Value and Limitations of Ambulatory ECG Monitoring for Assessment of Myocardial Ischemia

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Ambulatory ECG monitoring (AEM) is the only available method to assess the presence and severity of myocardial ischemia during daily life. Several investigators have shown that the recording systems currently used can detect ischemic changes with similar accuracy as treadmill exercise testing. Ischemic changes on AEM are, however, present in only 40%-60% of patients with coronary artery disease (CAD) and positive exercise tests. For this reason, and because of the high day-to-day variability in daily ischemic changes, AEM cannot be used as a screening tool for detecting CAD or for evaluating severity of ischemia in individual patients. In patients with proven CAD, ischemic changes on AEM are associated with an adverse outcome in patients with stable and unstable ischemic syndromes, and in postmyocardial infarction patients. Suppression of daily ischemia seems to be associated with improved outcome. The mechanism of daily ischemia is not identical to exercise-induced ischemia. In addition to increased demand, which is a major contributor to AEM detected-ischemia, increased coronary tone also seems to play a major role. AEM has been shown to be a useful and reliable tool to assess the efficacy of various antiischemic drugs.

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Ischemic changes as recorded by ambulatory ECG monitoring (AEM) were reported already by Gilson in 1964.¹ Despite this very early description of ST-T changes, the use of AEM for evaluation of ischemic changes lagged behind its use for arrhythmia monitoring for many years. It was only after several studies validated the ischemic nature of these changes that the cardiology community accepted the existence of ischemic changes during daily life, even in the absence of chest pain = silent myocardial ischemia.²⁻⁶ Exercise testing is the most commonly used method for detection of ischemic changes and for assessing their severity. The appearance of ST depression of more than 1 mm during stress testing, in the general population, is associated with a sensitivity of 23% and a specificity of 89% for the presence or absence of coronary artery disease.⁷ If more strict electrocardiographic

criteria are used (≥ 1.5 mm ST depression) the sensitivity drops to 8.8% and the specificity approaches 98%. Callahan and co-workers⁸ demonstrated that the presence and severity of both silent and symptomatic ischemia during treadmill testing is associated with increased mortality rate.

AEM in Patients with Stable Coronary Artery Disease

Ambulatory ECG monitoring is the only available method to assess the presence and severity of ischemic changes during daily living. In 1974, we described ischemic changes during daily life, and demonstrated that these changes are related to subsequent cardiac events.² In 1988 we demonstrated that during a 27-month follow-up period of 224 postmyocardial infarction patients, there was a 39% event rate among 74 patients with ST depres-

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sion, compared to only 9.3% among the 150 patients with no ST depression.⁹ The main cardiac events were hospitalization for unstable angina and the need for coronary angioplasty or bypass surgery. In this study we also demonstrated that ischemic changes contributed to the prognostic assessment of these patients beyond the extent of coronary artery disease and also beyond the presence or absence of reduced left ventricular function. Ruberman and co-workers¹⁰ compared the findings on Holter monitoring of 261 patients who died, to 261 matched patients who survived. In this study, transient ST depression was associated with a relative risk of 1.73. The risk was related to the duration of ischemia. Patients who had ST depression for 1-30 minutes had a relative risk of 1.9, while among those with ST depression that lasted for more than 30 minutes, the relative risk was 4.3. Patients who were treated with β blockers had reduced mortality, suggesting that propranolol reduced mortality by reducing myocardial ischemia. The prognostic importance of Holter-detected ischemia was also reported by Rocco and co-workers¹¹ and Deedwania and co-workers.¹² In 1996 Madjlessy-Simon and co-workers¹³ compared 229 patients without ischemia on AEM with 84 patients with ischemia. These patients had a similar extent of coronary artery disease. During a 30 month follow-up period, death or myocardial infarction occurred in 5% of patients without ischemia, compared to 17% of patients with ischemia ($P = 0.09$). The need for coronary intervention was 15% in the patients without ischemia compared to 31% in those with ischemia ($P = 0.0018$). In the Asymptomatic Cardiac Ischemia Pilot study (ACIP), 558 patients who had coronary anatomy suitable for revascularization were followed for 2 years.¹⁴ Patients were divided into three treatment strategies; angina guided ($n = 173$), angina + ischemia guided ($n = 183$); in this group treatment was guided by reduction of ambulatory ischemia. In the third group, patients had coronary revascularization ($n = 192$). During the 2-year follow-up period, frequency of death and myocardial infarction was 12.1% in the angina-guided therapy group, 8.4% in the ischemia-guided therapy group, and 4.7% in the revascularization group. The difference in event rate was significant between the groups. Based on these findings, in an editorial published in *Circulation* in 1997,¹⁵ Killip wrote that "these are exciting findings, medical therapy designed to reduce or avert ischemia appears to be prognostically

better than symptomatic therapy, but is not as effective as revascularization." He suggested that improved medical therapy combined with lipid lowering drugs may further improve prognosis of patients with coronary artery disease. Patients who require vascular surgery may benefit from the use of AEM, as they are unable to perform a stress test. Raby et al.¹⁶ performed AEM in 176 patients prior to elective vascular surgery. Thirty-two patients (18%) had 75 ischemic episodes, of which 73 were asymptomatic. Thirteen patients had postoperative cardiac events, 12 had ischemia on AEM. In multivariate analysis, perioperative AEM ischemia was the best predictor of postoperative cardiac events ($RR = 24.4$). In a more recent study, Raby et al.¹⁷ demonstrated that treatment with intravenous esmolol was associated with lower postoperative AEM ischemia (33%) compared to placebo (73%) in patients undergoing vascular surgery.

AEM in Patients with Acute Coronary Syndromes

Silent myocardial ischemia was found to be of prognostic significance by Gill and co-workers in patients recovering from acute myocardial infarction.¹⁸ He studied 406 postinfarction patients who had 48 hours of AEM and submaximal exercise testing. Holter detected ischemia in 23.4% of these patients. During a 1 year follow-up period, death or infarction occurred in 9.6% of patients with no ischemia and 23.2% in patients with ischemia ($P = 0.001$). In this study, results of ischemia on AEM provide better prognostic information than exercise testing. Silent myocardial ischemia was found to be of prognostic value also among patients with acute coronary syndromes. Gottlieb and co-workers¹⁹ studied 70 patients with unstable angina and found that those with silent myocardial ischemia despite maximal therapy had increased in-hospital mortality. The presence of ischemia was the best predictor of survival out of fifteen variables tested. Similar findings were reported by Nademanne and co-workers.²⁰ Gottlieb and co-workers studied the prognostic significance of myocardial ischemia as assessed by AEM in 103 high-risk postinfarction patients; 30 of these patients had a median number of five episodes per day and a median total duration of ischemia of 157 minutes.²¹ Death rate among patients with ischemic changes was 30% during a 1-year follow-up, compared with 11% of patients without ischemia. In the multicenter silent

ischemia study, 936 patients, after myocardial infarction or unstable angina pectoris, had ambulatory and exercise electrocardiogram and stress thallium 201 imaging within 6 months after hospitalization and were followed for a mean period of 23 months.²² Patients with silent ischemia ($n = 378$) demonstrated less severe and less extensive reversible defects on thallium 201 stress imaging, longer exercise duration, and longer time to ST depression and less frequent ST segment depression during ambulatory monitoring, compared to patients with symptomatic ischemia. Patients with symptomatic ischemia had a higher frequency of subsequent cardiac events, compared to patients with silent myocardial infarction. Larsson and co-workers²³ assessed the importance of ischemic episodes in 198 patients after unstable angina or non-Q wave myocardial infarction; 18% of them had ischemic changes. After 30 days, death or infarction rate among the 163 patients without ischemia, was 3.2% compared to 17.1% among the 35 patients with ischemia ($P = 0.05$). The difference between the two groups was maintained at 3 months and at 1 year. In the TIMI 3B study,²⁴ the investigators found that Holter monitoring data contributed very little independent prognostic information in a large cohort of patients with unstable angina and non-Q wave myocardial infarction. The widespread use of aggressive antiplatelets and antithrombotic therapy combined with increased frequency of percutaneous coronary interventions in patients with acute coronary syndromes has reduced the frequency of ST deviation as recorded by AEM from 60%-80% to about 15%. Therefore, according to Yeghiazazians and co-workers,²⁵ AEM cannot be recommended as a tool for risk assessment.

Exercise Testing versus Holter Monitoring for Assessing Myocardial Ischemia

When comparing ischemic changes by AEM and by exercise testing, two central questions arise. The first question relates to the accuracy of AEM in comparison with exercise testing in detecting and assessing the severity of myocardial ischemia. Secondly, how is the information obtained with AEM distinct from that derived by exercise testing? In order to evaluate the diagnostic accuracy of ischemia during Holter monitoring, our group as early as 1985, validated the accuracy of the Del-Mar

Avionic System in reproducing ischemic changes by comparing these changes with those of the 12-lead electrocardiogram.²⁶ In a more recent study²⁷ we wanted to compare the accuracy of the Marquette system in reproducing ischemic changes. We studied 29 patients with proven CAD and positive treadmill exercise tests, and 19 individuals with low likelihood of CAD and negative exercise tests. Three leads were recorded; modified-V5, modified-V3 and aVF-like. We used split leads that transmitted the ECG signal from the same chest electrodes to the AEM recorders and the 12-lead ECG. A Bruce protocol exercise test was simultaneously recorded by both the AEM and 12-lead ECG. Ischemia was detected by both methods in all patients. On AEM, lead V5 detected ischemia in 26 patients compared to 24 on the 12-lead ECG, V3 detected ischemia on the AEM in 15 compared to 7 patients on the 12-lead ECG. The striking difference was in the inferior leads. While the aVF-like lead on AEM detected ischemia in only 4 patients, it detected ischemia in 23 of the patients on the 12-lead ECG. Severity of ST depression was identical on both recording methods. Of the 19 patients with negative exercise tests, only 1 had 1 mm ST depression on AEM. Thus we validated the accuracy of the three lead Marquette system in reproducing ischemic changes. We also found that the addition of an aVF-like lead is of little value for assessing myocardial ischemia.

Several previous studies have indicated that ischemic changes are more common on exercise testing than on AEM in patients with CAD. As the accuracy of detecting ischemic changes is similar by both methods, it seems that the reason for this difference is that during daily life, ischemic changes are less frequent than during the provocation of exercise testing and not due to inaccuracy of the AEM systems in detecting these changes.

The relationship between exercise-induced and ambulatory ischemia was assessed by Stone and co-workers.²⁸ They compared the exercise data of 659 patients with ischemia on AEM with 143 patients with no ischemia. They found that patients with ischemia on AEM had longer exercise duration (6.9 vs 8.0 minutes, $P = 0.001$), longer time to 1 mm ST depression (4.3 vs 5.9, $P = 0.01$), and lower ischemic threshold, i.e., heart rate, at 1 mm ST depression (123 vs 132 beats/min, $P = 0.001$). It seems therefore that ischemic indices on exercise testing are more severe in patients with ischemia on AEM compared to those with positive exercise

tests but without ischemia on AEM. However, when the authors correlated between the severity of ischemic changes as assessed by the number and duration of ischemic episodes and exercise parameters, they found a significant yet very limited relation between the number of ischemic episodes and time to 1 mm ST (r values of 0.19 to 0.37). We studied 60 patients who had Bruce protocol exercise testing and AEM within 2 weeks; all patients had ischemic changes on both tests. We found an extremely poor correlation between the exercise test duration, maximal ST depression, heart rate at ST depression, and the number of ischemic episodes, maximal ST depression and heart rate at ST depression on AEM.²⁹ Overall the correlation between ischemic indices on both procedures were very weak (mean $r^2 = 0.054$). This finding indicates that a great portion of the variability of Holter ischemic indices is dependent on factors other than those represented by exercise testing indices, and that Holter recording might provide clinically relevant information in addition to that obtained by exercise testing.

The differences in mechanism of ischemia on exercise and on AEM is exemplified by the different ischemic thresholds as observed during daily ischemic episodes and during exercise testing. Most ischemic episodes during daily activities are associated with mild to moderate increase in heart rate. Ischemic threshold, which is heart rate at 1 mm ST depression, is significantly lower during daily ischemic episodes compared to exercise testing.³⁰ The difference of 15-30 beats/min indicates that increased coronary tone, which is responsible for the reduced threshold, plays an important role in daily ischemia. Even in the same individual, ischemic threshold changes during daily life, in some episodes the threshold is similar to that of exercise testing while in others the ischemic threshold is much lower (increase in coronary tone?). This difference in ischemic threshold between exercise testing and ambulatory ischemia is probably responsible for the poor correlation between ischemic parameters during daily life and during exercise testing, suggesting different mechanisms of ischemia.³¹

Assessment of Antiischemic Drugs

Holter monitoring has been used for many years for assessing the effect of anti-anginal drugs. In most of these studies it was combined with re-

peated exercise testing. The effect of metoprolol OROS, a long-acting formulation, on daily myocardial ischemia was compared to the regular formulation of metoprolol given bid or tid.³² The once-daily OROS formulation 190 mg/d and 285 mg/d reduced the number of ischemic episodes observed in 23 patients, from 239 at baseline to 126 and to 86 episodes, respectively ($P = 0.0001$) for both. The 190 mg/day of the OROS formulation was as effective as the 100 mg taken bid and tid. In addition, we observed that metoprolol OROS exerted its effect throughout the 24 hours of the day. In the TIBET trial, 682 patients with stable CAD had exercise test and Holter monitoring and the efficacy of atenolol and nifedipine and their combination was assessed.³³ During treatment with atenolol, time to ischemia on exercise testing increased by 59% and by nifedipine by 60% and by their combination by 62%. On Holter monitoring the number of ischemic episodes was reduced by atenolol by 46%, by nifedipine by 48%, and the combination was similarly effective. Another study that compared β blockers to calcium antagonists was the TIBBS trial.³⁴ This study compared the anti-ischemic effects of bisoprolol and nifedipine in 330 patients with CAD, positive stress test and at least two ischemic episodes per 48 hours. Bisoprolol reduced the number of ischemic episodes per patient per 48 hours from 8.1 at baseline to 3.2 episodes on 10 mg/day and to 2.6 episodes on 20 mg/day. Nifedipine was also effective in reducing the number of episodes, however, bisoprolol was more effective than nifedipine ($P = 0.0001$). Only bisoprolol reduced the morning peak ischemic episode by 68%. Davis and co-workers reported the results of the CASIS trial³⁵ in which the effect of amlodipine, atenolol, and their combination on exercise and daily ischemia was assessed. Fifty-one patients received amlodipine 5 mg followed by 10 mg/day, and 49 patients atenolol 50 mg followed by 100 mg/day. While atenolol significantly reduced the number of ischemic episodes from 5.9 to 2.5 per 48 hours, amlodipine had only borderline effect in reducing the number of ischemic episodes. However, the combination of amlodipine and atenolol was more effective than either therapy alone ($P = 0.001$ vs placebo). In this study amlodipine increased exercise time to ST depression by 21% ($P = 0.001$) while atenolol increased time to ST depression by only 3% ($P = \text{ns}$). In the ASIST trial 306 patients with mild or no angina and positive exercise tests and evidence of ischemia on

Holter monitoring were studied.³⁶ Atenolol 100 mg/day compared to placebo significantly reduced the number of daily ischemic episodes. In addition, treatment with atenolol improved the one-year outcome. Absence of ischemia at 4 weeks was the best predictor of event-free survival.

The effect of various calcium antagonists on daily ischemia was also assessed. Theroux and co-workers compared the effects of diltiazem slow release 180 mg bid to placebo in 60 patients with positive exercise tests.³⁷ Diltiazem treatment was associated with a significant reduction in the number of ischemic episodes (from 4.5 to 1.5 per patient, $P = 0.0001$) and the duration of ischemia (from 78 minutes to 24 minutes, $P = 0.001$). Diltiazem slow release also increased time to 1 mm ST depression from 296 seconds to 341 seconds ($P = 0.005$). It seems that the effect of diltiazem in reducing ischemia was more pronounced on daily ischemia than on exercise induced ischemia.

More recently, we reported results of a multicenter study assessing the effect of mibefradil on daily ischemia.³⁸ Mibefradil is a selective T-channel calcium blocker that is an arterial vasodilator with negative chronotropic effect. This prospective randomized double-blind placebo-controlled trial involving 23 centers in seven countries, randomized 309 patients with stable angina to either mibefradil 50 mg, 100 mg, and 150 mg, or to amlodipine 10 mg/day or to placebo. At a dose of 50 mg, mibefradil improved exercise test parameters with no further improvement. Amlodipine only borderline improved exercise test parameters. The beneficial effect on daily ischemia was observed at the dose of mibefradil 50 mg/day, reducing the duration of ischemia by about 40%, at the dose of 100 mg it reduced it by 60%-80% and similar effect was observed at 150 mg. Mibefradil as a monotherapy was more effective than amlodipine in improving exercise and AEM ischemic parameters. Ischemic episodes in this study were divided into those with and without an increase in heart rate. At low dose of 50 mg/day, mibefradil suppressed ischemic episodes associated with increase in heart rate. At the higher dose (over 100 mg/day) mibefradil also suppressed ischemic episodes not associated with increase in heart rate. Thus, mibefradil at a low dose has a negative chronotropic effect while at the higher dose it is also a vasodilator. A similar approach to examine the effect of antiischemic drugs on episodes with and without increase in heart rate was used by Andrews and his group.³⁹ Recently

Deedwania and co-workers reported that amlodipine 10 mg/day significantly reduced the number of ischemic episodes, from 4.4 to 2.5 ($P > 0.005$).⁴⁰ In the second phase of this study, the number of ischemic episodes increased significantly in the group who received placebo following treatment with amlodipine.

The effect of nitroglycerin on daily ischemia was also assessed in several studies. Pepine and co-workers⁴¹ found that both silent and symptomatic episodes of ischemia were suppressed in patients who took sublingual nitroglycerin hourly. In another study by Pepine and his group⁴², 72 patients with positive exercise tests and ambulatory ischemia who had nitroglycerin patches from 8 AM to 10 PM were studied. An increase in ischemia and angina frequency during the "patch-off" hours was observed, thus in this study AEM was used to assess the possibility of rebound ischemia in patients off nitroglycerin. Knutti and co-workers⁴³ compared the effect of intermittent versus continuous transdermal nitroglycerin treatment on daily ischemia. They studied 185 patients with positive exercise tests. After the baseline period, patients were randomized to continuous or intermittent treatment with 10 hours off patch. Forty-eight hours of AEM was performed at baseline, after 2 weeks, and after 12 weeks of treatment. Intermittent treatment was found to be superior to continuous treatment, as the number of ischemic episodes was significantly higher in all phases with continuous treatment.

In a recent study, Patel and co-workers⁴⁴ reported the effect of nicorandil, a potassium channel opener, on ischemia in patients with unstable angina. The 108 patients were on maximal therapy and were randomized to nicorandil 20 mg bid or placebo, all had 48 hours AEM. Nicorandil added to aggressive anti-anginal therapy, significantly reduced myocardial ischemia (number of episodes was reduced from 74 to 37, $P < 0.028$). It is important to stress that most spontaneous ischemic episodes were not associated with an increase in heart rate, indicating that the mechanism of ischemia in these patients is not increased demand, but probably increase in coronary tone.

Ischemia detected by AEM can by itself aggravate a patient's prognosis or it can be a marker for a more extensive coronary disease or an indication of the activity of the coronary plaques. In the ACIP trial,⁴⁵ in the two medical treatment groups ($n = 328$) the number of AEM ischemic episodes were

predictive of cardiac events at 1 year ($P = 0.003$). In the AEM ischemia guided group reduction of ischemia by antiischemic therapy was associated with borderline reduction in cardiac events ($P = 0.06$). Among patients in the revascularization arm, this effect was not observed, in spite of improved prognosis. In this group, the most marked suppression of AEM ischemia was observed. However, in patients in the revascularization arm who had persistent AEM ischemia after surgery, these changes were not predictive of worse outcome. It is possible the revascularization improved blood supply to the most vulnerable territories or that the most vulnerable plaques were bypassed. It seems that AEM ischemia is associated with both more advanced CAD and more active CAD. Patients with similar anatomical extent of coronary artery disease may have different frequency of angina pectoris, different responses to exercise tests and markedly different frequency of ischemic episodes. It is probable that AEM ischemia is an expression of both the extent and activity of the coronary disease. However, in the era of extensive use of coronary interventions in patients with evidence of ischemia, it seems that no randomized studies will be able to address the issue of whether AEM ischemia contributes to prognosis assessment beyond exercise tests or thallium imaging, which probably represent the extent of coronary disease more than the coronary activity.

CONCLUSION

Holter monitoring is not a substitute for exercise testing for assessing myocardial ischemia. Exercise testing is less expensive, readily available and when performed in a population with a medium or high probability of CAD has reasonable sensitivity and specificity. Therefore, for the diagnosis of CAD and for assessment of its severity in an individual patient, exercise testing is the preferred method. As there is a marked day-to-day variability of ischemia frequency, AEM cannot be used to assess ischemia in an individual patient. It can be used for assessment of ischemia in a group of patients, for risk stratification of patients with known or suspected CAD, and for assessing the effect of an antiischemic drug. As the mechanism of ischemia during daily life is markedly different from that of exercise testing, the addition of AEM to exercise testing for assessing the antiischemic effects of a drug is of clinical importance and helps under-

standing the mechanism of action of the tested drug.

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