ST-Segment Analysis in Ambulatory ECG (AECG or Holter) Monitoring in Patients with Coronary Artery Disease: Clinical Significance and Analytic Techniques

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Since the invention of the ambulatory ECG (AECG or Holter) monitor by Norman Holter in 1961, the methodologies and applications of continuous recording of the ECG have evolved tremendously. The pioneering work of Bruce DelMar led to the first commercially available AECG in 1962 and the methodologies have become refined to the degree that the devices now only weight a few ounces and use solid-state memory circuits to record up to 7 days of continuous ECGs. The original AECGs were primarily used to detect rhythm disturbances, but early pioneering studies investigated the presence and significance of ST-segment depression.¹ With better fidelity of the low-frequency signal of the ST segment, monitoring for the presence of myocardial ischemia has now become routine.

Ambulatory or continuous monitoring of the ECG provides a unique insight into the presence and severity of myocardial ischemia in patients with coronary artery disease (CAD). AECG monitoring is generally performed in two clinical settings to assess ischemic risk: as outpatient evaluation of stable CAD patients and as inpatient evaluation of patients with an acute coronary syndrome (ACS) who need more prolonged recordings (1–7 days). AECG monitoring of stable CAD patients allows for assessment of ischemic jeopardy in their usual environment when the patient is exposed to the physical and emotional stresses of routine daily life. Such insights concerning ischemia are fundamentally different than assessments of ischemia in a supervised laboratory setting, where exercise stress testing is usually performed. Although there is a relationship between indices of ischemia during AECG monitoring (e.g., number and duration of ischemic episodes) and indices during exercise stress testing (e.g., exercise duration to 1.0 mm ST-

segment depression, depth of ST-segment depression, etc.), these correlations are quite weak.² An assessment of ischemic jeopardy by one technique is not a surrogate for ischemic jeopardy by the other technique. In the context of a hospitalized patient with an acute coronary syndrome, continuous ECG monitoring provides a unique insight into the stability of the underlying pathophysiologic process and the adequacy of treatment strategies.

The vast majority of episodes of transient ST-segment deviation during AECG monitoring occur in the absence of symptoms. Episodes of asymptomatic ischemia occur in 25–50% of patients with each of the coronary syndromes, i.e., stable angina, unstable angina, and acute myocardial infarction (MI), and the asymptomatic episodes may outnumber the symptomatic episodes by more than 20 to 1. Why certain episodes of ischemia are associated with angina while others are asymptomatic remains unknown. Suggested explanations include: (1) episodes of asymptomatic ischemia may be less "severe" than symptomatic episodes so that an "anginal threshold" is not reached;³ (2) disorders of peripheral autonomic nerves, such as diabetic neuropathy, may blunt the noiceptive signal of ischemia;⁴ (3) increased beta-endorphin levels may decrease the central perception of myocardial pain, and (4) abnormal central processing of afferent pain messages from the heart may occur due to non-myocardial factors, as well as emotional or personality characteristics, i.e., the cerebral cortex itself modulates the noiceptive signal that it receives (the so-called "gate theory" of cortical perception).⁵

The purpose of this review is to discuss the significance of the presence of ischemia during AECG monitoring in the coronary syndromes and then to

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review the methodologies currently available to detect and quantify such ischemia.

SIGNIFICANCE OF AECG ISCHEMIA IN THE CORONARY SYNDROMES

Stable Coronary Artery Disease

There has been substantial controversy concerning the mechanisms responsible for ischemia developing during routine daily outpatient activities in patients with stable coronary disease. Ischemia occurring during routine daily activities, identified by AECG monitoring, typically occurs at a heart rate 10–20% lower than the heart rate at which ischemia develops during an ETT,⁶ and the heart rate threshold at which ischemia occurs varies substantially,^{7,8} suggesting that varying degrees of coronary vasoconstriction play an important role in ambulatory ischemia. A variety of stimuli typically experienced during outpatient activities consistently provoke episodic coronary vasoconstriction in the laboratory: mental or emotional stress,^{9,10} anger,¹¹ exercise,¹² cigarette smoking,¹³ and exposure to cold.¹⁴

Andrews et al.¹⁵ related the minute-by-minute heart rate profile of stable coronary patients to the episodes of daily life ischemia and found that only 20% of ischemic episodes occurred in the absence of a heart rate increase, which would be the case if vasoconstriction was the primary pathophysiologic mechanism, and that approximately 80% of ischemic episodes were preceded by an increase in heart rate. Furthermore, the likelihood of developing ischemia throughout the day was proportional to the magnitude and duration of the heart rate increase and the baseline heart rate before the increases in heart rate (Fig. 1). Thus, the vast majority of daily life ischemia is preceded by some evidence of an increase in myocardial O₂ demand. The treatment implications of this finding are important, as discussed below.

Incidence of Asymptomatic Ischemia during AECG Monitoring

Asymptomatic ischemia identified by AECG monitoring during routine daily activities in stable CAD patients is extremely common, occurring in approximately 20–60% of patients. Those patients who experience episodes of asymptomatic AECG ischemia are generally those with more threatening coronary anatomy: more severe epicardial obstructions, more proximal lesions, and more “complex”

Figure 1. Graph showing likelihood of developing ischemia after a heart rate increase by the duration and magnitude of the preceding heart rate increase. Likelihood of developing ischemia was directly proportional to both the magnitude and duration of heart rate increases (bpm; $P < 0.001$). (From Andrews et al.¹⁵)

plaques, characterized by the presence of thrombus, ulceration, and irregular lumen borders.¹⁶ There is a correlation between the development of a progressively more abnormal exercise test and an increased likelihood of experiencing more frequent and more prolonged episodes of AECG ischemia.²

Pharmacologic Treatment of Asymptomatic Ischemia

Therapies that are effective at reducing myocardial O₂ demand are most effective at suppressing episodes of daily life ischemia in stable coronary patients. A comparison of efficacy of various classes of antianginal drugs is displayed in Figure 2.

Beta Adrenergic Blockers

As a class, beta-adrenergic blockers have been extremely effective in treating episodes of daily life ischemia during AECG monitoring. The particularly beneficial effect of beta-blockers is to be expected because daily life ischemia has been found to be almost entirely accounted for by changes in heart rate alone.¹⁵ In a recent cumulative analysis, beta-blockers were found to reduce the frequency of ambulatory ischemic events by 60%, reduce their cumulative duration per 48 hours by 70%, and abolish ischemia entirely in 50%.¹⁷ When beta-blockers are used in combination with other agents, such as calcium channel blockers, there is even greater anti-ischemic efficacy: 71% reduction in frequency,

Figure 2. Effect of treatment with various classes of antianginal drug therapy and myocardial revascularization on frequency, duration, and total suppression of transient ischemic episodes. (From Carbajal and Deedwania et al.¹⁷)

77% reduction in duration, and complete resolution of ischemia in 60%.

Diltiazem and Verapamil

Diltiazem has generally been effective in the treatment of episodes of daily life ischemia. However, the heart rate reduction observed during diltiazem treatment is less than that observed during propranolol therapy and diltiazem has been correspondingly less effective than propranolol. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, the reduction in ischemic episodes was similar using a regimen either of diltiazem or atenolol, as long as the mean heart rate was reduced to a similar degree.¹⁸ Verapamil, which is similar to diltiazem in its effect on heart rate and coronary vasomotor tone, has been found to have an efficacy similar to that of diltiazem.

Dihydropyridines

Clinical trials using conventional release nifedipine as single agent therapy have generally not observed a therapeutic benefit. When the heart rate patterns have been analyzed, nifedipine has been

shown to exert either no effect on heart rate or to significantly increase it compared to the values observed on placebo. Even though nifedipine may be exerting an anti-ischemic effect by preventing coronary vasoconstriction or by lowering systemic blood pressure, the reflex-mediated increase in heart rate, and consequent increase in myocardial oxygen demand, overshadowed the favorable effects and led to a lack of therapeutic benefit. The sustained release formulation of nifedipine, which may not be associated with as significant a reflex tachycardia, is associated with a 30–50% reduction in frequency and duration of silent ischemia episodes compared to placebo.¹⁹ In the TIBBS study, nifedipine GITS reduced the number of ischemic events by 24% and their duration by 12%, although it had no effect on heart rate. In contrast, however, bisoprolol in the same study substantially reduced the heart rate and reduced ischemia by 49% and 39%, respectively.²⁰

The addition of amlodipine to a background regimen of a beta-blocker reduced the frequency and duration of ischemia by 62% and 56%, respectively, compared to adding placebo to the beta-blocker, which reduced ischemia frequency and duration by 50%.²¹ In the CASIS trial, amlodipine alone reduced the frequency of ischemic episodes by 28% ($P = \text{NS}$), compared to 57% by atenolol alone ($P < 0.001$), and by 72% using a combination regimen ($P < 0.001$).²²

The recent CAPE II trial compared the efficacy of amlodipine and diltiazem, and the combination of amlodipine/atenolol and diltiazem/isosorbide 5-mononitrate on ischemia during 72-hour AECG monitoring and during ETT in patients with stable CAD.²³ Both amlodipine and diltiazem significantly reduced episodes of ambulatory ischemia, with no significant difference between the two treatments. The combination regimen of atenolol and amlodipine produced a highly significant reduction in ambulatory ischemia, while the combination regimen of diltiazem and isosorbide 5-mononitrate showed no significant improvement compared to monotherapy. During exercise testing, the benefits of the combination regimens parallel the benefits observed during AECG monitoring.

Nitrate Preparations

There have been remarkably few studies investigating the role of nitrates in the treatment of daily life ischemia. Von Arnim and Erath²⁴ compared

isosorbide-5-mononitrate tablets 20 mg t.i.d. in the usual formulation and 50 mg in the sustained-release formulation and found that each reduced the frequency and duration of episodes of silent ischemia by about 70% compared to placebo. Use of high-dose transdermal nitroglycerin patches (mean dose 52 mg/day) has been associated with 46% reduction in the daily frequency of episodes of silent ischemia ($P < 0.05$) and a 51% reduction in the daily duration of ischemia ($P = \text{NS}$) on the first day of treatment compared to placebo, but the beneficial effect is lost by the second day.²⁵ Use of intermittent dosing with a 12-hour nitrate free period did not prevent the development of tolerance.

Lipid-Lowering Therapy

Recent studies have suggested that therapies directed at improving coronary endothelial function itself may improve the incidence of daily life ischemia. The beneficial effect of lipid lowering may be due to the prevention of plaque rupture and restoration of a more healthy coronary arterial endothelium. Patients with ischemia during daily life activities frequently have ulcerated, irregular coronary plaques, or with minor thrombus,²⁶ and the daily ischemia may be improved with restoration of normal endothelial function. Pilot studies supported the hypothesis that marked lipid lowering may be associated with a marked reduction in the number and duration of daily life ischemic episodes,^{27,28} and a recent large scale trial, The Vascular Basis for the Treatment of Myocardial Ischemia Study has confirmed the earlier findings.²⁹ In the Vascular Basis Study, however, flow-mediated dilation of the brachial artery did not change in response to lipid-lowering therapy and so the mechanism(s) responsible for the anti-ischemia effect could not be ascertained.

Angiotensin-Converting Enzyme Inhibitors

A recent study investigated whether angiotensin converting enzyme (ACE) inhibitors, which are known to be vasculoprotective and improve endothelial function, could reduce myocardial ischemia during ambulatory ECG monitoring or ETT testing.³⁰ Stable CAD patients without hypertension or left ventricular dysfunction were treated with quinapril 40 mg/day ($n = 177$) or placebo ($n = 159$) for 8 weeks; the placebo group was then titrated to 80 mg/day. ETT and 48-hour AECG monitoring were performed at 8 and 16 weeks. In

this low-risk population, ACE inhibitors had no effect on ischemia during either AECG monitoring or ETT.

Prognosis Associated with Transient Asymptomatic Ischemia during AECG Monitoring

Most observational studies have demonstrated that the presence of asymptomatic ischemia during AECG monitoring of routine daily life activities is associated with an adverse cardiac prognosis (Table 1). There is a linear association between the number of ischemic episodes present off medications and the subsequent 1-year incidence of death, MI, revascularization, or an ischemic event requiring hospitalization in patients subsequently treated medically ($P = 0.003$) (Fig. 3). The Total Ischemic Burden Bisoprolol Study (TIBBS)³¹ indicated that patients with 6 episodes of AECG ischemia/48-hours at baseline had a 32% event rate at 1 year (death, MI, unstable angina, or revascularization) compared with 25% for patients with 2–5 episodes and 13% for patients with <2 episodes ($P < 0.001$).

In some studies that compared the significance of ischemia detected by AECG, ETT, as well as angiographic and clinical variables in stable coronary patients, the presence of daily life ischemia, detected by AECG monitoring, has been the most powerful predictor of cardiac mortality in follow-up to 2 years ($P = 0.003$), and of all cardiac events (death, MI, PTCA, CABG) for up to 5 years ($P = 0.009$).^{10,32} Madjlessi-Simon et al. found that the presence of transient AECG ischemia, the number of coronary stenoses, and beta-blocker withdrawal were the only significant prognostic factors of cardiac events.³³

A fundamental problem with virtually all the previous prognosis studies is that the event rates for "hard end points," such as cardiac death or MI, are very low in these stable patients and, consequently, essentially all the studies have relied upon much less definitive end points, such as revascularization procedures, worsening angina, or unstable angina, to obtain statistical power. Use of these softer end-points opens up these studies to important biases.

Randomized Clinical Trials to Assess the Effect of Anti-ischemia Strategy on the Prognostic Significance of Daily Life Ischemia

The ability of anti-ischemic therapies to improve the adverse prognosis associated with AECG

Table 1. Observational Studies Defining the Incidence and Prognostic Significance of Asymptomatic Ischemia Identified during Routine Daily Activities

Author, Year	No. of patients	Incidence of AECG ischemia (%)	End Points	Mean Follow-up (months)	Event rates(%)		P Value	Comments
					With AECG Ischemia	Without Ischemia		
Rocco et al. 1988	86	57	Death, MI, UA, revasc.	12.5	40	3	0.003	Patients monitored once off Rx
Tzivoni et al. 1988	118	33	Cardiac death, MI, UA, revasc.	28	51	20	<0.001	All patients with previous MI
Hedblad et al. 1989	394	25	Cardiac death & nonfatal MI	43	15	3	<0.001	
Deedwania and Carbajal, 1990	107	43	Cardiac death	23	24	8	0.02	Monitored on Rx
Raby et al. 1990	176	18	Cardiac death, nonfatal MI	20	38	7	<0.0001	Patients with peripheral vascular disease
Yeung et al. 1991	138	59	Death, MI, revasc.	37	56	42	0.02	Monitored off Rx
Deedwania and Carbajal, 1991	86	45	Cardiac death	24	23	4	<0.008	Monitored off Rx which controlled symptoms
Quyyumi et al. 1993	116	39	MI, UA, revasc.	29	13	15	NS	Very low-risk patients
Moss et al. 1993	936	5	Cardiac death, nonfatal MI, or UA	23	27	24	NS	Very low-risk patients
deMarchena et al. 1994	50	32	Cardiac death, MI, UA, revasc	10	56	21	<0.02	All patients monitored on Rx which controlled symptoms
Madjlessi-Simon et al. 1996	331	27	Death, MI, revasc., or worsening angina	21	33	17	0.004	All patients initially treated with a beta-blocker

AECG: ambulatory ECG; MI: myocardial infarction; UA: unstable angina; revasc.: revascularization; Rx: anti-angina medication.

ischemia has been inadequately studied (Table 2). Pepine et al.³⁴ studied 306 patients with ischemia detected both by ETT and by AECG and found that those patients treated with atenolol had improved event-free survival and increased time to the occurrence of a first adverse event compared with those patients treated with placebo. The most powerful univariate and multivariate correlate of event-free survival was the absence of AECG ischemia after

4 weeks of treatment. The control group, however, received no antianginal therapy, and the study consequently does not address the question of the incremental value of treating asymptomatic ischemia detected by AECG monitoring in addition to treating asymptomatic ischemia. In the TIBBS study,³¹ patients whose AECG ischemia was entirely abolished by bisoprolol or nifedipine had a 17.5% event rate at 1 year compared with 32.3% for those

Figure 3. Relationship between AECG ischemic episodes and incidence of combined cardiac events (death, MI, coronary revascularization, or hospitalization for an ischemic event) between week 12 and 1 year. Patients in the two medical groups are indicated by closed circles and patients in the revascularization group are indicated by open triangles. The r values represent the correlation between the number of AECG ischemic episodes and the incidence of combined cardiac events in the respective groups. (From Stone et al.³⁸).

patients who had at least one episode of residual ischemia ($P = 0.008$). The Total Ischemic Burden European Trial (TIBET)³⁵ found no difference in the occurrence of cardiac events after an average follow-up of 2 years in patients treated with fixed doses of either atenolol, nifedipine, or the combination, but there was no dose titration to determine the incremental benefit of escalation of anti-ischemic therapy, and there was substantial withdrawal (up to 40%) of assigned medication over the 2-year follow-up.

The Asymptomatic Cardiac Ischemia Pilot (ACIP) study was designed to determine the feasibility of performing a large-scale clinical trial to assess the prognostic significance of daily life ischemia. In the pilot study, 558 patients with coronary anatomy amenable to revascularization, one or more episodes of daily life ischemia on a 48-hour

AECG, and ischemia on an ETT were randomized to one of three treatment strategies: (1) medication to suppress angina alone (angina-guided strategy, $n = 183$); (2) medication to suppress both angina and daily life ischemia (ischemia-guided strategy, $n = 183$); or (3) revascularization strategy (angioplasty or bypass surgery, $n = 192$). Patients were evaluated with serial AECGs and medication was titrated to reduce anginal symptoms (all patients) and to eliminate daily life ischemia (ischemia-guided strategy patients). At the 12-week, 6-month, and 1-year follow-up, daily life ischemia was suppressed in each of the three treatment groups, but was more often completely suppressed in patients assigned to revascularization ($P < 0.001$ at each follow-up interval) (Fig. 4). The escalation of medication regimens in the ischemia-guided group was, unfortunately, quite minimal, and better ischemia reduction might have been achieved if the dose titration had been more aggressive.

Although not powered to be a prognosis study, the ACIP pilot study nevertheless provides important suggestions concerning the prognostic value of treating daily life ischemia.^{36,37} While the number of fatal events was small, the percentage of patients who died during the 2-year follow-up was significantly lower for patients assigned to the revascularization strategy (1.1%) than for those assigned to the angina-guided strategy (6.6%; $P < 0.005$) (Fig. 5A). The ischemia-guided strategy patients had an intermediate mortality rate (4.4%) between the revascularization strategy and the angina-guided strategy. There was no difference in mortality rate between the revascularization and the ischemia-guided strategies. Similar results were found combining the end points of death or MI (Fig. 5B). The incidence of death, MI, or nonprotocol revascularization was less common with revascularization than with either of the two medical strategies, but there was no significant difference between the two medical strategies (Fig. 6). Medical titration in the ischemia-guided strategy patients was not aggressive enough to eradicate ischemia, however, and a better prognostic effect might have been achieved if the medical regimen had been more effective.

Nevertheless, in the two medical strategies, there was a trend associating greater reduction in AECG ischemia at 12 weeks with an improved subsequent prognosis ($P = 0.04$).³⁸ This trend was evident primarily in the ischemia-guided group ($P = 0.06$) compared to the angina-guided group ($P = 0.32$). These observations suggest that AECG-guided treatment

Table 2. Clinical Trials to Assess Effect of Anti-Ischemic Strategies on Prognostic Significance of Asymptomatic Ischemia During Routine Daily Activities

Authors, Year	No. Patients	End Points	Follow-up (year)	Event Rate by Treatment Group	P
Pepine et al. 1994	306	Death, MI, UA, worsening angina, or revascularization	1 year	25% placebo 11% atenolol	0.001
Rogers et al. 1995	558	Death, MI, revascularization, hospital admission	1 year	32% angina-guided medical strategy 31% ischemia-guided medical strategy 18% revascularization strategy	0.003
Dargie et al. 1996	682	Cardiac death, nonfatal MI, and UA	2 year	13% atenolol 11% nifedipine 8% combination	NS
		Revascularization, worsening angina		8% atenolol 9% nifedipine SR 3% combination	NS
von Armin et al. 1996	520	Death, MI, UA, or revascularization	1 year	32% for non-100% responders 18% for 100% responders	0.008
				33% for nifedipine 22% for bisoprolol	0.03

MI: myocardial infarction; UA: unstable angina.

of ischemia may enhance prognosis in patients with stable coronary disease. There was no uniform consistency regarding the benefit of reducing the frequency of AECG ischemia in ACIP, however, and the results only provide a hypothesis for future investigation.

ACIP: Prevalence of AECG Ischemia in Followup

Figure 4. Percentage of patients free of ischemia on the AECG. At 12-week, 6-month, and 1-year follow-up, ischemia on the AECG was suppressed in each of the three treatment groups, but was more completely suppressed in patients assigned to revascularization. (From Rogers et al.³⁶)

In contrast to the observations in the two medical groups in ACIP, in the revascularization group there was no association between the number of AECG ischemic episodes at baseline and the incidence of subsequent cardiac events (Fig. 3), nor in the change in ischemic episodes from the baseline to the week 12 AECG. These observations suggest that revascularization is effective in lowering the incidence of subsequent cardiac events, regardless of the number of ischemic episodes present prior to revascularization. The lack of relationship between the change in ischemic episodes and improvement in clinical events may indicate that the clinical benefit resulting from revascularization may not be due to suppression of ischemia per se, but instead to an improvement in the underlying anatomic substrate that is responsible for the subsequent development of cardiac events.

Unstable Angina Pectoris

With the advent of AECG monitoring in the early and mid-1980s it became clear that many patients with unstable angina exhibited refractory episodes of asymptomatic ischemia, which persisted despite adequate control of symptoms with an intense medical regimen. In the era of treatment with a combination regimen of nitrates, beta-blockers,

Figure 5. (A) Two-year cumulative mortality rates for three treatment strategies. Significant differences were seen between revascularization and angina-guided strategies ($P < 0.005$) and between revascularization and ischemia-guided strategies ($P < 0.05$). Angina-guided and ischemia-guided strategies were not significantly different from each other. (B) Two-year cumulative rates of death and MI. Revascularization strategy was significantly different from angina-guided strategy ($P < 0.01$). Differences were not significant between revascularization and ischemia-guided strategies and between angina-guided and ischemia-guided strategies. (From Davies et al.³⁷)

and calcium channel blockers, approximately 50–70% of patients exhibited transient episodes of asymptomatic ST-segment deviation (Fig. 7). Since heparin, aspirin, and even glycoprotein IIb/IIIa inhibitors have become included in the current regimens, however, the incidence of asymptomatic ischemia has dramatically decreased to approximately 10–20% (Fig. 7).

As noted earlier for patients with stable angina, patients with unstable angina who exhibit episodes of transient asymptomatic ischemia are those with high-risk coronary anatomy and a corresponding adverse prognosis.³⁹ A recent report has even suggested that active inflammation is associated with increased ischemia during continuous ECG monitoring: a high plasma CRP value at admission was

Figure 6. Two-year cumulative rates of death, MI, or cardiac hospitalization. Differences were significant between revascularization strategy and both angina-guided strategies and ischemia-guided strategies ($P < 0.003$). The latter were not significantly different from each other. (From Davies et al.³⁷)

significantly associated with the extent of spontaneous ischemia detected by continuous ECG monitoring⁴⁰ and there was a significant positive correlation between CRP values and the total ischemic burden.

Although the presence of asymptomatic ischemia often is among the most important predictors of an adverse outcome in unstable angina,^{41–44} the infrequent incidence of this abnormality in the TIMI IIIB study casts doubt on the widespread utility of AECG monitoring to identify risk in the current therapeutic era. Among 733 patients with

Figure 7. Incidence of asymptomatic AECG ischemia in patients with unstable angina based on pharmacologic regimen. (Adapted from Stone.⁵⁷)

unstable angina or non-Q-wave MI treated medically, only 10% exhibited >1 episode of asymptomatic ischemia and only 4% exhibited ischemia >20 minutes/24 hours.⁴⁵ Furthermore, the patients with a high risk AECG were generally identified by the other risk stratifying tests: the AECG uniquely identified risk in only 3% of the patients, while the exercise thallium test uniquely identified risk in 34% of patients and the exercise test alone in 33% of patients at risk.⁴⁵

A recent meta-analysis of three large studies evaluating glycoprotein IIb/IIIa blockers in 995 patients with non-ST-elevation ACSs has re-invigorated interest in using continuous ECG monitoring to identify high-risk populations with ACS.⁴⁶ These investigators found that ischemic episodes occurred in 27% of patients with NSTEMI ACS and that there was a direct proportional relationship between the number of ischemic episodes/24 hours and the probability of cardiac events at 5 and 30 days.⁴⁶ Both in univariable and multivariate analyses, the independent relationship between recurrent ischemia and adverse outcomes was remarkably consistent.

Episodes of transient ST-segment deviation have also been used to gauge therapeutic efficacy from a variety of interventions for patients with an ACS. In the CAPTURE study, for example, asymptomatic recurrent ischemia was detected in 18% of abciximab-treated patients and in 23% of placebo-treated patients ($P = \text{NS}$),⁴⁷ although only 5% of abciximab patients had >2 episodes, compared to 14% of placebo patients ($P < 0.01$). Abciximab also significantly reduced the total ischemic burden ($P < 0.02$). In a small group of 100 patients with ACS randomized to either atorvastatin 80 mg/day or placebo, there was a trend towards a lower risk of developing recurrent or prolonged episodes of ST-segment deviation during 48-hour continuous ECG monitoring in the patients treated with atorvastatin.⁴⁸ Hormone replacement therapy with conjugated estrogen plus medroxyprogesterone for 21 days had no effect on recurrent ST-segment deviation in 293 postmenopausal women with ACS.⁴⁹

Acute Myocardial Infarction

The largest study designed to systematically investigate the incidence and significance of asymptomatic ischemia detected by continuous ECG monitoring compared with other risk-stratifying

tests was performed in 406 patients who were studied 5–7 days after MI.⁵⁰ Recurrent ischemia detected by ECG monitoring was the most powerful predictor of adverse cardiac events. In contrast to the prognostic value of ECG monitoring, the development of ischemia during the ETT did not predict an adverse cardiac event, although the rates for all cardiac events were markedly higher among the patients in whom exercise testing was not performed.⁵⁰ Among clinical variables, ejection fraction variables, ETT and continuous ECG monitoring variables, the presence of ECG ischemia contributed the most significant prognostic information.⁵⁰ Although continuous ECG ischemia had a low predictive value for death alone (12%), it had a 44% predictive value when nonfatal MI and unstable angina were included as outcomes.

Continuous ECG monitoring has been of enormous value to identify the efficacy of treatments in the management of patients with ST-elevation MI.⁵¹ The speed with which ST-segment elevation resolves following a therapeutic intervention using static or serial ECGs has been associated with improved myocardial tissue perfusion and improved prognosis,⁵² and continuous ECG monitoring of ST-segment recovery characteristics provides better characterization of the entire process of reperfusion.⁵³ In the recently reported INTEGRITI trial investigating 50% of standard dose tenecteplase plus high dose eptifibatide compared to full dose tenecteplase 24-hour continuous ECG monitoring in 140 patients demonstrated that the combination regimen achieved faster median time to stable ST-segment recovery and less recurrent ischemia.⁵³ These improved ECG markers of ST-segment recovery were also correlated with improved angiographic results at 60 minutes. Larger studies involving more patients and with different therapeutic interventions will be necessary to confirm the value of ST-segment recovery characteristics as a biomarker for clinical outcomes for patients with STEMI.

METHODOLOGY FOR AECG RECORDING, PLAYBACK, AND ANALYSIS

Equipment

The conventional format for recording has been magnetic cassette-type tape.⁵⁴ This format allows for playback and interrogation of the entire

recording period (so-called "full disclosure"). An inadequate low-frequency response, such as the ST-segment, or marked phase shift from the higher frequency QRS signal, can lead to artifactual distortion of the ST-segment that may be incorrectly interpreted as ischemic, particularly using some amplitude modulated (AM) systems. Recent AM systems have been designed with improved low-frequency recording and playback characteristics, however, and have been documented to record accurately ST-segment deviation. The frequency modulated (FM) systems avoid this bias because they can be designed with an ideal low-frequency response without a low-frequency "boost" and are less prone to phase shift. However, FM systems are not as widely available, are more costly, and are subject to more baseline "noise" than AM systems. Regardless of whether AM or FM recording techniques are used, the tape itself may also stretch and consequently distort the electrical signal.

Rapidly evolving technologies now allow for direct recording of the ECG signal in digital format using solid-state recording devices.⁵⁴ The direct digital recording avoids all of the biases introduced by the mechanical features of tape recording devices and the problems associated with recording data in an analog format, which requires analog-to-digital conversion prior to analysis. These solid-state recordings can be analyzed immediately and rapidly, and some recorders are now equipped with microprocessors which can provide "on-line" analysis of the QRS-T complex as it is acquired. If ST-segment deviation is identified, immediate feedback can be provided to the patient. The solid-state format also provides for ready electronic data transfer to a central analysis facility. Limitations of this technology include its expense, the limited storage capacity of digital data, and, in the case of on-line analysis, reliance on a computer algorithm to identify abnormalities accurately. A 24-hour recording includes approximately 100,000 QRS-T complexes and requires almost 20 Mb of storage per channel. Newer technologies of enhanced storage capacity allow for all of the technical advantages of solid-state recording and now allow "full disclosure" and adequate reconstruction of the entire waveform with no loss of information.

Selection of Leads to Be Monitored

Most recorders utilize 5 or 7 electrodes attached to the chest, which record the signal from 2 or 3

bipolar leads onto 2 or 3 channels, although some systems utilize Frank orthogonal X-Y-Z leads and calculate averaged QRS-T complexes. A variety of bipolar lead configurations are used, the most common being a chest modified V5 (CM5), a chest modified V3 (CM3), and a modified inferior lead. If a patient undergoing AECG monitoring for ischemia has had an exercise stress test demonstrating ischemic changes, the AECG lead configuration should mimic those leads with the greatest ST-segment change during exercise. Using simultaneous recordings of a 3-lead AECG and a conventional 12-lead ECG recording during an exercise treadmill test,⁵⁵ CM5 was the single lead with the highest sensitivity (89%) in detecting myocardial ischemia. The addition of CM3 to CM5 increased the sensitivity to 91%, and the addition of an inferior lead to CM5 increased the sensitivity to 94%, particularly improving detection of isolated inferior ischemia. The combination of all three AECG leads had a sensitivity of 96%, only 2% more than the best combination of two leads (CM5 plus an inferior lead). Thus, routine identification of ischemic ST-segment deviation may only require two leads. Use of an inverse Nehb J lead, where the positive electrode is placed on the left posterior axillary line, may enhance sensitivity to detect ischemia.⁵⁶ Some new AECG monitor systems can record a true 12-lead ECG, whereas others derive a 12-lead ECG from 3-lead data using a mathematical transformation.

Variability of Ischemia during AECG Recording and Optimal Duration of Recording

The variability of the frequency, duration, and depth of ischemic ST-segment depression is substantial.⁵⁴ Since most ischemic episodes during routine daily activities are related to increases in heart rate, the variability of ischemia between recording sessions may be due to day-to-day variability of physical or emotional activities. It is therefore essential to encourage similar daily activities at the time of AECG recording. The optimal and most reasonable duration of recording to detect and quantify ischemic episodes is probably 48 hours, although more experience is necessary in using currently available digital recording systems that allow for more prolonged recordings and are sufficiently secure that patients can bathe and participate in all usual activities.

QRS-T Morphology Characteristics Suitable for Interpretation

Morphology characteristics for optimal interpretation include normal sinus rhythm, QRS duration ≤ 0.10 seconds, and R wave height in lateral precordial leads (V3–V6) ≥ 15 mm. For inferior leads, the R wave height should be ≥ 10 mm. At rest, the baseline J point should not exhibit depression ≥ 1.0 mm or elevation ≥ 1.0 mm compared to the isoelectric line. Ideally, the ST-segment morphology will be gently upsloping with an upright T wave. An ST segment which is flat or associated with an inverted T-wave is acceptable; downsloping or scooped ST-segment morphology should be avoided. The baseline or resting ST-segment morphology should not change ≥ 1.0 mm in response to changes in the body position. Identification of the ST-segment changes associated with postural changes will help in the accurate interpretation of ST-segment changes during unsupervised activities at home.

Conditions precluding accurate interpretation of ST-segment activity include left ventricular hypertrophy based on the assessment of a 12-lead ECG, presence of a Q wave ≥ 0.04 seconds in a lead considered for monitoring, atrial fibrillation/flutter, use of digoxin or other medications known to affect ST-segment morphology, such as antidepressants, and left bundle branch block. In the presence of right bundle branch block, the frontal plane leads and the lateral precordial leads remain suitable for interpretation of ischemia.

Technical Features of AECG Analysis Procedures

The AECG recorder automatically records a 1.0 mV calibration pulse for 5–8 minutes at the beginning of the recording, and the computer playback system automatically corrects the entire tape so that the deflections identified in absolute millimeters are accurate (i.e., 1.0 mV equals 10 mm). Calculation of accurate ST-segment depression from baseline, as well as of its slope, is thus possible. Baseline ST-segment values may be determined once at the beginning of the recording, or may be determined prior to each observed episode of ST-segment deviation. Those systems that redetermine a baseline ST-segment value before each episode identify an "average" ST segment every 30–60 seconds. The computer algorithm then scans the entire 24-hour tape and identifies those periods in which the ST-

segment baseline is "stable" using a moving window of ST-segment values. This value then serves as the new "baseline." If the ST-segment values are found to deviate from the identifiable "stable" preceding values, they are identified as being "unstable" and subsequently undergo quantitative analysis to determine whether criteria for a discrete episode of ST-segment deviation are met.

A trend of the ST-segment activity and morphology is plotted on paper displaying the deviation of the J point and a point 60 ms after the J point to the isoelectric P–Q value. Figures 8 and 9 illustrate the ST-segment trend from a representative patient with coronary disease monitored during daily activities. In the uppermost panel, a significant episode of ST-segment depression with downsloping morphology is displayed in both leads modified V5 (channel 1) and modified aVF (channel 2). The heart

AECG Monitoring of Ischemia *Temporal Trend of ST-Segment Deviation and HR*

Figure 8. Temporal trend of ST-segment deviation and heart rate during a typical episode of ambulatory ischemia.

AECG Monitoring of Ischemia *Real-Time Presentation of ECG During Ischemic Episode*

Figure 9. Real-time presentation of ECG during the ischemic episode displayed in Figure 8.

rate, R-R interval, VPB count, and SVPB count are also displayed in panels underneath the ST-segment trend on the corresponding pages to identify concomitant changes in these parameters that may accompany episodes of ST-segment deviation. Note, for example, that an increased heart rate and frequent ventricular ectopic activity accompanies the episode of ST-segment deviation. This format allows for insight as to whether a particular episode is a true physiologic event, which is usually accompanied by a primary or secondary change in heart rate, or simply represents an artifact (e.g., postural changes, etc.). An ST-segment deviation that is artifactual often shows an abrupt change in the J-point value that persists for hours without any variation and without accompanying heart rate changes (Figs 10–12). The reader is referred to a recent review for extensive examples of both real and artifactual ST-segment deviation.⁵⁷

An episode of ischemia is typically defined by the presence of ST-segment depression ≥ 1.0 mm compared to its baseline, which lasts for ≥ 1.0 minutes, and which is separated from other episodes by 1–5 minutes, but there has not been consensus concerning other details of characterizing episodes of ST-segment deviation.⁵⁸ For example, some investigators have required the presence of depression of both the J point and a point on the ST segment 60–80 ms after the J point to qualify as ischemia, while others rely solely on the ST-segment value 60–80 ms after the J point.⁵⁸ Some investigators classify the onset and offset of an ischemic episode that satisfies the definition of ischemic ST-segment depression when the ST segment first deviates from, and then returns to, its stable baseline, while others classify onset and offset only when the ST-segment is deviated 1.0 mm below baseline ST-segment value. These different definitions do not affect the number of ischemic episodes, but clearly affect the duration of each episode. Other variables of ischemia episodes include combination variables that incorporate both the depth of depression and the duration of the episode ("ischemic burden"). These variables may be defined as the area-under-the-curve of the ST-segment depression, or a "product" of the depth of ST-segment depression and the duration of the episode. The independent significance of these combination variables is unknown.

SUMMARY AND CONCLUSIONS

Asymptomatic ischemia is common in patients with stable coronary disease during routine daily activities. The perception of ischemic pain (angina) may in part be related to modulation of pain sensation by peripheral neuropathic changes or modulation of central processing of afferent stimuli by physiologic and psychological influences. Since asymptomatic ischemia is not associated with any symptoms or discomforts, the detection of ischemia by AECG monitoring would only be of clinical significance if its presence was independently associated with an adverse prognosis.⁵⁴ Observational studies and small-scale randomized clinical trials suggest that more aggressive and thorough treatment of ischemia would lead to an improved outcome, but a more definitive large-scale study is necessary to confirm this relationship.

The incidence of ischemia in patients with unstable angina has declined dramatically with use of aspirin, heparin, and the more powerful

Figure 10. Temporal trend of ST-segment deviation and heart rate. Artifactual ST-segment deviation is due to changes in body position.

Figure 11. Real-time presentation of ECG complexes during "episodes" identified in Figure 10.

AECG Monitoring of Ischemia
Documentation of Artifactual ST-Segment Deviation
Based on Supervised Recordings During
Body Position Changes

Figure 12. Documentation of artifactual ST-segment deviation based on supervised recordings during body position changes.

antithrombotic agents. Identification of ischemia by continuous ECG monitoring in unstable angina patients indicates high risk, but the unique contribution of continuous ECG monitoring to identify high risk may be quite low. Other risk stratifying tests such as exercise testing or exercise perfusion scintigraphy may be more appropriate than continuous ECG monitoring for widespread clinical use.

In patients with acute MI, continuous ECG monitoring is valuable both to identify patients at high risk, based on the presence of recurrent ischemia, and to gauge efficacy of treatment, based on the characteristics of resolution of ST-segment elevation.

The technical analysis of ST-segment changes indicative of ischemia require careful attention to detail both in the setup of the patient prior to the recording session and in the analysis of the recording itself. Careful preparation will allow for a clear QRS-T signal that lends itself to proper interpretation. Identification of ischemic episodes can be accomplished accurately with close scrutiny of both baseline QRS-T morphology and episodic deviations in morphology. Such analyses provide accurate identification and characterization of the high-risk patient with coronary artery disease.

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