Effects of Asymptomatic Ischemia on Long-term Prognosis in Chronic Stable Coronary Disease

Alan C. Yeung, MD; Joan Barry, BA; John Orav, ScD; Edina Bonassin, BA; Khether E. Raby, MD; and Andrew P. Selwyn, MD

Background. Ischemia on ambulatory electrocardiographic monitoring has been shown to adversely affect short-term prognoses in patients with unstable angina, after myocardial infarction, and with chronic stable angina.

Methods and Results. In this long-term study, we followed 138 patients (mean age, 59±9 years) with chronic stable angina and positive exercise tests for cardiac events (e.g., death, myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery). In 105 patients, ambulatory electrocardiographic monitoring was performed after all antianginal medication was withheld for 48 hours. In 26 patients, the diagnostic tests were repeated while on their usual medication. In addition to the 105 patients, 33 patients had their monitoring performed only while on their usual medication. During 37±17 months of follow-up, there were nine deaths, nine myocardial infarctions, and 35 revascularization procedures. In patients monitored off medication, Cox survival analysis showed that the occurrence of ischemia on electrocardiographic monitoring was the most significant predictor of death and myocardial infarction in the subsequent 2 years (p=0.02) and of all adverse events for 5 years (p=0.009). Patients who were monitored on medication and did not have ischemia (n=18) appeared to have more adverse events than patients who had no ischemia while being monitored off medication (n=43).

Conclusions. Asymptomatic ischemia on ambulatory electrocardiographic monitoring in patients with stable angina predicts death and myocardial infarction for 2 years and all adverse events for 5 years. Monitoring performed while on medication may show no ischemia; however, this may not indicate low risk of future coronary events. (Circulation 1991;83:1598–1604)

Transient myocardial ischemia during daily life has been shown to predict increased risk of coronary events in patients with unstable angina,1–3 with chronic stable angina,4–6 after myocardial infarction,7,8 and undergoing vascular surgery.9,10 However, coronary atherosclerosis has a patchy evolution, and a single measure of ischemia may not predict increased risk over long periods of time. The purpose of the present study was to determine if evidence of ischemia in ambulatory continuous electrocardiographic monitoring indicates increased risk that continues over time and the validity of using continuous electrocardiographic monitoring to assess risk when patients are on medical therapy.

Methods

One hundred thirty-eight patients with stable symptoms of coronary artery disease on routine medical therapy were recruited for continuous electrocardiographic monitoring if they had symptom-limited exercise tolerance tests that demonstrated horizontal or downsloping ST segment depression of 1 mm or more. The presence of coronary artery disease was documented in 100 of the 138 patients (72%) by angiographic evidence of 70% stenosis of one or more coronary arteries. Among the remaining 38 patients, five had documented previous myocardial infarction, and 33 had exercise tolerance tests that were highly predictive for coronary artery disease (2 mm or greater ST segment depression in association with anginal symptoms [n=26] or reperfusion defect on thallium-201 imaging [n=7]). Patients on digoxin or with electrocardiographic abnor-
malities known to influence the ST segment (e.g., left ventricular hypertrophy, bundle branch block, Wolff-Parkinson-White syndrome, or significant baseline ST segment abnormalities) were not recruited for this study. The initial follow-up of 86 patients at 12 months was reported previously.

Patient Characterization

All patients were characterized according to age, sex, history of myocardial infarction, previous revascularization with coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, measurement of risk factors, history of angina, coronary angiography results, and left ventricular ejection fraction. Angina pectoris was classified according to New York Heart Association functional class severity.

Diagnostic Testing

All medication was discontinued 48 hours before monitoring and exercise testing in 105 patients. During this period, patients were instructed to take nitroglycerin only as needed for symptoms. In 26 of these patients, the diagnostic testings were repeated while they were on their usual medication. In addition to the 105 patients, 33 patients had their monitoring and exercise testing performed only while they were on their usual medication.

Ambulatory monitoring. All sessions were recorded on 24-hour tapes with a calibrated Oxford MR 35 frequency-modulated recorder (Clearwater, Fla.). Two 24-hour monitoring periods were performed on consecutive days for a total of 48 hours of continuous monitoring. Bipolar electrodes were attached with the exploring electrodes at the standard V₅ and modified inferior positions. The electrode positions were altered when necessary to record the leads showing the most ST segment depression as determined from exercise tolerance testing. During monitoring, patients were instructed to engage in their usual activities and maintain diaries to record symptoms of angina or the equivalent.

Tapes were analyzed visually at 60–120-fold that of real time with an Oxford Medilog 20 scanner and a technician-interactive Cardiodata MK4 computer (Northboro, Mass.) by two technicians or physicians blinded to patient characteristics. Results were compared; if they differed by 5% or more, the tapes were reanalyzed. Only tapes with interpretable signals for at least 90% of the 24-hour recording session were analyzed. This represented a total of 293 periods of 24 hours in the 138 patients, including 26 patients monitored both on and off medication. An episode of significant ST segment depression was defined as 1 mm or greater horizontal or downsloping ST depression persisting at 80 msec after the J point and lasting for 60 seconds or longer in consecutive beats. Separation of one episode from another required that the electrocardiogram returned toward baseline for more than 3 minutes. For each patient, the ambulatory electrocardiographic monitoring was considered positive if there was at least one 60-second episode during the monitoring period. Also, the total number of episodes, total ischemic time per 24 hours, and duration per episode were recorded. For each individual episode, heart rate at 5 minutes before onset, heart rate at onset, heart rate at peak of ST segment change, maximal degree of ST segment depression, and association with symptoms were recorded.

Exercise tolerance testing. Maximal symptom-limited exercise tolerance tests were performed on a treadmill using the Bruce protocol. The tests were performed with or without medication in accordance with the ambulatory electrocardiographic monitoring to follow. Exercise tolerance tests were terminated at exhaustion or with the development of 4 mm or greater ST depression, severe angina, three or more premature ventricular contractions in succession, dyspnea, claudication, or a decrease in blood pressure of more than 20 mm Hg. Time to onset of ST depression, heart rate and blood pressure at onset of 1 mm of ST segment depression and at peak exercise, exercise duration, and maximum ST segment depression were recorded for each test.

Follow-up

Subjects were contacted at 3–6-month intervals from the time of initial monitoring to determine the occurrence of death, myocardial infarction, and need for revascularization with coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty because of new or worsening symptoms. These decisions were determined independently by the clinicians without knowledge of the monitoring results. In-hospital records and physician charts were reviewed for confirmation. Deaths were classified as cardiac or noncardiac. Myocardial infarctions were confirmed by standard electrocardiographic evolution and creatine phosphokinase isoenzyme patterns.

The physicians caring for patients during the follow-up were blinded to the result of the electrocardiographic monitoring and independently determined the need of medication change or revascularization. Classification of cardiac events was made by the authors without knowledge of monitoring results.

Statistical Analysis

Descriptive statistics are presented as mean±SD for approximately normally distributed data; otherwise, they are reported as median and range. Comparisons of subgroups were made with t test for continuous variables and χ² analysis for categorical variables. Comparison of nonuniformly distributed data were made with nonparametric Wilcoxon rank-sum test. Life-table curves were constructed with the Kaplan-Meier technique and compared by the log-rank method. Univariate and multivariate models to assess risk factors of the patients were constructed with the Cox proportional hazards model. To examine the time-dependent nature of this model, the covariates were allowed to be time dependent and exert zero influence after 2 years. Statistical significance was assessed using a likelihood ratio test.
TABLE 1. Comparison of Patients With and Without ST Segment Depression on Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Off medication</th>
<th></th>
<th>On medication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STD (n=62)</td>
<td>No STD (n=43)</td>
<td>STD (n=22)</td>
<td>No STD (n=37)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60±9</td>
<td>57±10</td>
<td>60±10</td>
<td>60±8</td>
</tr>
<tr>
<td>Men (%)</td>
<td>84</td>
<td>77</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>Angina class (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>55</td>
<td>49</td>
<td>50</td>
<td>51</td>
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<tr>
<td>II</td>
<td>35</td>
<td>37</td>
<td>41</td>
<td>35</td>
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<tr>
<td>III</td>
<td>8</td>
<td>9</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td>92</td>
<td>95</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>52</td>
<td>42</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>15</td>
<td>12</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td>Catheterization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One vessel</td>
<td>6</td>
<td>11</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Two vessels</td>
<td>26</td>
<td>28</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Three vessels</td>
<td>42</td>
<td>26</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>67.8</td>
<td>67.7</td>
<td>67.2</td>
<td>66.2</td>
</tr>
<tr>
<td>ETT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to ST (min)</td>
<td>3.4±2.0</td>
<td>4.6±2.1*</td>
<td>3.2±1.5</td>
<td>4.7±2.2*</td>
</tr>
<tr>
<td>ETT HR @ ST (bpm)</td>
<td>116±18</td>
<td>127±20*</td>
<td>116±20</td>
<td>117±22</td>
</tr>
<tr>
<td>HR×SBP @ ST (×10³)</td>
<td>18.5±4.4</td>
<td>20.9±5.2*</td>
<td>18.6±4.1</td>
<td>18.8±5.6</td>
</tr>
<tr>
<td>HR×SBP @ peak (×10³)</td>
<td>20.8±5.7</td>
<td>23.4±6.3*</td>
<td>22.2±6.5</td>
<td>20.8±5.9</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>5.8±2.8</td>
<td>6.7±2.9</td>
<td>5.4±2.5</td>
<td>6.7±2.5</td>
</tr>
<tr>
<td>Maximum ST (min)</td>
<td>2.3±0.9</td>
<td>1.8±0.7*</td>
<td>2.2±1.2</td>
<td>1.9±1.0</td>
</tr>
</tbody>
</table>

STD, ST segment depression; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; ETT, exercise tolerance test; HR, heart rate; SBP, systolic blood pressure.

*p<0.05.

Results

Clinical and Exercise Test Characteristics

The mean age of the 138 patients was 59±9 (age range, 36–81 years) with men composing 79% of the patients. Table 1 shows the baseline clinical and exercise characteristics of the 105 patients monitored while they were off medication and the same characteristics for 59 patients monitored while they were on medication. In each group, the characteristics of those with or without ST segment depression are listed separately. Overall, there were no significant differences in the clinical variables between those who were monitored off medication and those who were monitored only on medication. In patients who were monitored off medication, there were no significant differences in the clinical variables with regard to age, sex, angina class, number of risk factors, history of myocardial infarction or prior revascularization procedures, angiographic extent of disease, and left ventricular ejection fraction in patients with or without ST segment depression during ambulatory electrocardiographic monitoring. However, the patients with ST segment depressions had shorter times to ST segment change, lower heart rates, lower double-products at ST depression, and more severe ST depressions at maximal exercise (p<0.05). Similarly, in patients who were monitored on medication, there were no differences in the clinical variables except for shorter times to ST depression during exercise tests in those patients with ST depression on ambulatory electrocardiographic monitoring (p<0.05).

Ambulatory Monitoring Results

In patients who were monitored off medication, 62 patients (59%) had one or more episode of ST segment depression, with a median number of episodes of 3.3 per 24 hours (range, one to 25 episodes) (Table 2). The median total ischemic time per 24 hours was 17 minutes (range, 1–488 minutes). Heart rate at onset (95±15 beats/min) was lower than that during the exercise test (116±18 beats/min). In patients who were monitored on medication, there was a median number of two episodes per 24 hours (range, one to nine episodes). Median total ischemic time was 15.8 minutes with a range of one to 67 minutes. There were significantly fewer episodes per 24 hours (two versus 3.3 episodes) and lower heart rates at onset of ST depression (87±24 versus 101±16 beats/min) and at peak ST (89±23 versus 105±18 beats/min) in patients who were monitored on medication compared with those monitored off medication.

Clinical Outcomes

Of the 138 patients, eight patients (6%) were lost to follow-up. The mean duration of follow-up was
Table 2. Characteristics of ST Segment Depression

<table>
<thead>
<tr>
<th></th>
<th>STD off medication (n=62)</th>
<th>STD on medication (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes/24 hr (n) (range)</td>
<td>3.3 (1–25.5)</td>
<td>2 (1–9)*</td>
</tr>
<tr>
<td>Total ischemic time (min) (range)</td>
<td>17 (1–488)</td>
<td>16 (1–67)</td>
</tr>
<tr>
<td>Duration per episode (min) (range)</td>
<td>4.5 (1–93)</td>
<td>5.7 (1–17)</td>
</tr>
<tr>
<td>HR before onset (beats/min)</td>
<td>95±15</td>
<td>85±23*</td>
</tr>
<tr>
<td>HR at onset (beats/min)</td>
<td>101±16</td>
<td>88±24*</td>
</tr>
<tr>
<td>HR at peak ST (beats/min)</td>
<td>105±18</td>
<td>89±23*</td>
</tr>
<tr>
<td>Maximum ST (mm)</td>
<td>1.5±0.8</td>
<td>1.2±0.4</td>
</tr>
</tbody>
</table>

STD, ST segment depression; HR, heart rate.
*p<0.05.

37±17 months (range, 1–62 months) with 29% followed for 1 month to 2 years, 41% for 2–4 years, and 30% for more than 4 years. During this time, there were nine deaths, nine myocardial infarctions, 28 coronary artery bypass graft operations, and seven angioplasty procedures in the total cohort of 138 patients (Table 3).

In 105 patients who were monitored off medication, the Kaplan-Meier actuarial analysis of cumulative survival free of myocardial infarction or death is shown in Figure 1. At 24 months, no deaths or myocardial infarctions had occurred in patients who had no ischemia on ambulatory electrocardiographic monitoring, whereas those who had ischemia had six events. Cox regression analysis showed that the presence of ischemia on monitoring was the only significant predictor for death or myocardial infarctions with follow-up truncated at 2 years (p=0.02) with a relative risk of more than 10. The variables measured during ambulatory electrocardiographic monitoring and exercise testing were then used as time-varying covariates with no influence after 2 years. At 60 months, there was a total of eight events in the ischemia group and two events in patients without ST depression. The difference was not statistically significant even though the relative risk was still 2.58 (95% confidence limits, 0.5 to 12), whereas the relative risk as measured by the best predictor (time to ST depression) during exercise testing remained insignificant at 1.09 (95% confidence limits, 0.8 to 1.3).

If all events were combined (i.e., death, myocardial infarction, revascularization), the prognosis was clearly worse in the group with ischemia on ambulatory electrocardiographic monitoring at all follow-up times with a relative risk of 2.82 (25 versus 7 events; confidence limits, 1.2 to 6.5; p=0.009), whereas time to ST depression during exercise testing had a relative risk of 1.34 (confidence limits, 1.0 to 1.9) (Figure 2). Symptoms did not appear to have independent predictive value; with or without symptoms, ST segment depression predicted a worse outcome (Figure 2). Interestingly, patients who had symptomatic ischemia tended to have events occur sooner. By multivariate analysis, ischemia on ambulatory electrocardiographic monitoring was the only factor that predicted cardiac events independently.

The Kaplan-Meier survival curve for patients who were monitored on medication only is shown in Figure 3. Compared with patients who had no ischemia while being monitored off medication, the patients who had no ischemia while on medication had worse prognoses (relative risk, 3.68; 95% confidence limits, 1.2 to 10.8; p=0.02), similar to those who had ischemia while off medication.

Further survival analyses of the ambulatory monitoring results examining the number of episodes of ischemia, total ischemic time, or heart rate at onset did not provide additional prognostic information in these patients with stable angina.

Discussion

Silent ischemia has been clearly shown to affect prognosis in patients with stable or unstable angina or recent myocardial infarction as well as in elderly asymptomatic men. However, most studies in patients with stable coronary artery disease have reported short-term findings and have not followed the patients beyond 8 months to 2 years. The present study shows that transient myocardial ischemia, even if it is silent, indicates increased risk of myocardial infarction and death but only for 2 years and for all events for 5 years. Patients who have no ischemia while off medication are initially at low risk and then begin to have coronary events after 2 years, presumably because of the evolution of the underlying coronary disease. We have also shown that pa-
patients who are monitored while on medical therapy may show no ischemia but still experience increased occurrences of coronary events.

In patients who are monitored while off medication, the prognostic value of silent ischemia for identifying high-risk patients with stable coronary artery disease is consistent with our previous short-term follow-up and the study by Deedwania and Carbajal. However, in the present study, we also demonstrate that the prognostic value of ambulatory electrocardiographic monitoring diminishes over time, especially in predicting the "hard" end points. This is not surprising given that coronary disease has a patchy evolution and a stuttering course. It is likely but not proven that patients who have no ischemia during initial testing may eventually enter an active phase of disease, resulting in myocardial infarction and death. Most of the other prognosis studies have lacked sufficient follow-up to show this time dependency.

The event rate in the present study is lower than that reported by Deedwania and Carbajal. In that study, patients had a higher rate of ischemia on medication (death rate, 11 of 46, or 24%, in patients with ischemia). However, the overall event rate of 13% at 2 years in patients who did not have ischemia was comparable to the rate (18%) in our cohort of patients who had no ischemia on medication at 2 years. This event rate was substantially higher than the event rate (7%) of patients who had no ischemia while off medication. Thus, the results of these two studies are complementary, reflecting the heterogeneous severity of risk and outcomes in a group of patients who appear to have stable coronary artery disease. The lesser degree of ischemia in our cohort of patients may also explain why the exercise test variables did not have strong predictive values in patients who had positive exercise tests as inclusion criteria.

In the present study, patients who had no ischemia while monitored only on medication (18 of 33)
showed surprising outcomes. We expected all of these patients without ischemia while monitored on medication to exhibit low risk and suffer few events. However, the data from this small study population show that overall these patients appear to experience worse prognoses than those who have no ischemia while monitored off medication. On the other hand, ambulatory monitoring that shows ischemia obtained while on medication is suggestive of even higher risk, as shown by Deedwania and Carbajal. This preliminary finding implies that when ambulatory electrocardiographic monitoring shows no ischemia while the patient is on medication, low risk is not reliably indicated, and more accurate prognostic stratification may be obtained by performing ambulatory monitoring while off medication.

Study Limitations

The lack of a statistically significant difference in the myocardial infarction or death rates between the ischemic and nonischemic groups at 60 months may be the result of a $\beta$-error. Given the event rate, to obtain a power of 80%, we needed to enroll 297 patients at the onset of the study. However, it is clear that the predictive powers of the ambulatory electrocardiographic monitoring and exercise testing decrease over time (from a relative risk of more than 10 to 2.5). The early increase in event rate (especially coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty) in patients who are symptomatic may be because of the tendency of physicians to recommend invasive therapy earlier due to symptoms, not because of any intrinsic difference in the underlying pathophysiology. Because the number of patients who were monitored only while on medication is small and there may be potential clinical differences between this group and those monitored while off medication, the observed effect is preliminary and must be confirmed in a larger randomized trial monitoring all patients on and off medication. It is also important to point out that the present study does not provide a comparison between the prognostic value of the exercise test and ambulatory monitoring because all of the patients had positive exercise tests. Rather, we aimed to show that in patients with coronary artery disease and positive exercise tests, ambulatory monitoring provides additional prognostic value for adverse events.

Conclusions

In the present study, we confirmed that asymptomatic ischemia on ambulatory electrocardiographic monitoring predicts the increase risk of cardiac events. The absence of ischemia while off medication is predictive of essentially event-free survival for 2 years, after which cardiac events began to occur. Positive monitoring results predict death and myocardial infarction for 2 years and for all events for 5 years. Monitoring on therapy may show no ischemia; however, this does not indicate a low risk of future coronary events. Therefore, in patients with stable coronary artery disease, ambulatory electrocardiographic monitoring should be performed if the exercise test is moderately positive and the patient is minimally symptomatic. Severe symptoms and a negative or strongly positive exercise test provide clinical decision points that probably do not require information from ambulatory monitoring. The patient should be monitored while on medication first, especially if he or she is symptomatic while off medication. If the ambulatory monitoring shows ischemia, this result clearly places the patient at higher risk for future coronary events. However, if the recordings show no ischemia, we think it is prudent to repeat the monitoring while off medication to better assess the risk. Given the changing nature of atherosclerosis and ischemia, repeat monitoring should probably be performed in 2-year intervals, especially if there are progressive symptoms.
References

KEY WORDS • ischemia, asymptomatic • coronary artery disease • angina
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