T3 MANUAL OF OPERATIONS

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CHAPTER 20

HOLTER CORE LABORATORY PROCEDURES

20.1 INTRODUCTION

20.1.1 Rationale for Utilization of Ambulatory ECG Monitoring in the Study of Unstable Angina and Non-Q-Wave Myocardial Infarction

It has been acknowledged recently that both stable and unstable syndromes of coronary artery disease are associated with manifestations of ischemia that may be either symptomatic (i.e. producing angina or "angina-equivalents") or asymptomatic. Appreciation of the existence of episodes of asymptomatic or "silent" ischemia was not possible until techniques became available to identify episodes of ischemia objectively in the absence of characteristic symptoms. Invasive techniques such as monitoring left ventricular pressure have been used, as well as minimally-invasive techniques such as radionuclide imaging, but these techniques are not feasible for long-term monitoring. Transient ST segment deviations are one of the hallmarks of myocardial ischemia and the techniques of ambulatory ECG (AECG) monitoring have been refined and validated in recent years to the point that even subtle changes in the ST segment can be accurately detected (1-3). Episodes of myocardial ischemia can now be objectively identified and quantified using inexpensive and reliable recording and playback machinery.

The symptomatic perception of myocardial ischemia (i.e., angina) appears to be a useful, but extremely imprecise measure of the activity of coronary disease. As in patients with stable coronary disease (4-8) episodes of silent ischemia are frequent in patients with unstable angina and are associated with a particularly adverse prognosis (9-16). Preliminary experience indicates that such episodes of asymptomatic ST segment deviation are also seen in the first few days following

myocardial infarction and are associated with a similarly poor prognosis (17, 18). Langer and colleagues (16) recently reported that episodes of ST-segment deviation occurred in 89 (66%) of 135 patients with unstable angina treated with nitrates, beta blockers, and calcium blockers and that such episodes were strongly associated with high-risk coronary anatomy and an adverse hospital course. Multivessel coronary disease occurred in 76% of patients with episodes of ST-segment deviation vs 54% of patients without such episodes ($p < 0.01$), left main coronary stenosis in 18% vs 4% ($p < 0.05$), and an unfavorable hospital outcome (myocardial infarction, death, or refractory symptoms requiring a revascularization procedure) in 48% vs 20% ($p < 0.005$). Gottlieb and coworkers (10) observed at least one episode of silent ischemia during 2 days of ECG monitoring in 37 (53%) of 70 patients with unstable angina treated intensively with nitrates, beta blockers, and calcium-channel blockers and found in addition that such episodes were associated with a poor outcome following hospital discharge. Episodes of angina were infrequent (0.2 episodes/day) both in those with or without episodes of silent ischemia, and the angina was frequently unassociated with ECG changes. During the one-month follow-up there was a significantly higher cumulative probability of infarction or need for revascularization in the group with silent ischemia compared to the group without silent ischemia (43% vs 12%, respectively, $p < 0.01$). Furthermore, among the 37 patients with silent ischemia the cumulative probability of an unfavorable outcome was significantly higher among the 17 patients who had 60 minutes or more of silent ischemia per 24 hours than in the 20 patients who had less than that amount ($p = 0.04$). The stepwise Cox regression analysis of 15 variables indicated that the presence of silent ischemia as detected by continuous ECG monitoring was the most powerful predictor of infarction or need for revascularization

($p < 0.002$), followed in predictive power by the occurrence of chest pain within the same two-day monitoring period ($p < 0.02$) (10).

Similarly, Nademanee and coworkers performed 24-hour monitoring on 49 patients with unstable angina after they received intensive medical therapy and were stable (11). Twenty-nine patients (59%) experienced episodes of silent ST segment deviation. There was a positive correlation between the duration of ischemia observed during AECG monitoring and the number of diseased vessels. These investigators also observed that episodes of silent ischemia were associated with a poor prognosis. Of 18 patients with more than 60 minutes of silent ischemia during the 24-hour recording, 17 (94%) either developed an acute myocardial infarction or required revascularization during a six-month follow-up. In contrast, these adverse outcomes occurred in only 3 of 11 patients (27%) with less than 60 minutes of silent ischemia, and in only 1 of 18 patients (6%) who had no episodes of silent ischemia. Episodes of angina were infrequent during the monitored period in this study and the prognostic significance of silent versus symptomatic episodes of ischemia was not addressed.

20.1.2 Use of Heart Rate Patterns During AECG Monitoring to Investigate Mechanisms of Ischemia and Response to Therapy

In an effort to identify the pathophysiologic mechanisms responsible for silent ischemia, the heart rate preceding an episode of ischemia in a pilot group of 11 patients with unstable angina treated with an aggressive regimen of medical therapy was analyzed at Brigham and Women's Hospital. Of the 7 patients (64%) who exhibited episodes of silent ST segment depression, 31 episodes (89%) not associated with an increase in heart rate 5 minutes before the ST segment depression were observed, suggesting that the ischemia was due to a primary decrease in myocardial perfusion (transient platelet aggregation or vasoconstriction). Only 4 episodes (11%) were associated with a preceding increase in myocardial oxygen demand, reflected by a 10% increase in heart rate compared to the heart rate 5 minutes before the episode. Although others have observed a similar pattern of heart rate activity prior to

episodes of silent ischemia in patients with unstable angina (12), no one has evaluated the differential response to an intervention on the basis of heart rate activity prior to an episode of ischemia. One would anticipate that administration of a thrombolytic agent would be particularly effective in reducing episodes of silent ischemia that are not associated with an increase in heart rate since ischemia in unstable angina appears predominantly due to waxing and waning of a subtotally occlusive intracoronary thrombus and consequent reductions in blood flow.

20.2 SPECIFIC AIMS

The specific aims of the AECG Core Laboratory are to identify episodes of myocardial ischemia during a 24-hour recording session in study patients with unstable angina or non Q-wave myocardial infarction and to characterize episodes based on their relationship to experimental therapy. The duration of ST-segment deviation, its maximum extent, and the pattern of heart rate activity prior to and during an ischemic episode will be recorded.

20.3 PERFORMANCE OF AECG

20.3.1 Schedule of AECG Recordings

Patients enrolled in T3B will undergo a 24-hour AECG recording between day 3-5 after randomization. Patients enrolled in T3A will undergo a 24 hour AECG recording on day 2 between the initial and follow-up cardiac catheterization.

20.3.2 Acceptable AECG Recorder Models

The following AECG recorders are adequate for ST-segment analysis.

Manufacturer	Model or Recorder Type
ACS	8500
Avionics	456A
CardioData Corp	PR3
DMI	DMI
Marquette	8500 series

	Oxford
Medilog 4000-III	
	Scole
Omega 4	
	Spacelabs
ICR 7200	

All of these recording units have 5 leads, 2-channel recording, and have automatic insertion of calibration signal. Other recorders may also be suitable for ST-segment analysis; please contact the AECG Core Laboratory for additional information.

20.3.3 Application of AECG Recorder

In order to allow for accurate analysis of the recordings at the AECG Core Laboratory, special attention to skin preparation and electrode placement as well as absolute compliance to the sequence of events must occur when initiating Holter monitoring.

The following pages give step-by-step directions and descriptions for application of the Holter monitor.

20.3.3.1. Preparation of AECG Recorder and Tape Cassette

The actual model of Holter monitor may vary from site to site, but each cassette recorder will have basically the same function and will be compatible with the analysis computer. The accuracy of the actual recording equipment must be certified by the AECG Core Laboratory (see "Acceptable AECG Recorders Models", Section 20.3.2.). It will be critical for you to know the operation of the particular model you will be using. The most important features to focus on are:

a. Clock function (how to set time--most are toggle switches).
b. Cassette tape insertion (some models have a swing bar, some do not).
c. Battery compartment (some have a separate compartment to which the battery snaps in).
d. Power switch (usually a toggle switch)
e. Test cable capabilities
f. Basic maintenance

(1) Legibly print the patient's study identification number and visit number in ball point pen on the cassette tape.

(2) Remove old battery and install a new battery in the battery holder, as shown in the diagram in the battery compartment. Make certain that the battery is pressed firmly into the clip and makes good contact. Check the clock and set, if necessary, to the correct time of day.

(3) Using an unrecorded cassette properly labeled, hold the cassette with the A label upwards and facing you and turn the empty spool (your right hand) (see ---> in lower corner) counterclockwise to remove the slack until the tape leader is past the center of the cassette. <u>THE BROWN MAGNETIC TAPE MUST BE DIRECTLY IN FRONT OF THE CENTRAL OPENING IN THE CASSETTE AND WRAPPED AROUND THE SPOOL AT LEAST TWICE</u>. Swing back the head arm, insert the cassette, and check to see that the tape is correctly located in front of (and not outside) the capstan. The cassette should preferably have been checked to see that it is free running. A stiff cassette can often be freed by tapping it on each side a few times to remove irregularities in the tape spool. Close the head arm.

(4) Proceed with skin preparation.

20.3.3.2. Skin Preparation for AECG Monitoring

The presence of artifact or baseline shift on the recorded ECG waveform can, in almost all instances, be traced to problems in electrode application or skin preparation. If the electrodes are not clean and securely attached to the patient, ECG recordings of diagnostic quality cannot be obtained. The following procedure is recommended for application of the electrodes:

a. Shave areas where electrodes are to be placed. Shave women as well as men (if necessary).

b. Using alcohol swabs, thoroughly cleanse skin in these areas to remove body oils and dead skin layer. Proper skin preparation should produce a slightly reddened skin condition. Allow skin to dry completely.

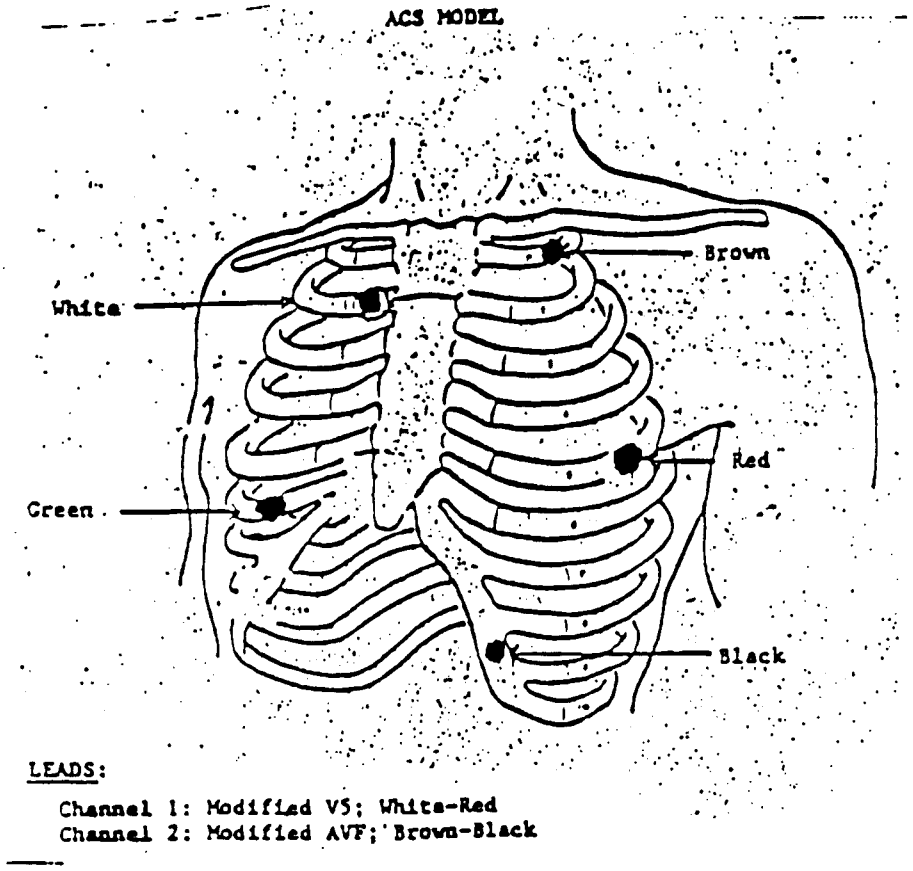
c. Choose the electrode sites (over bony areas when possible) to reduce DC shift from muscle artifact) and mark with a felt-tip pen.

d. Abrade electrode sites with emery tape to reduce skin resistance (care should be taken not to break the skin as this tends to give poor recordings [if bleeding occurs] and causes discomfort).

e. Attach electrodes to lead wire before attaching to the patient in order to avoid leakage of the electrode conducting gel due to pressure. Attach electrodes to the patient firmly, avoiding pressure on the center.

The diagram below illustrates the specific lead placement for the Holter monitor.

HOLTER ELECTRODE PLACEMENT



20.3.3.3. Electrode Placement

The ACS Model 8500 AECG Recorder is one type of 24-hour, 5-lead ECG recorder. You may be using a different model and should therefore determine the specifics for lead placement with that model. Two channels (or leads) are being recorded simultaneously. Channel 1 is the primary viewing channel during playback while Channel 2 is a secondary lead for analysis. The patient event marker (which is pressed if the patient is experiencing any symptoms) is recorded and later displayed on Channel 2, thereby deleting the QRS complex which would normally

occupy that space. Channel 1 recording is unaltered by activation of the patient event marker.

Channel 1 and Channel 2 each have an exploring electrode and a reference electrode, and share a common ground electrode.

Below is a table describing the color coded patient leads, which Channel they service, lead placement, and the respective electrocardiographic lead they represent for the ACS 8500 model.

	ELECTRODE	COLOR	PLACEMENT
Channel 1			
Modified V5	CMR -	White	Right side of manubrial portion of sternum, second rib
Left ventricular lead	EXP +	Red	Left anterior axillary line, fifth rib
Channel 2			
Modified AVF	CMR -	Brown	Left side of manubrial portion of sternum, first rib
Inferior Lead	EXP +	Black	Left side of manubrial portion of sternum, eighth rib
Ground	GND	Green	Right lower rib margin

20.3.3.4 Micronta Impedance Meter

Measure skin resistance with the Micronta Impedance Meter.

The Micronta Impedance Meter measures AC and DC voltages, DC current, and resistance. The only function of the Micronta Impedance Meter which is of importance to this study is the measurement of resistance between the electrodes.

a. Prepare the skin as outlined.

b. Place electrodes on the patient.

c. Place the black test lead into the negative jack 5 and the red test lead into the positive jack 4 (see diagram - Exhibit 20-1).

d. Set the switch to the ohm position (6) (Rxlk) and touch the test probe tips together. If the meter does not read zero "0" on the top (red) K OHMS scale 1 , then use the OHMS Adjust dial 2 to set the meter indicator to zero. If there is no activity of the meter when turned on, replace the battery.

e. Touch the black lead wire to one of the electrodes and the red lead wire to the other electrode previously placed on the patient.

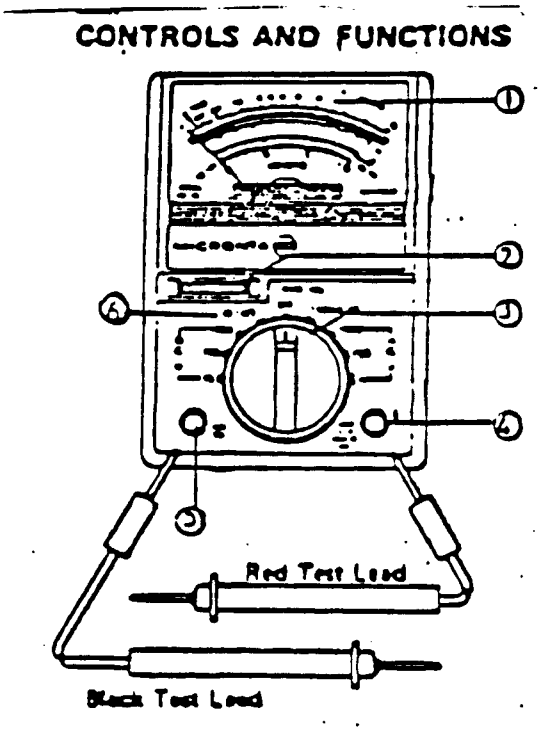
f. Read the resistance on the red OHMS scale. <u>If the resistance is less than 5 K OHMS, and preferably less than 2 K OHMS, the electrodes are fine</u>. If the reading is greater than 5 K OHMS, remove the electrodes and repeat skin preparation until the reading is at the required level.

g. Using one of the electrodes as the reference, test the remaining three electrodes until all impedance levels are in the acceptable range.

h. Turn off the Impedance Meter and continue the AECG application procedure.

Exhibit 20-1

Figure of Micronta Impedance Meter



1. K OHMS SCALE
2. OHMS ADJUST
3. RANGE SWITCH
4. RED LEAD INPUT JACK
5. BLACK LEAD INPUT JACK
6. K OHMS POSITION SETTING

20.3.3.5. Electrode Adherence

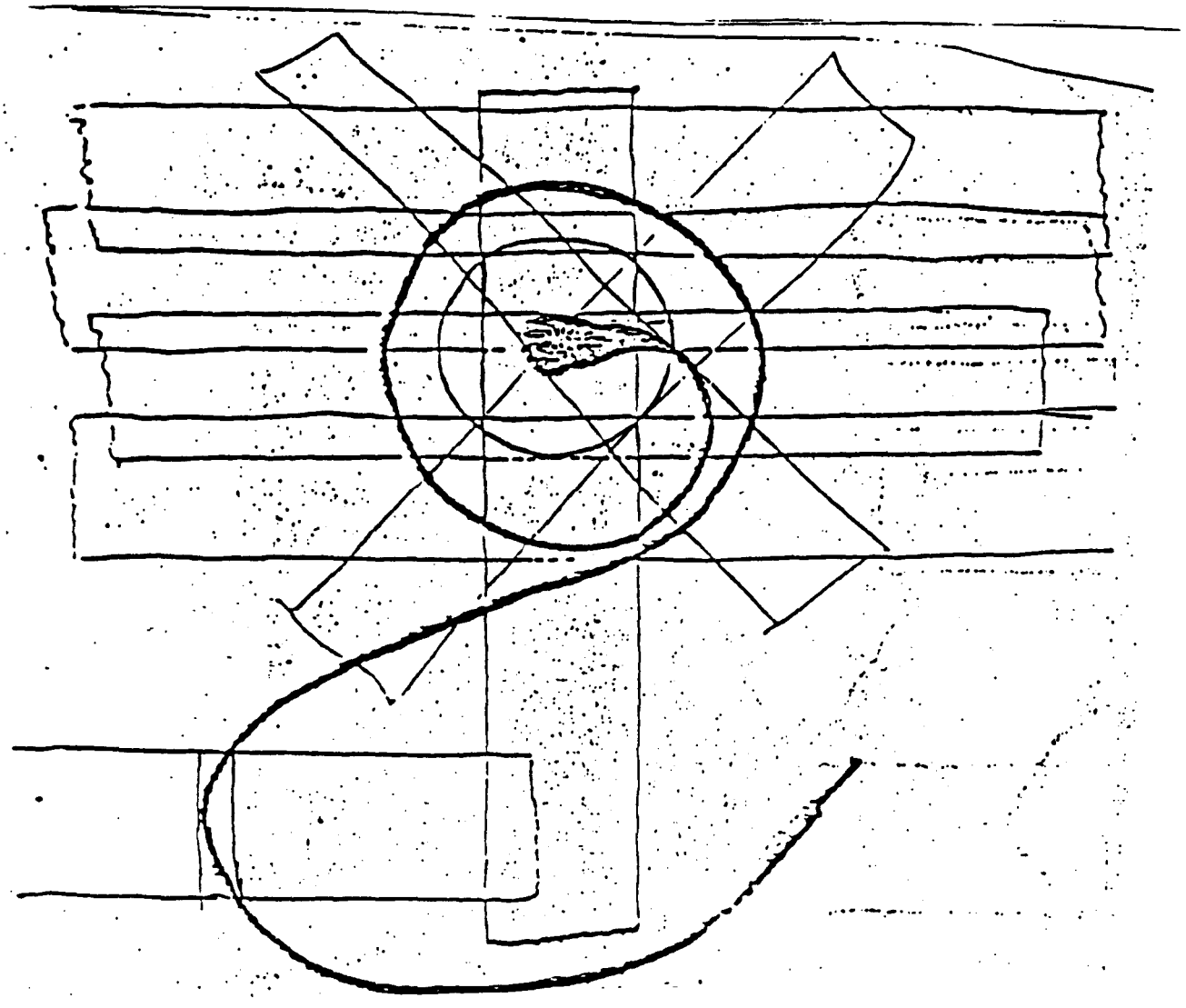
Secure electrodes and lead wires to the patient by looping the wires to take any strain and securing both the electrodes and lead wires with micropore tape.

a. Loop wire.

b. Secure with 1 strip of tape vertically or with an "X".

c. Secure further with serial horizontal strips.

d. Secure the first several inches of leadwire with a butterfly of tape (illustrated below).



20.3.3.6. Initiation of AECG Recording

a. Turn monitor on, note start time from monitor clock and record on cassette tape the TIME ON: _____.

b. Attach position test cable to AECG monitor and ECG machine (single-channel or triple-channel can be used).

c. Generate a six-second ECG strip ("signature strip") of both channels, using the standard lead I and II. Place the patient's ID number on the strip, date, sign, and attach to the back of the AECG report form.

d. Perform patient "position test" in the following order by using the patient's event marker and the following code. Firmly press the patient event marker for one second, then completely release prior to initiation of the second or subsequent marks.

(1) Standing 4 4 = one mark

(2) Sitting 4 4

(3) R-lateral decubitus 4 4 4

(4) Supine 4 4 4 4

(5) L-lateral decubitus 4 4 4 4

(6) Standing with handgrip. (Encourage maximum gripping for approximately 15 seconds) 4 4 4 4 4

(7) Hyperventilation (30 seconds) 4 4 4 4 4 4

e. Approximately 30 seconds after the end of the "position tests," press the event marker for one second which will indicate the end of the "position testing" and the beginning of the 24-hour recording.

f. Send these position strips to the AECG Core Laboratory with every tape.

g. Disconnect the test cable from the AECG Recorder.

h. Secure recorder by strapping around patient's waist or patient may carry it as a shoulder bag.

Advise patient not to bathe, shower, or swim while connected to the Holter monitor. Advise the patient NOT to wear nylon or other nonconducting materials, especially over the chest. Also advise the patient to avoid high electromagnetic fields, e.g. electric blankets, CB radio, microwave ovens, etc.

Instruct the patient in the use of the angina diary. Explain that it is not necessary to record activity but that it is important to record any and all symptoms they may experience during monitoring.

The patient should also be instructed in the use of the event marker to identify the presence of symptoms. A firm press of the event marker is necessary only at the beginning of a symptom. An explanation of the symptom with the associated activity and any interventions (i.e., rest, NTG) should be made in the patient diary. Noting the time from onset of symptom to cessation is most important. The more complete the patient diary, the better the analysis.

The Core Laboratory will be receiving a very high volume of AECG tapes. Proper labeling of data and completing the correct form will be of utmost importance for accurate data management. When an AECG monitor is applied, the following information will be necessary.

On the cassette label:

Clinical unit/Patient ID

Study name

Date

Time on (from Holter clock only)

Time off (from Holter clock only)

20.4 CERTIFICATION OF ACCEPTABLE AECG RECORDING TECHNIQUE

Clinical centers that did not undergo the certification procedure for UNSA will need to perform this process to become a certified center for T3. The certification process consists of full performance of a 24-hour AECG recording on any individual, who may be a normal volunteer. There must be strict adherence to the guidelines outlined in this operations manual. Included with the "test recording" should be the certification slip (Appendix A) that also will note the make and model of AECG recorder used.

20.5 ENDPOINTS TO BE USED FROM AECG RECORDINGS

Patients will have received the conventional anti-ischemia medications and their assigned T3 medication and the AECG will assess the adequacy of the treatment to decrease or prevent episodes of myocardial ischemia. Adequacy of the treatment will be assessed using the number of episodes of ST-segment deviation defined as $\geq$ 1.0 mm of ischemic ST-segment depression or $\geq$ 2.0 mm of ST-segment elevation from baseline lasting for at least one minute which occur during the monitored

period. Twenty minutes of ischemic ST-segment deviation will be considered to represent failure of therapy. Notation will be made of those episodes of ST-segment deviation associated with chest pain, those episodes not associated with chest pain (i.e., "silent" ischemia), and those episodes of chest pain not associated with ST-segment deviation.

Episodes of objective ischemia will be further characterized by the following variables: the maximum ST-segment deviation observed during the episode; the duration of the ST-segment deviation; the ST-segment "product," which is calculated as the product of maximum ST-segment deviation and duration; the ST-segment "integral," which is calculated as the sum of the ST-segment deviation for each 30-second period during the entire episode of ST-segment deviation; the heart rate five minutes prior to the episode; the heart rate at the onset of the episode; and the difference in heart rate from five minutes prior to the episode to

that at the onset of the episode. The pattern of heart rate activity prior to an episode of ischemia may identify those episodes due to a primary decrease in coronary blood flow to the ischemic zone (i.e., episodes not preceded by an increase in heart rate) and those episodes due to a primary increase in myocardial oxygen demand (i.e., episodes preceded by an increase in heart rate). The total number of minutes of $\geq$ 1 mm ST-segment depression and the number of patients with more than 20 minutes of ischemia will be calculated.

20.6 AVAILABILITY OF AECG CORE LABORATORY PERSONNEL

Core Laboratory personnel will be available to answer any questions or resolve problems at any time. The Core Laboratory phone number is (617) 735-0685. The physicians and nurses in the Core Laboratory can also be reached via the Brigham and Women's Hospital page operator (617) 732-6987.

For clinical situations or questions regarding techniques of AECG application, Call Gail McCallum, B.S. at (617) 735-0685. For any other questions, you can also call Dr. Peter Stone or Dr. John Rutherford at (617) 732-7139. You can also page Dr. Peter Stone (beeper #1846) or Dr. John Rutherford (beeper #1707).

20.7 TECHNICAL DESCRIPTION OF AECG ANALYSIS PROCEDURES

A technical overview of the system is as follows: The CardioData Mark 4 computer initially converts the entire 24-hour recording from analog to digital format, which then allows separate analysis of all aspects of the recording using a dedicated DEC PDP-11 computer. Using a "normal" baseline QRS-T morphology, the technician identifies the isoelectric line (P-Q line) and the J-point with moveable cursors, and a third cursor automatically identifies the ST-segment 60 msec after the J-point. The Holter recorder automatically records 1 mV calibration pulses for eight minutes at the beginning of the recording and the computer playback system automatically corrects the entire tape so that deflections identified in absolute millimeters are accurate. Calculation of accurate ST-segment depression from baseline, as well as its

slope, is thus possible. An "average" ST-segment is identified from every 30 seconds in which there are at least 16 normal sinus beats. The algorithm is devised to scan the entire 24-hour tape and identify the periods in which the ST-segment baseline is "stable" using a moving window of ST-segment values. If the ST-segment values are found to deviate from the identified "stable" preceding values, they are identified as being "unstable" and subsequently undergo quantitative analysis to determine if criteria for a discrete episode of ST-segment depression are met. The entire "unstable" ST-segment period is compared to the "stable" baseline ST-segment shifts. If the stable baseline after an ischemic episode is different from the stable baseline preceding the episode, the computer automatically creates an interpolated "baseline" that joins the baselines that frame the episode. The ST segments during the unstable period are then compared with the interpolated baseline. The concept of this interpolated baseline is a major advance since automated techniques have not previously been able to correct for a wandering ST-segment baseline.

A trend of the ST-segment activity and morphology is plotted on paper displaying the deviation of the J-point and a point 60 msec after the J-point compared to the isoelectric P-Q value. The value of the ST segment 60 msec after the J-point is presented as a "tick" appended to the J-point value. An "up-tick" therefore represents upsloping ST segment morphology, a "down-tick" represents downsloping ST segment morphology, and no evident "tick" represents horizontal ST segment morphology. Figure 1 illustrates the ST-segment trend from three patients included in a previous trial of unstable angina: Patient A is treated with placebo, patient B with heparin, and patient C with ancrod, a form of thrombolytic therapy. One can readily appreciate that patient A experienced a significant episode of ST segment depression with downsloping morphology whereas patients B and C had no ST segment deviations and the resting ST segment is slightly upsloping.

The heart rate, R-R interval, Ventricular Premature Beat (VPB) count, and Supraventricular Premature Beat (SVPB) count are also

displayed 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 patient A had frequent ventricular ectopic activity accompanying the episode of unstable angina. This format allows for insight as to whether a particular episode is a true physiologic event, usually accompanied by a primary or secondary change in heart rate, or simply represents an artifact (e.g. positional change, etc.). An ST segment deviation that is artifactual often has an abrupt change in the J-point value which persists for hours without any variation and without accompanying heart rate changes. Inspection of the QRS morphology, axis, and ST segment from the real-time ECG strip from the time period in question readily identifies whether the ST segment is artifactually abnormal or represents a true ischemic event.

The quantitative analysis of the ST-segment activity includes computer-derived identification of "stable" ST segment and "unstable" ST segment activity. The ST segment is considered "stable" if the values of the J-point and 60 msec after the J-point do not exceed the "deviation threshold" (typically 10-75 mm) compared to the preceding values. A "moving window" of ST segment values compared to the P-Q isoelectric line is utilized for this analysis. A period of "unstable" ST segment activity is identified when the ST segment values exceed the "deviation threshold". The episode onset and end are determined by backtracking and proceeding, respectively, from the ST segment trigger until the signal reaches the onset or termination point. Selection of the specific ST segment values to be used to define the "deviation threshold," "onset point," and "termination point" are at the discretion of the operator. The deviation threshold is set at 0.75 mm and the ischemic episode is considered to begin when the ST segment value exceeds 0.5 mm and to end when the values are less than 0.5 mm. An "ischemic episode" will be defined as $\geq$ 1.0 mm horizontal or downsloping ST segment depression lasting at least one minute.

The computer automatically prints the 30-second summary of ST segment values from the "unstable" ST segment periods when criteria for an episode of depression are satisfied (Figure 2). This display includes the 30-second time period, the heart rate at this time, the absolute ST segment deviation from the P-Q isoelectric line, the baseline ST segment deviation derived from the preceding "stable" ST segment period, the relative ST segment deviation compared to the baseline, and the "slope" of the ST segment (i.e. the relative value at the point 60 msec after the J-point). A "positive" value of the slope indicates upsloping ST segment morphology, a "negative" value indicates downsloping ST segment morphology, and a zero indicates horizontal ST segment morphology. As shown in Figure 2, which is taken from the episode of ST segment depression in patient A with unstable angina presented in Figure 1, one can easily track the progression of ST segment activity to evaluate depth of depression and ST segment morphology. Note that the maximum ST segment depression in this patient's episode was 2.16 mm, with a downsloping morphology, which occurred at 1:45 p.m. when the heart rate was 92 bpm.

At the end of each episode of ST-segment deviation, the computer provides summary characteristics which include:

1. the Channel being presented (1 or 2);
2. the onset time;
3. termination time, duration of the episode;
4. heart rate 5 minutes prior to episode;
5. heart rate 2 minutes prior to the episode;
6. the baseline heart rate during the preceding "stable" period;
7. the heart rate at the onset of the episode;
8. the maximum heart rate observed during the episode;
9. the maximum J-point value compared to the isoelectric line;
10. the maximum J-point value compared to the baseline J-point value;
11. the heart rate when the ST segment deviation was maximal

12. the "ST segment product" which is calculated as the product of the maximum ST segment depression and the duration of the episode;
13. the "ST segment integral" which is calculated as the sum of ST segment depression for each 30-second period during the entire episode of ST segment deviation;
14. the heart rate when the ST segment first was depressed $\geq$ 1.0 mm; and
15. the "type" which is based on a hierarchical categorization scheme of ST segment depression based on the morphology.

Figure 3 presents the summary characteristics of the episode of ST segment depression illustrated in Figures 1 and 2 from the patient with unstable angina.

The technician prints a 6-second real-time presentation of the QRS-T morphology at specified times: at the baseline(s), prior to each event, at the peak of each event, and after each event. Figure 4 displays the real-time ECG from the episode of unstable angina described in Figures 1-3. The validity of the ST segment deviation as indicative of ischemia is evident.

The physician investigator then manually reviews all the quantitative print-outs as well as the real-time ECG's from each of the episodes to insure that the episode is identified and categorized properly. Episodes that are confirmed to be "ischemic" are then indicated to the technician who enters all of the summary characteristics of the episode and the presence or absence of symptoms accompanying the episode into an IBM PC AT computer dedicated to the management of the AECG database.

20.8 SUMMARY AND CONCLUSIONS

Identification and characterization of episodes of silent ischemia in patients with unstable angina has become extremely useful in studying the nature of the disease process. The presence of episodes of silent ischemia during the index hospitalization are often associated with a poor outcome during the subsequent six months of follow-up. Since

episodes of silent ischemia are frequent in patients with unstable angina, utilization of these episodes as an endpoint to assess treatment efficacy would allow for smaller sample sizes of patients to be studied than utilization of the more conventional, infrequent endpoints such as myocardial infarction and revascularization procedures.

Ambulatory ECG monitoring is an extremely reliable, objective, and inexpensive technique to quantify episodes of silent ischemia. The AECG Core Laboratory utilizes objective and reproducible computerized techniques to detect and quantify episodes of transient ST-segment deviation. Other available analysis methods are limited by lack of precise, reproducible, quantifiable measurement techniques. Visual scrutiny alone is inadequate since over- or under-estimation of ischemic episodes may frequently occur due to difficulties in objectively identifying the often subtle onset and end of ischemic ST segment depression and difficulties in adjusting for a baseline of ST segment activity which often wanders. Gallino and coworkers (19) described a computer analysis system which is markedly superior to visual scrutiny, but it is relatively cumbersome (mean analysis time 185 minutes) and has not been carefully evaluated for reproducibility of ST segment quantification. It also does not incorporate any technique for adjustment for changes in resting baseline ST segment deviation. The system used for T3 provides accurate, quantitative, and economical analyses of ST segment activity to investigate the nature of ischemic activity in patients with unstable angina and the response to treatment.

20.9 SOLUTIONS TO COMMON PROBLEMS

The following are examples of possible causes and solutions of the most common problems encountered when Holter monitoring patients.

PROBLEM	CAUSE/SOLUTION
Leads fall out of recorder	The original leads have been removed from the recorder and the operator is unaware of the necessary force to install new leads.
Blank tapes	The new tape was installed upside down. Load tape according to instructions in Section 20.3.3.1.

PROBLEM	CAUSE/SOLUTION
	Power switch to motor was not turned on. Verify power switch to motor is turned on and tape is moving prior to patient leaving.
	The leads have been broken due to normal wear.
Low amplitude	There is excessive residue on recording head. Clean recording head with Q-tip and isopropyl alcohol.
	The tape used was defective or wrong type. Use new tape and verify with internal calibration test.
Tape jamming	Excessive residue has accumulated in tape path. Clean tape path with Q-tip and isopropyl alcohol. Special attention to the pinchwheel and capstan will prevent tape jamming.
	The tape was not loaded properly.
	There is excessive slack in the tape. Many tapes have hub locks provided during shipping which prevent slack. Use a pencil to wind hub past clear leader and remove slack in tape.
	The take-up belt has broken. Replace take-up belt with spare.
Artifact in signal	The patient hook-up was inadequate. Verify hook-up using test cable.
	There is excessive residue on recording head. Clean recording head with Q-tip and isopropyl alcohol.
	The lead wire(s) are broken.

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Figure 1: Representative ST segment trend for three patients with unstable angina: Patient A received placebo, Patient B received heparin, and Patient C received ancrod. Note that Patient A experienced an episode of ST segment depression, associated with an increase in heart rate and frequent ventricular ectopic activity.

Figure 2: Quantitative print-out of ST segment activity at 30-sec intervals during the episode of ST segment depression illustrated in Patient A, Figure 1. Indicated are the time, heart rate, absolute ST segment depression, baseline ST segment depression, relative ST segment depression compared to baseline, and the ST-segment "slope." The slope represents the mm change from the J-point to 60 msec after the J-point. Thus, a positive number indicates an upsloping ST segment, a zero indicates horizontal ST segment, and a negative number indicates downsloping ST segment morphology. Note that peak ST segment depression occurs at 1:45 p.m.. There is -2.16 mm of depression at the J-point associated with downsloping ST segment morphology.

The full quantitative print-out includes ST segment activity before, during, and after each episode of ST segment deviation.

Figure 3: Computer derived summary of episode of ST segment depression identified in Figures 1 and 2.

Figure 4: Real-time presentation of the ECG before, during, and after the ischemic episode described in Figures 1 - 3.

APPENDIX A

Clinical Unit Certification Procedure for AECG Monitoring

Each participating center is required to provide a "24-hour test recording" from the AECG (Holter) monitor to be used for the T3 Trial. This "test recording" must be received before any patients for the trial are entered. The purpose of the "test recording" is to certify the quality of application and efficiency of equipment. Anyone willing to wear an AECG Holter monitor for 24 hours will be acceptable.

This form is to be sent to the AECG Core Laboratory along with the "test recording." The AECG Core Laboratory personnel will contact the clinical center promptly concerning certification.

STUDY CENTER NAME: _____

STUDY CENTER ID#: _____

TYPE OF AECG HOLTER (MAKE AND MODEL) RECORDER TO BE USED FOR T3:

_____

24-HOUR TEST RECORDING ENCLOSED: YES _____ NO _____

REASON NOT ENCLOSED: _____

DATE: _____

SIGNATURE: _____

T3 MANUAL OF OPERATIONS