limited treadmill exercise test did not reveal any significant difference between the two groups, the time to ischemia during exercise was significantly shorter (3.3 minutes) in the group 1 patients as compared with group 2 patients (4.9 minutes, p<0.01). Forty percent of the group 1 patients and 37% in group 2 had exercise-induced silent ischemia (Table 2); however, the presence of exercise-induced silent ischemia was not a predictor of silent ischemia during ambulatory ECG monitoring. The angiographic findings were available for 34 patients in group 1 and 42 patients in group 2. There was no significant difference between the two groups in the angiographic extent (±70% luminal
narrowing) of coronary artery disease or in ejection fraction (Table 2).

**Ambulatory Electrocardiographic Findings**

During the 2,568 hours of ambulatory monitoring, 46 patients (group 1) had one or more episodes of ST segment depression, meeting the criteria for transient ischemic events (Table 3). Most (87%) of these ischemic events were silent and comprised the majority (84%) of total ischemic time. Thirty-five patients (76% of group 1) had evidence of silent ischemia only, and 11 patients had both symptomatic as well as asymptomatic ischemic events. In these 11 patients, the average duration of symptomatic events was longer (54±60 minutes) than that of silent ischemic events (28±16 minutes) but did not reach statistical significance.

Because silent ischemia of 60 minutes or longer duration has been correlated with subsequent clinical outcome and prognosis in unstable angina, we also divided our group 1 patients into two subgroups: group 1A (n=35) patients with silent ischemia of 30 minutes or longer duration and group 1B (n=28) patients with 60 minutes or longer duration of silent ischemia during the 24-hour monitoring period.

**Clinical Outcomes**

**Cardiac mortality.** During the 2-year follow-up, 19 patients died, 16 from cardiac causes and 3 from noncardiac causes. Initial survival analysis was conducted for all deaths and revealed that group 1 patients had significantly (p=0.01) worse prognosis when compared with group 2. Because our primary objective was to evaluate cardiac mortality, we performed the survival analysis in the two groups for cardiac deaths only. The three patients with noncardiac deaths were considered lost to follow-up and were excluded from the final analysis. Of the 46 patients in group 1 exhibiting silent ischemia during ambulatory ECG monitoring, 11 (24%) had cardiac deaths, as compared with only five (8%) cardiac deaths in group 2 (Table 4). In group 1, five deaths were sudden and the remaining six were associated with an acute myocardial infarction; in contrast, all deaths in the group 2 patients were nonsudden. The cumulative survival at 1 year in group 1 patients was 89±10% (mean±2 SEM) as compared with 98±3% in group 2, and at 2 years, the cumulative survival was 73±14% in group 1 as compared with 93±7% in group 2 patients. Kaplan-Meier actuarial analysis of the cumulative survival revealed a significantly worse
TABLE 4. Comparison of Cardiac Deaths and Nonfatal Cardiac Events Between Patients With (Group 1) and Without (Group 2) Silent Ischemia Detected by Ambulatory Electrocardiogram Monitoring

<table>
<thead>
<tr>
<th>Event</th>
<th>Group 1 (n=46)</th>
<th>Group 2 (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac deaths (n)</td>
<td>11 (24)*</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Sudden</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nonsudden</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Nonfatal events (n)</td>
<td>15 (33)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Median event time (days)</td>
<td>538</td>
<td>851</td>
</tr>
</tbody>
</table>

*p=0.023 by Kaplan-Meier survival analysis. Numbers in parentheses are percentages.

prognosis (p=0.023) (Figure 1) for the patients with silent ischemia during ambulatory ECG monitoring.

We also evaluated the relation between the duration of silent ischemia and cardiac mortality. Of the 35 patients in group 1A (silent ischemia ≥30 minutes), five had fatal myocardial infarctions and three experienced sudden death. In the group 1B patients (silent ischemia ≥60 minutes), six of 28 patients died (three fatal myocardial infarctions and three sudden deaths). Compared with the patients without ischemia, the Kaplan-Meier actuarial analysis of cumulative survival revealed higher mortality for group 1A (p=0.04), as well as group 1B (p=0.06) patients. Finally, we compared the survival between patients with 1–59 minutes (n=18) and those with 60 minutes or more of silent ischemia (group 1B). Kaplan-Meier actuarial survival analysis did not reveal a significant difference in the cumulative survival between patients with prolonged duration (group 1B) versus those with shorter duration of ischemia.

Nonfatal cardiac events. The incidence of nonfatal cardiac events reported by others is difficult to evaluate because of varying definitions and criteria used in different studies.11,16 Because such data are commonly reported, however, we did compare the incidence of nonfatal cardiac events including nonfatal acute myocardial infarction, unstable angina requiring hospitalization, and the need for revascularization because of increasing symptoms (Table 4). The comparison of nonfatal cardiac events between the two groups by the Kaplan-Meier actuarial analysis did not reveal a statistically significant difference but showed a shorter median time (538 days) to a nonfatal cardiac event in group 1 patients as compared with group 2 (851 days) patients.

Multivariate Analysis

On the initial stepwise Cox’s hazard analysis (Table 5), presence of silent ischemia on ambulatory ECG monitoring was found to be the single most important predictor of 2-year cardiac mortality (p=0.04). None of the other variables contributed information in the presence of silent ischemia. The multivariate Cox’s hazard function analysis was repeated after excluding the silent ischemia variable. In this analysis, the exercise duration emerged as the most significant predictor of cardiac mortality (p=0.05). We did this to test the hypothesis that silent ischemia was a stronger predictor of cardiac death when compared with other established predictors of survival in patients with stable angina. The occurrence of silent ischemia during ambulatory ECG monitoring was added back into the model at the final step. This improved the predictive value of the model and revealed the presence of silent ischemia on ambulatory ECG monitoring as an independent and most powerful (p=0.01) predictor of mortality in the study population.

FIGURE 1. Graph showing Kaplan-Meier curves comparing cumulative proportion of patients surviving without cardiac death during mean follow-up of 2 years for 46 patients with silent ischemia (group 1) and 61 patients without ischemia (group 2) during ambulatory ECG monitoring (p=0.023).
In patients with positive exercise test (n=92), the multivariate Cox's hazard function analysis was repeated. The presence of silent ischemia during ambulatory ECG monitoring remained the most powerful predictor of mortality (p<0.001) in these patients. The other less powerful predictors of mortality were the patient's age at enrollment, current cigarette smoking, and the peak heart rate during exercise testing (Table 6). The multivariate Cox's hazard function analysis was also repeated in the subgroup of 76 patients who had angiographic data. This analysis also revealed presence of silent ischemia as an independent predictor of cardiac mortality (p=0.005) regardless of the extent of angiographic coronary artery disease.

**Discussion**

Although the assessment and management of patients with stable angina has traditionally been based on the subjective account of anginal symptoms during daily life and replication of these symptoms during exercise testing, recent studies have shown that nearly 75% of the ischemic episodes during ambulatory ECG monitoring are not associated with symptoms.2-5 Our results show that, in stable angina patients receiving conventional antianginal drugs, silent ischemia during daily life occurs frequently and is a powerful predictor of mortality.

Although the frequency of silent ischemic events observed in our patients was similar to that described in recent reports7,8,11,17 in comparable study populations of both unstable and stable angina patients, our data differ in that anginal symptoms were believed to be adequately controlled with conventional antianginal drugs prescribed by their primary physicians. These findings indicate that the subjective account of anginal symptoms is an insensitive marker of recurrent ischemia in patients receiving antianginal therapy because silent ischemia recurs frequently during ordinary daily activities and would otherwise be unrecognized without ambulatory ECG monitoring.

**Prognostic Significance of Silent Myocardial Ischemia**

Although the association between silent ischemia during daily life and subsequent survival is not estab-

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**Table 5. Stepwise Cox's Regression Multivariate Analysis of Clinical Variables, Exercise Duration, and Silent Ischemia During Ambulatory Electrocardiogram Monitoring**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial step of the analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>0.05</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>-0.19</td>
<td>0.63</td>
<td>0.76</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.24</td>
<td>0.67</td>
<td>0.72</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.28</td>
<td>0.63</td>
<td>0.66</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.05</td>
<td>0.64</td>
<td>0.94</td>
</tr>
<tr>
<td>Q waves</td>
<td>0.40</td>
<td>0.62</td>
<td>0.52</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>-0.17</td>
<td>0.14</td>
<td>0.23</td>
</tr>
<tr>
<td>Silent ischemia during ambulatory ECG monitoring</td>
<td>1.19</td>
<td>0.61</td>
<td>0.04</td>
</tr>
<tr>
<td>Final step of regression analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>1.37</td>
<td>0.58</td>
<td>0.01</td>
</tr>
</tbody>
</table>

n=107.

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**Table 6. Stepwise Cox's Regression Multivariate Analysis of Clinical Variables, Exercise Parameters, and Silent Ischemia During Ambulatory Electrocardiogram Monitoring in Patients With Positive Exercise Test**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SEM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial step of the analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.15</td>
<td>0.06</td>
<td>0.008</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>-0.97</td>
<td>1.10</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.66</td>
<td>0.89</td>
<td>0.45</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.56</td>
<td>0.87</td>
<td>0.50</td>
</tr>
<tr>
<td>Smoking</td>
<td>-2.29</td>
<td>1.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Q waves</td>
<td>0.33</td>
<td>1.10</td>
<td>0.77</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>-0.18</td>
<td>0.21</td>
<td>0.36</td>
</tr>
<tr>
<td>Exercise time to ischemia</td>
<td>0.43</td>
<td>0.27</td>
<td>0.10</td>
</tr>
<tr>
<td>Peak heart rate during exercise</td>
<td>-2.45</td>
<td>1.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak blood pressure during exercise</td>
<td>0.02</td>
<td>0.02</td>
<td>0.22</td>
</tr>
<tr>
<td>Silent ischemia during ambulatory ECG monitoring</td>
<td>3.74</td>
<td>1.38</td>
<td>0.0005</td>
</tr>
<tr>
<td>Final step of regression analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>2.46</td>
<td>1.06</td>
<td>0.002</td>
</tr>
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</table>
lished, numerous studies have demonstrated that presence of silent ischemia during exercise testing confers adverse clinical outcome and poor survival. The data from the coronary artery surgery study (CASS) registry of 2,982 patients showed that, in the group of 1,583 medically treated patients with proven coronary artery disease, those with exercise-induced myocardial ischemia had a fivefold increase in mortality during the 7-year follow-up. The presence or absence of angina or equivalents during exercise did not alter the prognostic significance of electrocardiographic evidence of ischemia. In another study of 131 patients with coronary artery disease who were either asymptomatic or mildly symptomatic, exercise-induced ischemia and an abnormal ejection fraction response to exercise identified patients at high risk of subsequent coronary events, regardless of the presence of anginal symptoms. Exercise-induced silent ischemia has also been correlated with higher mortality in patients recovering from myocardial infarction. Several recent studies have shown that presence of silent ischemia during continuous ECG monitoring in hospitalized patients with unstable angina is associated with a significantly higher risk of coronary events during the short- and long-term follow-up. Similar observations have been made regarding the prognostic significance of silent ischemia detected during continuous ECG monitoring in patients with myocardial infarction.

The prevalence of silent ischemia and its association with increased mortality in our study extends these observations to patients with stable angina receiving medical therapy directed toward symptom control. During the 2-year follow-up, there was a threefold increase in cardiac deaths in patients with silent ischemia during ambulatory ECG monitoring as compared with those without silent ischemia (24% vs. 8%, p=0.023). Whereas the longer duration of silent ischemia has been associated with a worse clinical outcome in patients with unstable angina, in our study, the risk of cardiac death was related to the mere presence of silent ischemia regardless of its duration. The stepwise multivariate analysis revealed silent ischemia during ambulatory ECG monitoring to be an independent predictor of mortality, and provided prognostic information exceeding that for the other clinical variables. This is noteworthy because the majority of these patients are symptom free and would not otherwise be identified as being at increased risk of mortality.

There is only one other study in which the prognostic significance of myocardial ischemia detected by ambulatory ECG monitoring was carefully evaluated in patients with stable coronary artery disease. In this study of 86 patients with stable symptoms of coronary artery disease and a positive exercise test, 57% of patients had one or more episodes of ST segment depression, of which only 14% were symptomatic. During the 1-year follow-up, presence of ST segment depression on ambulatory ECG monitoring identified the high-risk group with unfavorable outcome, which predominantly consisted of revascularization procedures and hospitalization for unstable angina. Because there were only two deaths, no definitive correlation between silent ischemia and subsequent poor survival could be established. The lack of correlation between silent ischemia and mortality might be due to some inherent limitations in that study. The mean follow-up period of 12 months (range, 1–25 months) might be too short for evaluation of survival in patients with stable coronary artery disease. Also, the initial ambulatory ECG monitoring was performed while all prophylactic antianginal drugs were withdrawn. Because patients were subsequently followed while receiving the prescribed antianginal drugs, the initial ambulatory ECG data might not reflect the extent of myocardial ischemia present during therapy. Thus, their results might not actually reflect the prognostic significance of residual silent ischemia that persists despite antianginal therapy effective in controlling symptoms.

The exact reason for increased mortality in association with silent ischemia during daily life in our patients is not clear. In an experimental model, repeated brief episodes of myocardial ischemia have been shown to produce small but distinct areas of subendocardial necrosis. These data are further supported by a recent report in which tissue biopsies taken during cardiac surgery in patients with coronary artery disease revealed abnormalities of nuclei and mitochondria, and a reduction of contractile material in the subendocardium. Although these patients did not exhibit any gross histological evidence of myocardial infarction, there was loss of myocytes and an increased amount of fibrosis. These changes were associated with evidence of localized hypokinesia. The effects of transient ischemia on myocardial structure and ventricular function were also evaluated in another recent study. The left ventricular myocardial biopsies obtained during open heart surgery showed muscle fiber hypertrophy and increased interstitial nonmuscular tissue in the endocardial layers of the transiently ischemic myocardium with normal function at rest, and ischemia-induced regional wall motion abnormalities during exercise. Although mortality in our patients could be related to progressive left ventricular dysfunction because of repeated episodes of silent myocardial ischemia, we did not observe an increased incidence of heart failure.

It is also possible that silent ischemia might have resulted in lethal ventricular arrhythmias. Although we cannot establish a clear association between ventricular arrhythmias and increased mortality in our study, recent studies show that silent ischemia can indeed be a forerunner of malignant ventricular arrhythmias. In our study, five of 11 patients with silent ischemia had sudden cardiac deaths. In contrast, none of the five deaths in the group without silent ischemia were sudden. Thus, it is appealing to speculate that the sudden deaths in the group with
silent ischemia were because of lethal ventricular arrhythmias triggered by silent ischemia.

Our findings show that silent myocardial ischemia that recurs during treatment with conventional antianginal drugs and would otherwise be unrecognized, carries adverse prognostic implications.

Limitations

There are some limitations of our study. The number of patients enrolled in our study is small and our data might not be applicable to all patients with stable angina. Because a large number of our patients had a history of hypertension, diabetes, hypercholesterolemia, smoking, and prior myocardial infarction (Table 1), our findings might apply only to patients with stable angina and these associated conditions. Additionally, the vast majority of group 1 patients were unable to complete the second stage of Bruce protocol and might represent a group at higher risk of silent ischemia and subsequent mortality.

Also, our results are applicable only to patients receiving antianginal drug therapy directed toward control of symptoms. It is likely that more aggressive therapy with titrated dosages of these drugs based on exercise test findings or other parameters of ischemia would have minimized the risk of residual silent ischemia during daily life. Because the primary goal of our study, however, was to examine the prognostic significance of silent ischemia in patients receiving the usual care provided by the primary care physician, we did not alter therapeutic regimens to suppress silent ischemic events and, thus, cannot examine the influence of therapy directed toward control of total ischemic burden on subsequent prognosis.

Clinical Implications

Our data confirm the results of previous studies and show that, despite control of anginal symptoms with antianginal drugs, more than 40% of patients with stable angina continue to have electrocardiographic evidence of myocardial ischemia on ambulatory ECG monitoring during ordinary daily activities.6,11,17,26 The presence of silent myocardial ischemia in this otherwise stable population predicts poor survival and helps identify the high-risk coronary artery disease patients. Because most clinicians prescribe and titrate antianginal drugs for control of symptoms, silent ischemia during daily life can remain unrecognized unless ambulatory ECG monitoring is performed.

It is important to note that, in our study, silent ischemia during ambulatory ECG monitoring was an independent predictor of mortality, and the clinical variables, exercise parameters, and angiographic extent of coronary artery disease did not provide additional prognostic information. It is also interesting that the degree of fixed coronary artery disease was similar in patients with and without silent ischemia, suggesting that other mechanisms such as dynamic narrowing of coronary arteries or platelet aggregation might play a role in the pathogenesis of silent myocardial ischemia.

Finally, because our data show that silent ischemia that recurs during treatment with conventional antianginal drugs is associated with poor survival, it seems reasonable to recommend antiischemic therapy for control of both symptomatic and silent ischemic events. Controlled clinical trials, however, are needed to determine the optimal therapy and its effects on survival in patients with clinically stable angina who continue to have silent ischemia during daily life.

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References


**KEY WORDS** • silent myocardial ischemia • cardiac death • long-term stable angina • ambulatory ECG monitoring
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