STUDIES OF LEFT VENTRICULAR DYSFUNCTION

REGISTRY

MANUAL OF OPERATIONS

December 28, 1987

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1. GENERAL OVERVIEW

1.1. Aims of the Registry

1.1.1. Primary Objective

The primary objective of the Registry is to study all-cause mortality at one, three, and five years in a large (approximately 6,000) consecutive and relatively unselected cohort of patients with heart failure and/or with left ventricular dysfunction. The patients will be stratified according to symptoms, etiology of disease, ejection fraction, and chest X-ray findings at entry into the Registry.

1.1.2. Subsidiary Objectives

The subsidiary objectives of the Registry are:

1. To study cardiovascular mortality at one, three, and five years globally and after stratification according to symptoms, etiology of disease, ejection fraction, and chest X-ray findings in the above populations.

2. To study morbid events at one year in the above population.

3. To relate other baseline covariates of prognostic importance to subsequent mortality and morbidity in the above population.

4. To characterize in greater detail clinical characteristics, echocardiographic abnormalities, arrhythmia status, functional capacity, and neurohumoral levels and to correlate these detailed findings with subsequent mortality and morbidity in a stratified randomly selected sample of 1000 patients from among the patients entering the Registry (Registry Substudy).

5. To compare baseline characteristics and follow-up events of this relatively unselected population with those of the SOLVD Trials.

1.2. Clinic Participation

Participation in the SOLVD Registry is limited to those clinical centers collaborating in the SOLVD trials that are on target for recruitment in the main study trials, are willing and able to perform high-quality M-mode and two-dimensional echocardiograms and ambulatory monitoring, obtain blood samples from approximately 55 randomly selected Registry participants, and provide follow up of Registry participants during the entire course of the study. See Appendix A for a list of participating clinics. Each clinic will enroll at least 350 patients (approximately 55 of which will participate in the Registry Substudy).

1.3. Study Time Table

The timetable for the SOLVD Registry is as follows:

YEAR 1 December 1, 1987 - November 30, 1988

Dec. 1, 1987 - Dec. 31, 1987: Phase-in month. Major activities include training session for clinic personnel and quality control for substudy procedures.

Jan. 1, 1988 - Sept. 30, 1988: Nine-month recruitment period

Oct. 1, 1988 - Nov. 30, 1988: Two-month phase-down. Major activities include completing data collection of recruitment, evaluating continuation of recruitment of rare etiologies, and planning for YEAR 2 follow-up activities.

YEAR 2 December 1, 1988 - November 30, 1989

Mailing of questionnaire on vital statistics

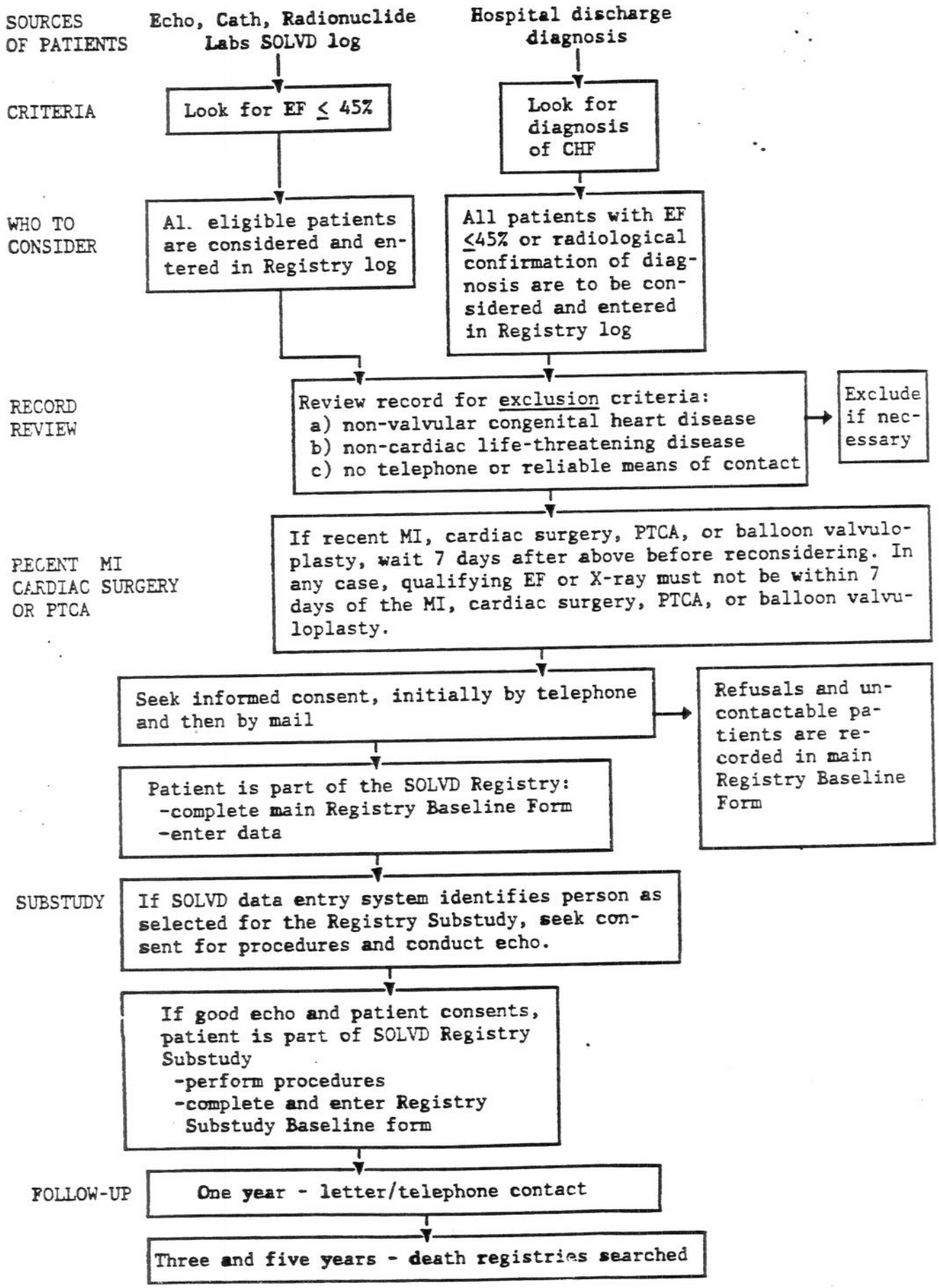
YEAR 3 December 1, 1989 - November 30, 1990

Vital status ascertained by the Coordinating Center with national death registries.

YEAR 5 December 1, 1991 - November 30, 1992

Vital status ascertained by the Coordinating Center with national death registries.

1.4. Flow Diagram of the SOLVD Registry and Substudy



2. INITIAL SCREENING AND RECRUITMENT

2.1. Recruitment

All consecutive patients potentially eligible for the Registry (i.e., who meet the preliminary eligibility criteria described in Section 2.3) during the nine-month recruitment period must be entered onto the Registry Log. Patients enter the Registry as a result of screening exams at echocardiographic, radionuclide, and cardiac catheterization laboratories or by surveying hospital discharge records. Any patient who had a screening exam or who was discharged from the hospital on or after January 1, 1988 is to be considered for enrollment. Do not include patients who do not have (1) hospital or out-patient records and (2) either a chest X-ray or EF measurement. Note that all patients randomized into one of the SOLVD trials from the Registry hospital during the nine-month recruitment period meet the Registry eligibilty criteria and therefore are to be considered for enrolement into the Registry.

2.2. Date of Enrollment

The date of enrollment is defined as the date of the qualifying measurement (EF or chest X-ray). If the patient has both a qualifying EF and a qualifying chest X-ray, use the earlier measurement's date as the enrollment date. See instructions for Registry Baseline Form Q. 3.1 for guidelines in choosing among more than one potentially qualifying EF measurement.

2.3. Eligibility Criteria

To be eligible for the Registry, the patient must have either (1) an ejection fraction less than or equal to 45% or (2) a diagnosis of congestive heart failure. Patients identified from discharge data should have (a) radiological evidence of CHF, (b) signs of pulmonary venous congestion, or (c) an EF of 45% or less. Do not use EF or chest X-ray information if the measurements were taken more than three months prior to date of evaluation for enrollment. Descriptive statements consistent with heart failure which may appear in the report include:

(1) Statements related to pulmonary blood flow redistribution to upper lobes.
(2) Signs of pulmonary venous congestion:
    - Basal or perihilar vascular blurring
    - Alveolar or pulmonary edema
    - Kerley B lines
    - Pleural effusion - judged secondary to congestive heart failure (to make this judgment may require correlation with clinical data).
(3) Cardio-thoracic ratio should be included whenever possible.

To validate these heart failure criteria as positive, use the interpretation on the chest X-ray report if it is definite. Follow-up reports indicating clearing of CHF are helpful. If you are uncertain about an interpretation, have the X-ray reviewed by a physician. Diagnosis of heart failure should be included only if it was made at the Registry hospital.

2.4. Exclusion Criteria

Patients who fit any of the categories below must be excluded from the Registry:

(1) Nonvalvular congenital heart disease.

(2) Any noncardiac life-threatening disease likely to significantly shorten the patient's survival, including criteria 11 (cor pulmonale), 12 (advanced pulmonary disease), 13 (major neurologic diseases), 17 (renal failure), 18 (malignancies), 21 (significant primary liver disease), and 23 (other life-threatening disease) in the SOLVD main trials protocol.

(3) Failure to consent to the Registry.

(4) Lack of a telephone or reliable means of contact/follow-up. Participants must have a Social Security number (or Canadian or Belgian ID number) for long-term follow up. If you cannot obtain this number through medical records or directly from the patient (at the time of the informed consent telephone call) the patient must be excluded for lack of means for follow up.

(5) Myocardial infarction within 7 days. This patient can be included after 6 days have passed if there is a qualifying chest X-ray or ejection fraction measurement made 7 or more days after the MI.

(6) Cardiac surgery, PTCA, or ballon valvuloplasty within 7 days. This patient can be included after 6 days have passed if there is a qualifying chest X-ray or ejection fraction measurement made 7 or more days after the cardiac surgery or PTCA.

Note that the following exclusion criteria for the SOLVD main trials are <u>not</u> exclusions for the Registry:

1	History of intolerance to enalapril
2	Currently taking ACE inhibitor and unwilling to discontinue
4	Hemodynamically significant valvular or outflow tract obstruction
5	Constrictive pericarditis
7	Syncopal episodes presumed to be due to life-threatening arrhythmias
8	Any major cardiac surgery likely
9	Unstable angina pectoris
10	Uncontrolled hypertension
14	Cerebrovascular disease
15	Collagen vascular disease other than rheumatoid arthritis
16	Suspected significant renal artery stenosis
19	Immunosuppressive therapy
20	Active myocarditis
22	Likely to be nonadherent (alcoholism, drug addiction, lack of of a fixed address, etc.)
24	Woman likely to bear children
25	Other investigational drug protocols (except compassionate use)
26	Failure to give consent for the SOLVD trials
27	Lack of adherence or tolerance to medication
28	Lack of adherence to placebo run-in

Furthermore, patients scheduled for cardiac transplantation are eligible for the Registry.

Coordination of screening efforts between Registry and SOLVD main trial personnel is strongly encouraged. The exact details of this coordination with vary among clinical centers.

Certain classes of patients are of particular interest to the Registry. Therefore, please make every effort to include patients with the following symptoms:

(1) pulmonary edema unrelated to acute myocardial infarction;

(2) valvular heart disease with EF <= 45%;

(3) Primary diagnoses of idiopathic cardiomyopathy and active myocarditis;

(4) unusual and specific causes (e.g., amyloidosis, hemochromatosis, hypertrophic hyperdynamic cardiomyopathy [IHSS], diabetic cardiomyopathy, alcoholic or cocaine-related cardiomyopathy)

2.5. Registry Logbook

All patients seen at the echocardiographic, radionuclide, and cardiac catheterization laboratories or who are admitted with a diagnosis of congestive heart failure and who meet the initial eligibility criteria described in Secion 2.3 are to be listed in consecutive chronological order in the SOLVD Registry Log (see Fig. 1a). All patients seen on a given day at a particular lab (e.g., echo lab) may be listed together as long as they are listed in chronological consecutive order within this group. Log all patients for a given day before proceeding to the next day's log. All patients entered on the log and considered suitable for the Registry must be contacted to obtain consent for a Registry Baseline Form (RBF) to be completed from their medical records. (Note: If a patient is entered into the log and dies during the same hospitalization, the clinic should determine eligibility and for eligible patients complete the Registry Baseline Form, Designation of Death Form, and Death Certificate Cover Sheet.) The original log or a copy should be filed with the SOLVD nurse coordinator at the clinical center.

Each month, the Registry Coordinator will send to the Coordinating Center a summary of the previous month's Registry Log (see Fig. 1b). This summary may be sent by electronic mail or by regular mail so as to arrive at the Coordinating Center by approximately the 10th of the month. (When using electronic mail, address to SV OPERATIONS.) If more than one hospital from a clinical center is participating in the Registry, summary data from each hospital should be compiled into one report before sending it to the coordinating center.

Figure 1A.

REGISTRY RECRUITMENT LOG

Clinic: | | |

Hospital: _____

Date	Patient's Name (or Hospital ID)	Recruitment Source (E,R,C,D)*	Is Patient Suitable for the Registry?** Y/N	If NO, give reason:	Written Consent Obtained?	Comments

* E = Echocardiography Lab
R = Radionuclide Lab
C = Cardiac Catheterization Lab
D = Discharge Records

** Exclusion criteria:
1. Nonvalvular congenital heart disease
2. Noncardiac life-threatening disease
3. Lack of reliable means for follow-up
4. MI, cardiac surgery, PTCA, or balloon valvuloplasty within past 7 days

Figure 1B.

REGISTRY MONTHLY LOG SUMMARY SHEET

Clinical Center: ☐☐ Hospital: _____

Reporting Period (Beginning and Ending Dates):

☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Month Day Year Month Day Year

1. Date Summary Completed: ☐☐/☐☐/☐☐

Month Day Year

2. Total number of potential Registry participants screened from:

Echocardiography Lab _____

Radionuclide Lab _____

Cardiac Catheterization Lab _____

Discharge Records _____

3. Number pending eligibility assessment _____

4. ELIGIBLE PATIENTS

4.1 Number of those screened who are eligible: _____

4.2 Number of eligible patients who have given consent _____

5. NONELIGIBLE PATIENTS _____

5.1 Number not eligible: _____

5.2 Reasons:

a. nonvalvular congenital heart disease _____

b. noncardiac life-threatening disease _____

c. no means of follow-up _____

d. MI, cardiac surgery, PTCA, or balloon valvuloplasty within past 7 days _____

6. Initials of person completing this form: ☐☐

2.6. Informed Consent

Eligible patients should be contacted initially by telephone so that the purpose of the Registry can be explained and any questions answered. Informed consent is then obtained by having the patient sign the consent form (if he or she is still hospitalized) or by sending the patient the consent form through the mail. "Giving consent" is defined as the patient signing and returning the written consent form; verbal consent without written consent is not acceptable. If the patient consents to participate and if you do not have his or her Social Security or ID number and date of birth, obtain this information at this time. (See Appendix B1 for a sample consent form; this form should be modified to meet local I.R.B. requirements and to be more oriented to the layperson.) Please consult Appendix A of the SOLVD [Main Trials] Manual of Operations for guidelines regarding obtaining informed consent.

3. REGISTRY MAIN STUDY DATA COLLECTION

3.1. Registry Baseline Form (RBF)

A Registry Baseline Form (see Appendix E) must be completed on all eligible patients entered onto the Registry Log. If a patient has refused consent, the RBF should be completed up through question 5.5.

It may be necessary to obtain records from the physician's office to get a more complete clinical history. Please make every effort to obtain the most complete and up-to-date information available, as the success of the Registry depends on having as much high-quality data as possible. For a similar reason, it may be valuable to re-review charts after a few months to see if data from lab tests and other procedures have been added. (See instructions for Q5 if the re-review uncovers information that disqualies the patient for the Registry.)

3.2. Completing the RBF

3.2.1 General Instructions for Completing the RBF

Because the Registry Baseline Form is completed only from medical records, which of course are designed to serve a variety of nonresearch purposes, in some cases it may be difficult to obtain needed information. Because of this, an "unrecorded" ("U") option is provided for most questions. If no "U" option is provided and you cannot obtain applicable information (for example, the date of most recent MI), cross through the response blanks with two horizontal lines to indicate that the question is unresolvable. (See the SOLVD Registry General Instructions for Completing Forms and SOLVD DES Tutorial for details.)

Guidelines for choosing between "N" (No) and "U" (Unrecorded). For certain items the absence of any mention in the medical record of the item under question can be assumed to mean "no." For example, if there is no statement in the record that the patient is taking digitalis, one can safely assume that he or she is not taking digitalis ("No") rather than that the patient is taking digitalis but the record neglects to mention it ("Unrecorded"). For these questions, no "U" option is provided.

In other cases, however, there may be some uncertainty whether the absence of a statement in the record regarding a particular item means "No" or "Unrecorded." For example, one person may consider the fact of an MI of such significance that an absence of any mention of previous MI would mean that the patient had no prior myocardial infarctions ("N") while another may respond with "U." To standardize data collection across all clinics, please follow this guideline:

> If a particular condition is not mentioned in the medical record but you can reasonably infer the answer by independent data, then answer "No." If a reasonable inference cannot be made, than answer "Unrecorded."

An example of a "reasonable inference" is the case in which no mention is made in the medical record about the presence of a permanent pacemaker (Q32) but one can see from the patient's ECG chart that he or she does not have a pacemaker. The

important criterion here is that the inference is supported by independent data and is not based on assumptions about what is expected to be included in a medical record.

3.2.2 Specific Instructions for Completing the RBF.

Guidelines and instructions for particular questions are provided below. Please consult the SOLVD Registry General Instructions for Completing Forms for additional information.

Registry ID: All participants in the Registry, even those who are also enrolled in the SOLVD main trials, will receive a Registry ID number. The Coordinating Center will provide labels for your use.

Section A (Identifying Information). Self-explanatory.

Q. 3 (EF): Please use the most recently measured ejection fraction. The EF must be after January 1, 1988, and 7 or more days after an MI, cardiac surgery, PTCA, or balloon valvuloplasty.

Q. 3.1 (EF Percentage): Use the same method for determining EF percentage as is used in the SOLVD main trials. These methods are as follows:

1. The EF must be assessed by one of the following techniques:

   a. Radionuclide left ventricular angiography (MUGA or first pass)
   b. Left ventricular contrast angiography (RAO or biplane)
   c. 2-D echocardiogram (either by area-length method or by modified Simpson's rule).

   Do not use estimated EFs.

2. If more than one method has been performed to determine an EF or if an EF has been performed several times within the previous three months, choose the most recent EF or if using a previous EF, the subsequent ones must be less than 45%. If more than one technique to determine EF has been used within the previous three months, then radionuclide techniques are preferable to angiograms and either of these are preferable to echocardiograms.

Q. 3.2-3.3 (Date and method used). Self-explanatory.

Q. 4.1-4.2 (chest X-ray): Self-explanatory.

Q. 5 (Exclusions): Note that for patients with nonvalvular congential heart disease (Q. 5.1), noncardiac life-threatening disease (Q. 5.2) or no reliable means of follow-up (Q. 5.3), no RBF is completed. These questions here serve as a doublecheck that the patient indeed meets eligibility criteria and to allow for disqualification after the patient has been enrolled in the Registry. If an RBF is entered into the data entry system (DES) and subsequent information is obtained that indicates that the patient should not have been enrolled in the Registry (for example, additional medical records show that the patient has a life-threatening disease), do not delete the form from the DES. Instead, correct Q5.1-5.5, as appropriate. Do not change any responses on the remainder of the form.

If a patient meets all eligibility criteria but refuses consent, the RBF should be completed to question 5.5.

Q. 6-7 (Sex, ethnic identity): Self-explanatory.

Q. 8.1 (Date of birth): This is very important for follow-up through national registries. Please make every effort to obtain this information.

Q. 8.2 (Marital status): Indicate marital status as of the date of the qualifying measurement.

Q. 9 (Social Security number/Canadian and Belgian ID number): These numbers are extremely important for determining long-term vital status. If this number is not available, the patient should not be enrolled in the Registry. (In the US, Social Security numbers can often be obtained from health insurance information since the Medicare number is also the Social Security number.)

Q. 10 (Participant's address): Self-explanatory. Use mailing address (e.g., post office box), if that is given in the records.

Q. 11 (Participant's home telephone number): Self-explanatory. Please record area code with telephone number.

Q. 12.1-12.6 (Hospital name and address): Self-explanatory.

Q. 13 (Patient's hospital ID number): This is the patient's hospital records number.

Q. 14.1-16 (Private physician information): Self-explanatory.

Q. 17.1-20 (Nearest relative or friend): Self-explanatory.

Q. 21.2 (Date of most recent X-ray): Note that this is the most recent X-ray, which may not necessarily be the qualifying X-ray.

Q. 21.3 (Qualifying X-ray): Self-explanatory.

Q. 22.1-22.5 (Evidence of pulmonary congestion): Use the X-ray report to answer these questions rather than reinterpreting the X-ray film. Evidence of pulmonary congestion is defined as the presence of basal or perihilar vascular blurring; Kerley B lines; alveolar or pulmonary edema; or pleural effusion secondary to CHF. This last category (Q22.5 may require corroboration with clinical data.)

Q. 23.1 (Primary etiology): Note that only one item is selected. This question is crucial to the algorithm for selecting participants for the Registry substudy; therefore it must be entered into the data entry system and cannot be skipped. Note that if option 7 (specific cardiomyopathy) is selected, the type of cardiomyopathy should be specified in Q. 23.2; if one of the options 1 through 6 is selected, Q. 23.2 is skipped.

Response to this question may be changed after the form is entered into the DES but any such change will not affect substudy selection.

Q. 24 (Other etiologies): Indicate the presence of all etiologies that apply, including the one specified as the primary etiology in Q. 23.1.

Q. 25 (EF >= 35): Self-explanatory.

Q. 25.1 (SOLVD Eligibility ID): If the participant is being considered for one of the SOLVD trials but has not yet been randomized, enter the temporary (eligibility) ID. If a Registry participant has already been randomized into one of the SOLVD main trials, Q 25.1 may be skipped and the patient's Randomization ID entered into Q. 25.2.

Q. 25.2 (Participant randomized): Self-explanatory.

Q. 25.3 (SOLVD Randomization ID): Self-explanatory. If the participant has been randomized, skip to Q. 27.

Q. 26 (Reasons for exclusion from SOLVD): If the participant was considered for randomization but excluded, indicate all reasons that apply.

Q. 27 (SOLVD trial): Self-explanatory.

Q. 28.1 (Date history taken): Use the most recent history if within three months prior to enrollment. Indicate the date the history was taken (i.e., the date of the most recent entry).

Q. 28.2-29.3 (History of several conditions): Self-explanatory. For Q. 28.9 (hypertension), if hypertension is not mentioned specifically in the record, define as systolic blood pressure greater than or equal to 160 mmHg or diastolic blood pressure greater than or equal to 90 mmHg. For Q. 28.14 (duration of asthma), round off to the nearest number of years, using standard rounding methods (when exactly a half year is indicated, round to even number of years (i.e., 6 years 6 months = 6 years; 7 years 6 months = 8 years). Calculate number of years from the date the history was taken.

Q 30.1-30.2 (Smoking history): Only cigarette smoking is to be considered.

Q. 31.2 (History of alcohol abuse): Symptoms of alcohol abuse that may be in the record include cirrhosis of the liver.

Q. 32-34.9 (History of various cardiac conditions): Self-explanatory.

Q. 35 (Date of last hospitalization or out-patient visit): Use most recent date within three months of enrollment.

Q. 36 (Medications): See Appendix C for list. Note in Q. 36.8 (ACE inhibitor) that "S" is to be selected if the participant has been randomized into the SOLVD trial. If the participant has been randomized into another clinical trial employing doubleblind test of a medication listed in Q. 36, indicate that the response is unresolvable.

Section I (Physical Examination): For hospitalized patients, use measurements taken at admission to the floor, not during emergency room admissions. For out-patients, use the most recent measurements, if taken within three months of enrollment.

Q. 37 (Date of physical exam): If all measurements were not taken on the same date, enter the date that pertains to the majority of measurements.

Q. 38 (Weight): Record weight in either pounds or kilograms (but not both).

Q. 39 (Height): Record height in either inches or centimeters (but not both).

Q. 40 (Heart rate): Use heart rate values taken after the patient has stabilized; i.e., after admission to the floor (but not during an emergency room admission). Record in beats per minute.

Q. 41-42 (Blood pressure): Use blood pressure measurements taken after the patient has stabilized.

Q. 43 (Presence of rales, edema, etc): Self-explanatory.

Section J (ECG): Use the most recent ECG but not within 72 hours of an MI and only if taken within three months of enrollment.

Q. 44 (Date of ECG): Self-explanatory.

Q. 45-53 (ECG findings): See Appendix D for instructions on measuring ECG amplitudes. The assistance of a research nurse or investigator may be necessary to interpret ECG findings.

Q. 54-55 (Q-wave MI): The assistance of the investigator or a qualified technician may be required to determine these answers.

Q. 56 (Date of laboratory tests): Use the most recent lab results but only if recorded within 6 months of enrollment. If all tests were not made on the same date, enter the date that pertains to the majority of measurements.

Q. 57-60 (Lab measurements): These are standard lab measurements; no specific instructions given. Make sure that the laboratory values are translated into the measurement units given on the form, if necessary.

Section L (Coronary angiography): A coronary angiogram may be used if it was taken within 12 months prior to enrollment in the Registry.

Q. 61-63 (coronary arteriogram): The assistance of the principal investigator or qualified technician may be required to answer these questions.

Q. 64 (Source of patient): This refers to the source of the medical records being abstracts. Choose "H" (hospitalized) if the patient had been hospitalized at the time of enrollment, even if he or she has since been discharged.

Q. 65 (Selection for Registry Substudy): The data entry system will determine whether or not the patient has been selected for the Registry Substudy. Therefore, leave this question <u>blank</u> on the paper form but complete it when the form is keyed.

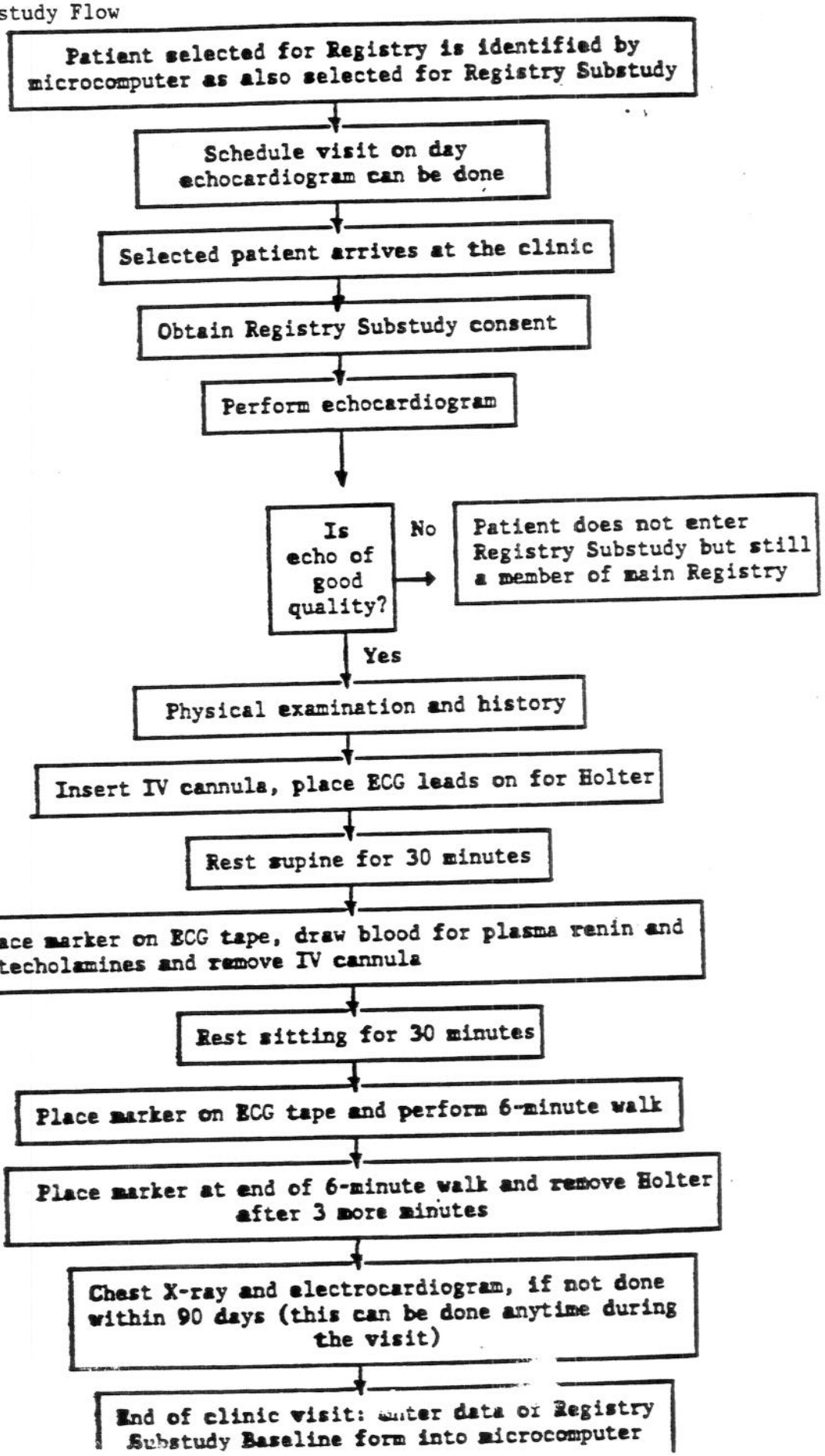
Q. 66 (Participant consents to substudy): Self-explanatory.

4. REGISTRY SUBSTUDY

The Registry Substudy is designed to study in greater detail the relation between mortality and morbidity and clinical characteristics, echocardiographic abnormalities, arrhythmias, functional capacity, and neurohumoral levels, particularly for participants with rare etiologies. The substudy will also test the validity of the Registry main study by establishing whether or not (1) the Registry sample is biased (i.e., toward "sicker" patients who obtain more tests) and (2) data collected from medical records are comparable to data collected in a direct and standard way. Through the Registry substudy we may also be able to compare the relatively less ill patients of the Registry with the SOLVD main trial patients.

The data entry system will determine which Registry participants are eligible for the substudy. A total of 1000 participants will be enrolled; 100% of Registry patients with rare etiologies will be eligible (an estimated 300 to 600 participants) and 7% - 13% of participants with ischemic heart disease (an estimated 400 to 700) will be eligible.

4.1. Registry Substudy Flow



4.2. Selection, Informed Consent, and Visit Schedule

Once a Registry participant has been selected by the data entry system for the substudy, the participant should be contacted by telephone to obtain informed consent and to schedule a clinic visit. The clinic visit should be scheduled no more than 90 days after enrollment. The consent form can be signed at the visit and need not be mailed. If possible, schedule the clinic visit for the same day the echocardiogram is to be taken. In any case, the clinic visit should be no more than two weeks after the echocardiogram has been taken, and any events occurring in the intervening period must be documented on the Registry Hospitalization Form (RHF). Inform the participant that he or she is not to have any liquids or cardiovascular medications and should not smoke at least 4 hours prior to the walking test.

If the Registry Substudy participant is also enrolled in one of the SOLVD main trial substudies, some procedures may not need to be duplicated.

- Neurohumoral measurements for the Registry substudy may also be used for the Neurohumoral Substudy Pilot. These measurements must be taken as per the Registry protocol (i.e., when the participant is on the Holter monitor). Note that the Neurohumoral Pilot requires four blood samples whereas the Registry substudy requires only two.

- Holter monitoring procedures for the Registry substudy and the Sudden Death substudy may be integrated in the following way. Schedule the patient's Registry substudy visit for the day prior to the Sudden Death substudy visit. During the first clinic visit, conduct the 70-minute Holter monitor procedures (with blood drawing and six-minute walking test) as described in this manual. At the completion of the Registry clinic visit, change tapes and begin the 24-hour Holter monitor for the Sudden Death substudy.

4.3. Echocardiogram

The echocardiogram must be done at the beginning of the clinic visit so that echo quality can be determined. An echo obtained within 2 weeks of the clinic visit may also be used if it is of good quality. It is crucial that the echocardiogram be of good quality. (See below for criteria for acceptable quality.) Participants with suboptimal echocardiograms cannot be enrolled in the Registry Substudy. (They do, however, remain in the Registry main study.) Echo quality is evaluated locally by a trained technician or the principal investigator; on the basis of this evaluation the participant does or does not continue with the rest of the substudy procedures. Echo quality will also be evaluated centrally at the core laboratory. In the unlikely event that the core laboratory determines that an echo that has already passed the local evaluation to be suboptimal, the participant will be disenrolled from the substudy.

4.3.1. Echo Quality

To be judged as good quality, an echocardiographic study must have the following:

(1) Adequate display of the aortic and mitral valve in the parasternal long axis view with minimal or no anterior angulation of LV apex.

(2) Adequate endocardial definition of both visualized LV walls in the parasternal long axis and apical view.

(3) Adequate endocardial definition of anterior septum and posterior wall in the short axis view with a circular appearance of the LV cavity at mid-papillary and mitral valve level.

(4) Adequate M-mode scan from LV at mid-papillary level to aortic root.

The first five echos from each clinic will be evaluated on all key variables by the echo core laboratory. Deficiencies will be communicated to the clinic.

4.3.2. Echo Procedures

4.3.2.1. Parasternal window

(1) Obtain a parasternal long axis view that shows good endocardial definition of septum and posterior walls, good visualization of mitral and aortic value as well as proximal aortic root. The view should be obtained from the intercostal space that places the LV long axis as perpendicular to the sound beam as possible. This location should be recorded for future serial studies.

(2) Obtain a parasternal short axis view at mitral valve and papillary muscles levels by rotating transducer from the long axis view. When properly angulated, the short axis view should show a circular or near circular geometry of the LV. Record an M-mode scan of the LV at papillary level gradually moving up the mitral valve and into the aortic value insuring that the M-mode cursor runs through the center of the LV cavity.

4.3.2.2. Apical window

(1) Obtain an apical four chamber view with the transducer as far laterally as possible to maximize size of the LV cavity and provide good visualization of mitral valve. Rotate towards the two-chamber view again insuring adequate angulation to maximize size of LV cavity.

NOTE: Doppler measurements will be available for those Registry substudy participants who are also enrolled in the SOLVD Echocardiography Substudy.

4.3.3. Storage and Shipping

The original copy of the echocardiogram tapes will be sent to Dr. M.A. Quinones' laboratory in Houston for evaluation. (See Appendix A for address.) All SOLVD Registry patients will be studied on designated SOLVD Registry tapes. Do not put more than five echo studies on a tape. Copies of each of the studies should be kept at the individual SOLVD center to be used locally (i.e., reports to the referring M.D.) and as backup in case the original tapes should be lost in transit.

4.4. Data Collection Forms

4.4.1. Ladder of Life

The Ladder of Life questions from the Quality of Life form are to be administered

to Registry substudy participants. This can be given at any point during the clinic visit. A self-administered "Ladder of Life" questionnaire has been designed for the Registry. (French- and Spanish-language versions are available from the Coordinating Center.) Before giving the form to the participant, write in the participant's Registry ID number where "Patient's code number" is indicated. Responses from this questionnaire are entered in Section K of the RSB. Participants should complete this form on their own but clinic staff may be needed to answer questions or to help participants who cannot read. For additional instructions on the Ladder of Life, consult the SOLVD [Main Trials] protocol and manual of operations regarding the Quality of Life questionnaire.

4.4.2. Registry Substudy Baseline Form (RSB)

At the visit, conduct a physical examination and history and record the information on the Registry Substudy Baseline Form (RSB) (see Appendix E). You will notice that number of the questions on the RSB duplicate questions on the Registry Baseline Form. Please do <u>not</u> simply copy responses from the RSF to the RSB. One of the objectives of the substudy is to compare data obtained from medical charts with those obtained in a direct and standardized way; this objective will be compromised if the substudy data were not collected independently from the baseline form.

4.4.3. Specific Instructions for the RSB

Guidelines and additional information for certain questions on the RSB are given below. Please consult the SOLVD Registry General Instructions for Completing Forms for further information.

Registry ID: Enter the nine-character number assigned to this participant.

Section A (Identifying Information): Self-explanatory.

Q. 3.1 (Date echos done): Self-explanatory.

Q. 3.2 (Echo quality): See above for criteria. IF THE ECHO DOES NOT MEET THESE CRITERIA THE PARTICIPANT CANNOT BE ENROLLED IN THE REGISTRY SUBSTUDY. If this is the case, answer "no" and exit form.

Q. 3.3-3.4 (Doppler echo): Self-explanatory. The Doppler echo is conducted as part of the SOLVD Echocardiography Substudy.

Q. 4.1 (Primary etiology): Only <u>one</u> option is chosen. See instructions for RBF Q. 23.1, above.

Q. 5 (Other etiologies): Indicate presence of any etiologies that apply, including the one specified in Q. 4.1 as the primary etiology.

Q. 6 (New York Heart Association CHF Class): Check only one option.

Q. 7 (Past clinical history): History up to date the Registry Baseline Form was completed. See instructions for RBF Section G.

Q. 8 (Smoking history): Consider only cigarette smoking.

Q. 8.1-8.2 (Smoking habit and onset): Self-explanatory.

Q. 8.3-8.9 (Extent of smoking): Self-explanatory. For Q. 8.2-8.4, round to nearest year. (See instructions for RBF Q. 28.14 for rounding rule.)

Q. 9.1-9.2 (Alcohol consumption history): Self-explanatory.

Q. 9.3 (Number of drinks last week): Self-explanatory. One drink is defined as 12 oz of beer, 4 to 5 oz of wine, or 1.5 oz of hard liquor.

Q. 9.4A (Drinking pattern): These options will be defined in this manual at a later date.

Q. 9.4B (Number of days currently drinks): Self-explanatory. After completing this question, skip to Q. 10.1.

Q. 9.5 (Number of days used to drink): Self-explanatory.

Q. 9.6 (Number of drinks used to drink): See instructions for Q. 9.3.

Q. 9.7 (Former drinking pattern): See instructions for Q. 9.4A.

Q. 10.1-10.2 (Myocardial infarction): Self-explanatory.

Q. 11-14.7 (Cardiac implantations or surgery): Self-explanatory.

Section E (Medications): Indicate medications used at time the Registry Baseline Form was completed. See instructions for RBF, Section H.

Q. 16 (Weight): Enter weight in pounds or kilograms (but not both). Measure the participant's weight without shoes or outdoor garments. He should not have been eating a heavy meal before the measurement. Be sure that the indicator is at zero when no weight is on the scale. The scale should be level and on a firm surface. The patient should be instructed to stand in the middle of the platform of the balance scale with the head erect and eyes looking straight ahead. Adjust the weight on the indicator until it is balanced.

Q. 17 (Height): Enter height in inches or centimeters (but not both).

Q. 18 (Heart rate): After every blood pressure recording, the radial pulse will be counted for 15 seconds and the value multiplied by 4. Record the heart rate in beats per minute.

Q. 19-20 (Blood pressure): The subject should be seated comfortably in a quiet room. The arm muscles should be relaxed and the forearm supported. The arm should be at the heart level when the measurement is done.

Measurement: A mercury sphygomanometer should be used and a cuff size selected according to the circumference of the arm (AC). Ordinary cuff up to AC of 33 cm, large cuff for AC of 33-41 cm and thigh for AC above 41 cm. The cuff is then applied evenly and firmly to the exposed upper arm. If possible, the right arm should be selected. The cuff should be inflated to about 30 mm Hg above expected systolic blood pressure. The cuff is then slowly deflated, about 2-3 mm Hg per beat, during which time the Korotkoff sounds are listened to through a stethoscope

placed over the brachial artery. The pressure at which the sounds are first heard is the systolic pressure. The diastolic pressure, phase V, is defined as the pressure at which the sounds disappear. The systolic and diastolic blood pressures should be measured at least twice over a period of at least 2 minutes and the mean value of those two is to be recorded.

Q. 21 (Presence of rales, edema, etc.): Self-explanatory.

Section G (ECG findings): Data from a previous ECG may be used if taken within 90 days prior to the substudy visit. See instructions for Registry Baseline Form, Section J. The assistance of a physician or research nurse may be required.

Q. 32-33 (Q-wave MI): See instructions for Registry Baseline Form, Q. 54-55.

Section H (X-ray): Data from a previous chest X-ray may be used if taken within 90 days prior to the substudy visit. The X-ray must taken 7 or more days following an MI, cardiac surgery, PTCA, or balloon valvuloplasty.

Q. 34 (Date of X-ray): Self-explanatory.

Q. 35 (CT ratio): Use only if taken from 6 ft. film; do not use portable X-ray data. The CT ratio should be calculated if not indicated in the record. Enter as a decimal value.

Q. 36 (Serial X-ray available): Self-explanatory.

Q. 37 (Evidence of pulmonary congestion): See instructions for RBF Q. 22.1-22.5.

Q. 38-39 (Holter monitoring): Self-explanatory.

Q. 40.1-40.6 (Neurohumoral measurements): Self-explanatory. Note that for Q. 40.4 (hour measurements taken) a 24-hour clock is <u>not</u> used. Indicate the time to the nearest hour (01-12) and indicate in Q. 40.5 whether the hour was in the morning (AM) or afternoon (PM).

Q. 40.7-40.8 (Neurohumoral values): These questions will be completed after the core laboratory analyzes the samples; leave them blank. Do <u>not</u> wait to complete these items before keying in the RSB form or the form will not be received by the Coordinating Center within protocol window.

Q. 41 (Procedures done on same day as echo): Self-explanatory.

Q. 42 (Major events in interim): Self-explanatory. Complete a Registry Hospitalization Form for <u>each</u> event.

Q. 43-46.5 (Six-minute walk test): Self-explanatory.

Q. 47 (Distance travelled): Self-explanatory. Enter feet or meters (but not both), rounding to nearest unit.

Q. 48-50 (Ladder of Life steps): Enter step numbers as 01-10 from the participant's Ladder of Life questionnaire responses.

4.5. Holter Monitoring

4.5.1. Technique Procedures

Standardization of the ambulatory recording devices is mandatory. Follow the instructions given by the Holter core laboratory for lead placement, calibration, etc. Note that the Registry protocol for Holter monitoring is very similar to that for the SOLVD Sudden Death substudy except that the Registry substudy includes analysis of S-T segment. Because of the S-T analysis, care regarding lead placement and calibration is extremely important.

For each center, the ambulatory ECG recording devices should be able to produce a high quality ECG signal which include the following requirements:

(1) All recordings must have a standard calibration signal of 1mV (10mm) pulses over at least 8 minutes in duration for S-T analysis. The duration of this recording after calibration is 70 minutes: from insertion of IV cannula up to 3 minutes after the end of six-minute walk test.

(2) A standard patient preparation utilizing a degreasing and an abrasive scrub to reduce surface impedance. (This will require an inservice with the clinic coordinators of the participating centers.)

(3) Recorders must be dual channel reel-to-reel recorders with frequency responses of .05-100 Hz with lead placement at V2 (channel 2) and V5 (channel 1) to allow for the detection of both ischemic events and ventricular arrhythmias. At the time of initial lead placement, alternative leads may be selected (by a predetermined algorithm) if R-wave amplitude is insufficient or evidence of MI or other factors would preclude S-T segment analysis. (Note: earlier versions of the protocol and manual of operations indicated that cassette recorders could be used. This is <u>not</u> the case.)

(4) Test strips for signal quality will be an absolute requirement so that an adequate signal is obtained in all cases. Each center will need a test oscilloscope with a strip recorder or a single channel ECG machine for testing signal quality in each patient. Standardization pulses can be produced either by recorders with internal calibrators or through a separate pulse generator box plugged into the recorder.

Be sure to note the exact time the Holter tape begins, as well as the times of blood drawing, removal of the IV cannula, and the beginning and end of the six-minute walk test (i.e., whenever you mark the Holter tape; see below). This information must be recorded on the Holter tape transmittal form that accompanies the tape to the core laboratory.

Tapes are to be stored in an environment with low humidity and protected from ultraviolet light.

4.5.2. Supplies

All participating clinics receive recording kits from the Holter Core Laboratory, consisting of five electrodes per participant, 1 9V battery, razor, abrasion pads, and 12-hour reel-to-reel tapes, tape mailers, diaries, and transmittal forms.

Additional supplies, such as preparation solution (Freon) and micropore adhesive tape are sent in bulk.

4.6. Neurohumoral Measurements

Note: The procedures for drawing neurohumoral measurements are the same as those used in the Neurohumoral Substudy Pilot.

4.6.1. Supplies

Each clinic will receive the following tubes from the neurohumoral core laboratory (University of Texas Medical Center, Galveston, TX). The insulated shipping box should be kept for use in returning the samples.

(1) **White top** - Collection tube for plasma catecholamines.
(2) **Lavender top** - Collection tube for renin samples.
(3) **Red top** - Storage tube for plasma catecholamines (store the separated plasma in these tubes).
(4) **Blue top** - Storage tube for renin samples.
(5) **Black top** - Quality control reference for plasma tubes for catecholamine storage. Keep this in -70°C with your samples.

Every two months the Galveston core laboratory will provide a fresh lot of collection and storage tubes.

4.6.2. Collection of Blood Samples

When the study patient is ready for blood drawing, a 21-gauge butterfly needle is placed in a suitable vein and is flushed with heparinized saline. The patient now rests supine quietly for 30 minutes. After the participant has rested supine for 30 minutes with the Holter ECG leads in place, a 30-minute marker is placed on the ECG tape, blood drawn for plasma renin and catecholamines, and the IV cannula removed.

Use LAVENDER TOP tubes (vacutainer B-D) for collecting samples for renin assay. Use the WHITE TOP tube for collecting the samples for catecholamine assay. Prechill these tubes in ice (4°C). Then a 20 ml sample of blood is collected into a heparinized syringe (to heparinize the syringe, aspirate some heparin [5,000 units/ml] into syringe, rinse the syringe and expell the excess liquid). Four ml of blood is placed in catecholamine collection tube (WHITE TOP) while 5 ml each is placed in 3 LAVENDER TOP tubes (do not use the vacuum--open the cap and gently expell the blood to prevent hemolysis).

Cap the tubes and gently invert them 3 to 4 times. Make sure that the white residue at the bottom of the catecholamine collection tube (WHITE TOP) is completely dissolved. Place all the tubes in ice (4°C). All the tubes are centrifuged within one hour of collection at 2500 x g in a refrigerated centrifuge for 12 min at 4°C (e.g., Beckman J6B with JS 4.2 rotor at 2,000 RPM).

(1) Plasma from catecholamine collection tube is placed in catecholamine storage tube (RED TOP) (see flow chart below).

(2) Plasma from renin collection tube is placed in renin storage tube (BLUE TOP).

Transfer plasma with disposable plastic pipettes. When transferring plasma sample, do not collect the buffy coat found above the red cell layer.

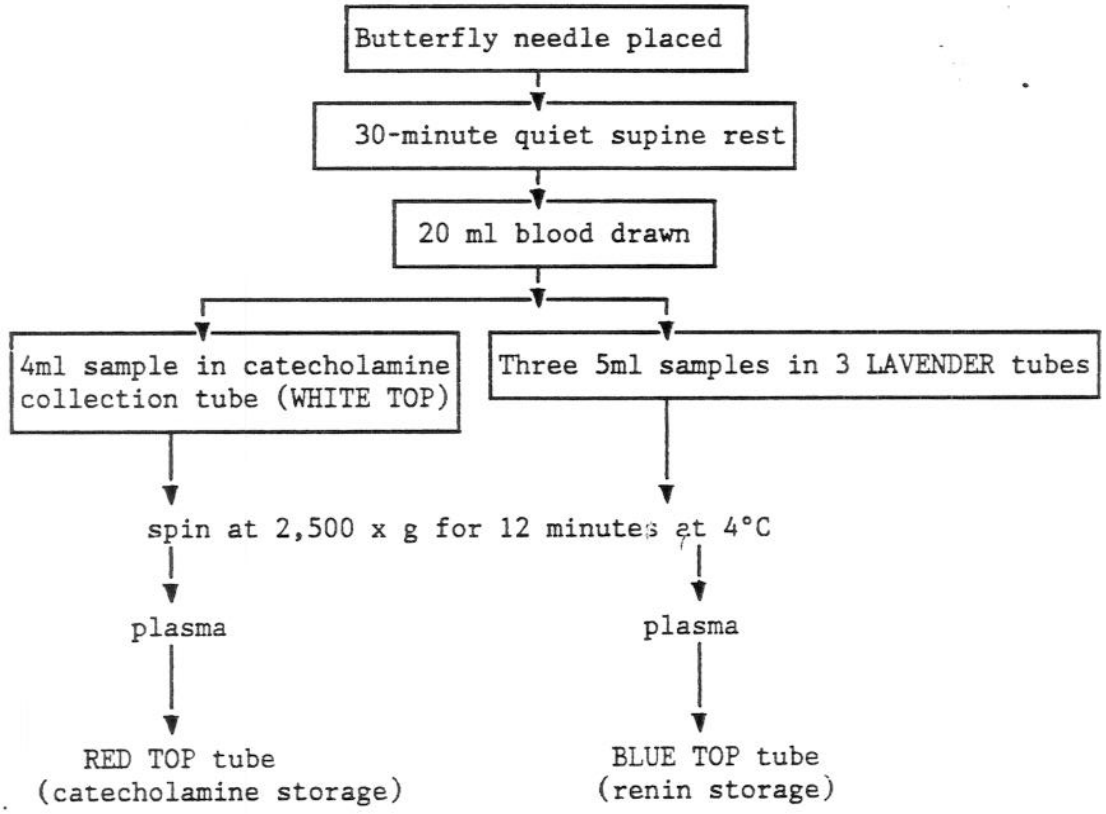
All tubes are to be labeled with the following:

(1) Participant's Registry ID number
(2) date of collection
(3) center code

Cover the label with transparent cellophane ("3M magic") tape to prevent the label from peeling or rubbing off in the freezer during storage. Store the samples in a -70°C freezer in the storage box provided. (Samples should not be stored for more than one week in a -20°C freezer. It is preferable to keep the samples in the -70° freezer during the entire storage period.)

Return plasma samples every two months to the central laboratory. Return the BLACK TOP quality control tubes with them. All tubes are packed in the styrofoam shipping container provided with 5 lbs of dry ice and handed to the carrier for air delivery. (We suggest that you retain the container sent by the lab.) Avoid shipping on Friday. For shipment from Canada, use 10 lbs (4.5 kilos) of dry ice in the container and avoid shipping on Thursday or Friday. For shipment from Belgium, use 15 lbs (7 kilos) of dry ice in the container and avoid shipping on Wednesday, Thursday, or Friday. Please contact the central laboratory prior to shipping the samples. The catecholamine reference sample has been assayed by the central laboratory prior to being distributed. When returned, these samples will be reassayed to check for stability during storage of the samples at the clinical center and during transport by the carrier (quality control).

Flow Chart for Collection of Blood Samples



from SCVP Registry Manual of Operations

4.7. Six-Minute Walking Test

After the participant rests in a sitting position, mark the ECG tape and begin the six-minute walking test. The walking test should be conducted in an enclosed corridor on a course 100 feet (approximately 30.5 meters) long. (If a corridor of this length cannot be found, use one that is at least 66 feet (22 m) long.) The corridor should not be heavily transited and should be free of obstacles and distractions. It should be inconspicuously divided into taped five-yard (five-meter) sections to allow easy measurement of the distance walked. Chairs are to be placed at both ends of the course so that patients may rest when needed and to provide clear markers of the beginning and end of the course.

It has been shown that the validity of the walk test can be affected by differences in procedure, particularly in the amount of encouragement. For this reason, please follow the instructions given here, including the "Helpful Hints," exactly.

You will need a stop watch, paper and pen to record the number of laps completed, and the walking test instructions.

Stand with the patient at one end of the course and read the following instructions verbatim. Pause between sentences so the patient can absorb the instructions. Make direct eye contact when reading the sentence "However, the most important thing about the test is that you cover as much ground as possible during the six-minute period."

Instructions:

> "The purpose of this test is to determine how far you can walk in six minutes. You will start here and go to the chair at the end of the hall, turn around, and walk back. After arriving back at the starting point, you will go back and forth again. Go back and forth as many times as you can in the six-minute period. If necessary, stop and rest and stay there until you can start again. However, the most important thing about the test is that you cover as much distance as possible during the six-minute period.
>
> I will let you know when the six minutes are up. When I say STOP, please stand right where you are.
>
> Do you have any questions about the test?
>
> Please explain to me what you are going to do.
>
> Are you ready?
>
> Start with I say GO."

Patients should be encouraged to exercise to the point of exhaustion and should only terminate the walk prior to six minutes if severe shortness of breath, muscular pain, dizziness, or anginal symptoms develop. To standardize the test, encouragement is to be offered by saying, every 30 seconds, one of the following two phrases: "You're doing well!" or "Keep up the good work!" When two minutes have elapsed you should state: "You have completed two minutes." When four minutes have elapsed you should state: "You have completed four minutes." After

six minutes have passed, the participant is told to stop and to not move until you have recorded the distance. Place a marker on the Holter tape, determine the distance walked, and complete Section J of the RSB.

At the conclusion of the test, you may wish to take the participant's pulse and/or blood pressure, etc. to continue rapport. These data will not be collected.

Additional Helpful Hints for the Walking Test

- At the 30-second encouragement, position yourself so that you can make eye contact with the participant.

- During the test, do not influence the patient's pace by your walking, i.e., you should:

  a. walk behind the participant
  b. do not rush up behind the participant
  c. do not rush past the participant

- Speak to the participant only at the 30-second encouragements. It is tempting to respond to the participant's questions about the time and distance elapsed but do not do this.

- The participant tends to respond to your encouragement by talking. If in your judgment they are not concentrating on the task, then at a 30-second mark, include a phrase such as "This is a walking test, not a talking test" or the excerpt from the instructions ("I'll tell you the time..."). You can repeat separate sentences from the instructions. For example, if the participant is slowing down and says that he or she wants to stop, say, "Remember, if you need to, you may stop and rest; just remain where you are until you can go on again."

4.8. Chest X-Ray and ECG

If the participant has not had a chest X-ray and electrocardiogram within the past 90 days, these procedures should be administered during the substudy visit. They can be given at any point during the clinic visit except during Holter/blood drawing/walk test segment.

5. FOLLOW-UP

5.1. One Year Follow-Up

5.1.1. For Participants Who Are Not in the SOLVD Trials

One year after the participant's enrollment in the Registry, the participant should be contacted for follow-up. The first contact attempt should be by mail. The follow-up interview letter must contain all questions on the participant's follow-up form, but clinic-specific paragraphs may also be included to continue participant rapport. (See Appendix E for a sample form.) Fill in the header information and the dates (date of enrollment in Registry and same date, one year later) in Question 1. The participant is to complete the remainder of the form and return it to the clinic. (Self-addressed stamped envelopes will increase response rates.)

If contact by mail is not successful, telephone calls or other means of contact should be attempted. The form can be completed over the telephone.

Once the participant's response is received, the clinic should use the information to fill out the Registry Follow-up Form (RFF).

5.1.2. For Participants Who Are in the SOLVD Trials

If a Registry participant is also participating in either the Prevention or Treatment trial of the main SOLVD study, do NOT make mail or telephone contact for Registry follow-up. Instead, follow-up information is to be obtained during the scheduled SOLVD visit that occurs closest to the one-year anniversary of the date of enrollment for the Registry. If the Quality of Life questionnaire is to be administered at that visit, the participant's responses to the Ladder of Life can be obtained from that questionnaire. If the Quality of Life questionnaire is not to be administered, ask the SOLVD nurse to administer the one-page Registry Ladder of Life questionnaire.

5.1.3. Additional Activities for One-Year Follow-Up

- If the participant is alive and has not been hospitalized during the preceding year, no further information is required after the completion of the RFF.

- If the participant is alive but was hospitalized one or more times in the preceding year, the clinic must obtain reports of the hospitalization(s) and complete a Registry Hospitalization Form for each hospitalization.

- If the participant has died, the clinic must (1) obtain reports of hospitalizations (if any) and circumstances of death as well as the death certificate and (2) complete and send to the Coordinating Center a Registry Hospitalization Form for each hospitalization, a Designation of Death form, and the Death Certificate Cover Sheet. (The Designation of Death and Hospitalization forms are sent via the weekly data transfer; see below. The death certificate and cover sheet should be sent via mail.)

Follow-up forms should be submitted to the Coordinating Center no more than 60 days after the participant's one-year anniversary of enrollment. Hospitalization and death certificate forms should be submitted within 60 days after the follow-up form is completed.

5.1.4. Registry Follow-Up Form (RFF), Hospitalization (RHF), and Death Forms (RDD and RDC)

The Registry Follow-up Form uses information from the follow-up interview letter that the participant completes (see Appendix E). All items are self-explanatory. Note that the participant is asked about other health concerns that he or she may have. This information is for the clinic's use and to continue rapport and is not reported to the Coordinating Center. (However, the question regarding health concerns must be included in the participant's interview letter.)

Registry hospitalization and death forms are very similar to those used in the main SOLVD trials (see Appendix E). Consult the SOLVD Manual of Operations or the SOLVD study coordinator at your clinic if questions arise. Registry hospitalization and death forms must be completed for SOLVD patients who are also in the Registry, but the SOLVD hospitalization and death forms, if they have already been completed, may be used to complete the Registry forms.

5.2. Long-Term Follow Up

Long-term follow-up of the vital status (mortality) of Registry participants is done approximately two years and approximately four years after the date of enrollment. The Coordinating Center is responsible for assessing vital status for clinics in the United States. Canadian and Belgian clinics collect these data from their respective bureaus of vital statistics and will send them, upon request, to the Coordinating Center.

6. DATA TRANSFER

6.1. Blood Samples

Return plasma samples every two months to the central laboratory (Dr. Claude Benedict, Associate Professor, Internal Medicine, Department of Cardiology, University of Texas Medical Center, Galveston, TX 77550). (See protocol for shipping procedures.)

6.2. Holter Tapes

Label and mail Holter tapes on a weekly basis to: Marilyn Francis, RN, SOLVD, Baylor College of Medicine, Dept. of Cardiology, 6535 Fannin, MS F905, Houston, TX 77030. Complete the tape labels and transmittal forms as per core laboratory instructions.

6.3. Echocardiograms

Each tape should be copied. Send the original echo tape to Dr. M. A. Quinones, Methodist Hospital, 6535 Fannin, MS F1001, Houston, TX 77030. Retain the copy for local use (e.g., reports to referring physician) and as back up against loss of original in transit.

6.4. Registry Forms

Monthly log summaries are sent to the Coordinating Center by electronic or regular mail. Registry forms are keyed into the SOLVD data entry system at the clinical centers and transmitted to the Coordinating Center as part of the weekly data transfer. Registry forms (RSF and, where applicable, RSB) should be transmitted to the Coordinating Center within 90 days of the participant being entered onto the Registry Log. Death certificates, with cover sheets, should be sent by mail to the Coordinating Center.

7. QUALITY CONTROL

7.1. Data Collection

Registry quality control consists first of all in the ability of Registry personnel to perform adequate records abstraction and to perform the substudy procedures in an accurate and uniform way. Registry personnel will be trained centrally by the Coordinating Center to be considered qualified. Personnel not trained centrally will need to be trained on-site by a qualified individual. Data quality checks for the Registry are subsumed under quality control activities for the main SOLVD trials.

7.2. Neurohumoral Measurements

The core laboratory maintains procedures for analyzing the quality of blood samples and neurohumoral measurements. See the Neurohumoral Substudy Pilot Protocol for details.

7.3. Echocardiography

The quality of echocardiographic studies will be judged locally as well as at the core laboratory as excellent, adequate, or suboptimal. Clinics with one or more suboptimal studies during the first 5 patients will be contacted directly by the director of the core laboratory to readdress the criteria used locally for quality judgment. The other participating centers will absorb in equal distribution the additional recruiment load.

7.4. Holter Monitoring

Quality control procedures for ambulatory electrocardiographic recordings will involve three phases. Phase I will address application techniques, Phase II ambulatory ECG equipment requirements, and Phase III ambulatory ECG tape analysis. See the SOLVD Registry protocol for details regarding these procedures.

Appendix C
List of Drug Classifications

Note: The following list is to be used as a guide in completing Registry forms. It is not intended to be exhaustive. Consult the Physician's Desk Reference or other suitable reference source when necessary.

Potassium-losing diuretics:

Aquatensen
Bumex
Diamox
Diulo
Diuril
Edecrin
Enduron
Esidrex
Hydrochlorotiazide
Hydrodiuril
Hydromox
Hygroton
Lasix
Lozol
Naqua
Naturetin
Oretic
Renese
Saluron
Zaroxolyn

Potassium-sparing diuretics:

Aldactazide
Aldactone
Dyazide
Dyrenium
Maxzide
Midamor
Moduretic

Antiarrhythmic drug other than beta-blocker or calcium blocker:

Cardioquin
Cin-Quin
Cordarone
Enkaid
Mexitil

Norpace
Procan
Pronestyl
Quinaglute
Quinidex
Quinora
Tambocor
Tonocard

Antiplatelet drug:

Dipyridimole
Persantine
Aspirine?

Beta-blocker:

Blocadren
Corgard
Corzide
Inderal
Lopressor
Lopressor HCT
Normodyne
Normozide
Propranolol
Sectral
Tenoretic
Tenormin or Atenolol
Timolide
Trandate
Trandate HCT
Visken

Long-acting oral nitrate or paste:

Deponit
Dilatrate-SR
Isordil
Nitrodisc
Nitro-Dur
Nitro Paste
Nitrogard
Nitrol
Nitrospan
Peritrate
Sorbitrate
Transderm-Nitro

Hydralazine:

Apresazide
Apresoline
Apresoline-Esidrex
Ser-Ap-Es
Serpasil-Apresoline (also an antihypertensive)
Unipres

ACE inhibitor:

Capoten
Capozide
Vaseretic
Vasotec

Digitalis:

Digoxin
Digitoxin
Crystodigin
Lanoxicaps
Lanoxin

Calcium antagonists:

Adalat
Calan
Cardiazem
Isoptin
Procardia

Antihypertensives (other than above)

Aldoclor (also contains a diuretic)
Aldomet
Dibenzyline
Esimil
Hylorel
Ismelin
Minipress
Raudixin
Rauzide
Serpasil
Serpasil-Apresoline (also contains hydralazine)
Serpasil-Esidrex (also a diuretic)
Wytensin

Anticoagulant:

Coumidin

Panwarfarin
Warfarin

Insulin:

Humulin
Iletin II Regular
Insulatard NPH
Insulin Purified
Insulin R
Lente
Mixtard
Novolin R
Sepilente
Ultralente
Velosulin

Steroids:

Aristocort
Celestone
Cortef
Cortison
Decadron
Deltasone
Dexone
Florinef
Hexadrol
Hydrocortisone
Kenalog
Liquid Pred
Medrol
Meticorten
Orasone
Pediapred
Prednisolone
Prelone

Beta-2 agonist inhalers:

Alupent
Brethaire
Duo-Medihaler
Duraphyl
Medihaler
Metaprel
Norisodrine
Proventil
Tornalate
Ventolinx

Potassium supplements:

Bi-K
Kaochlor
Kaon
Kay Ciel
K-dur
K-Lor
Klorvess
Klotrix
K-Lyte
K-Norm
K-Tab
Micro-K
Slow-K
Ten-K

Appendix D
ECG Amplitude Measurements

Note: The following instructions are given as a guide for measuring the amplitudes of ECG waves. Consult an ECG technician or other trained individual if questions arise.

14-JUL-8[illegible] :29 VANDERBILT UNIVERSITY MEDICAL CENTER

678226

5mm/s
[illegible]/mV
40Hz
Pgm 002A
12SL v68

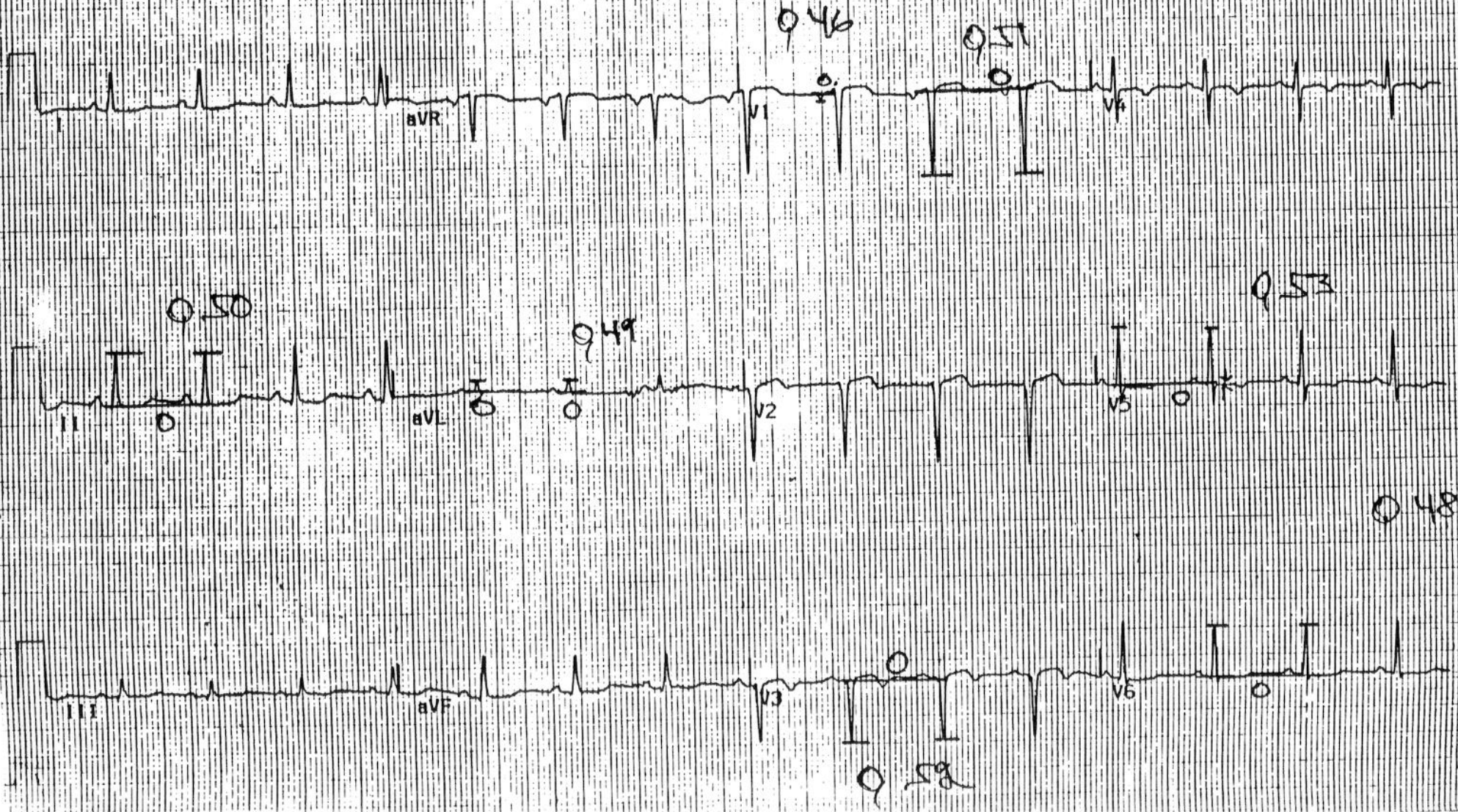
Med:
50yr 70 in 195lb
Sex: M Race: Cauc
Loc: 2 Room: 7018
Option: BP

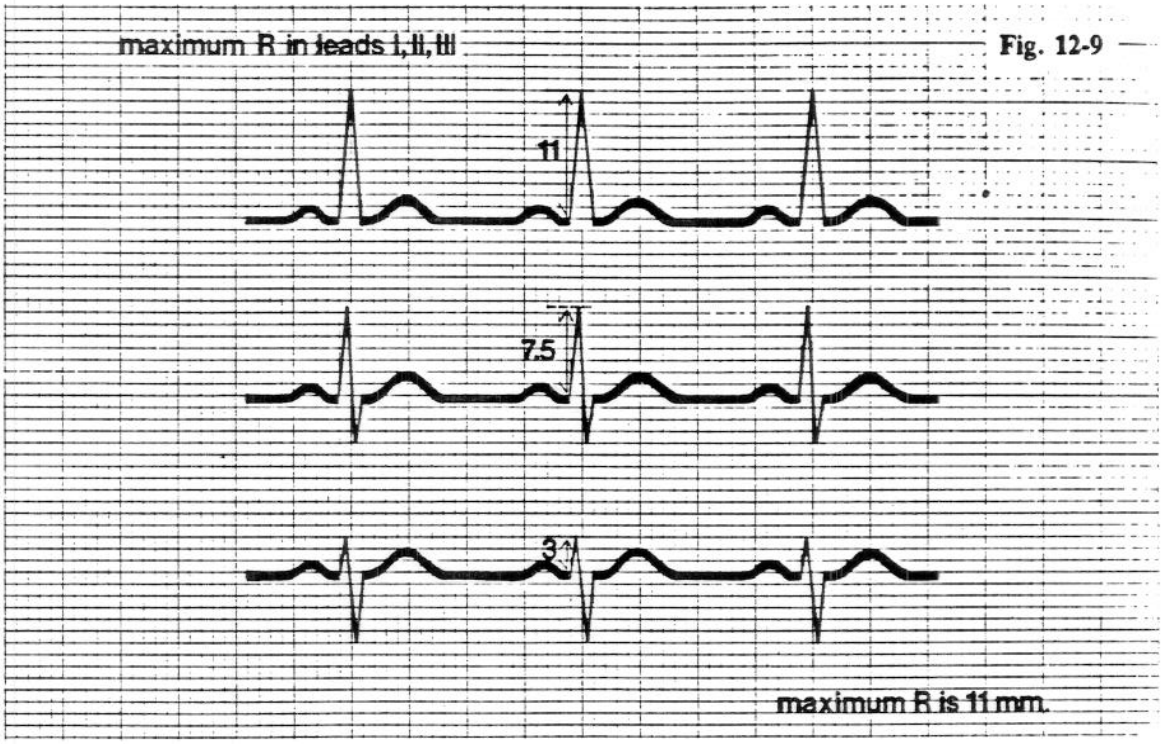
Vent. rate	92	BPM
PR interval	132	ms
QRS duration	84	ms
QT/QTc	320/394	ms
P-R-T axes	48 50 67	

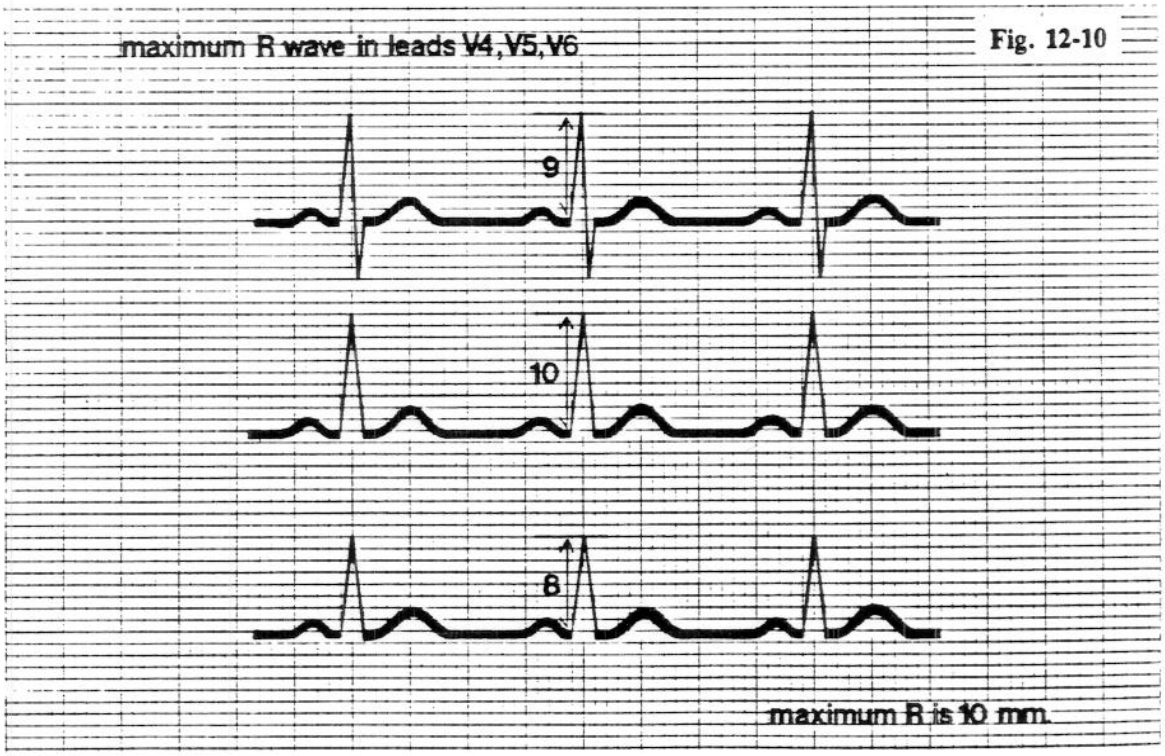
Normal sinus rhythm
Possible left atrial enlargement
Anteroseptal myocardial infarction, age undetermined.
Non-specific ST-T wave changes.
T wave inversion V3+V6 since previous tracing 7-9-86.
Abnormal ECG.

Referred by: J HAMMON

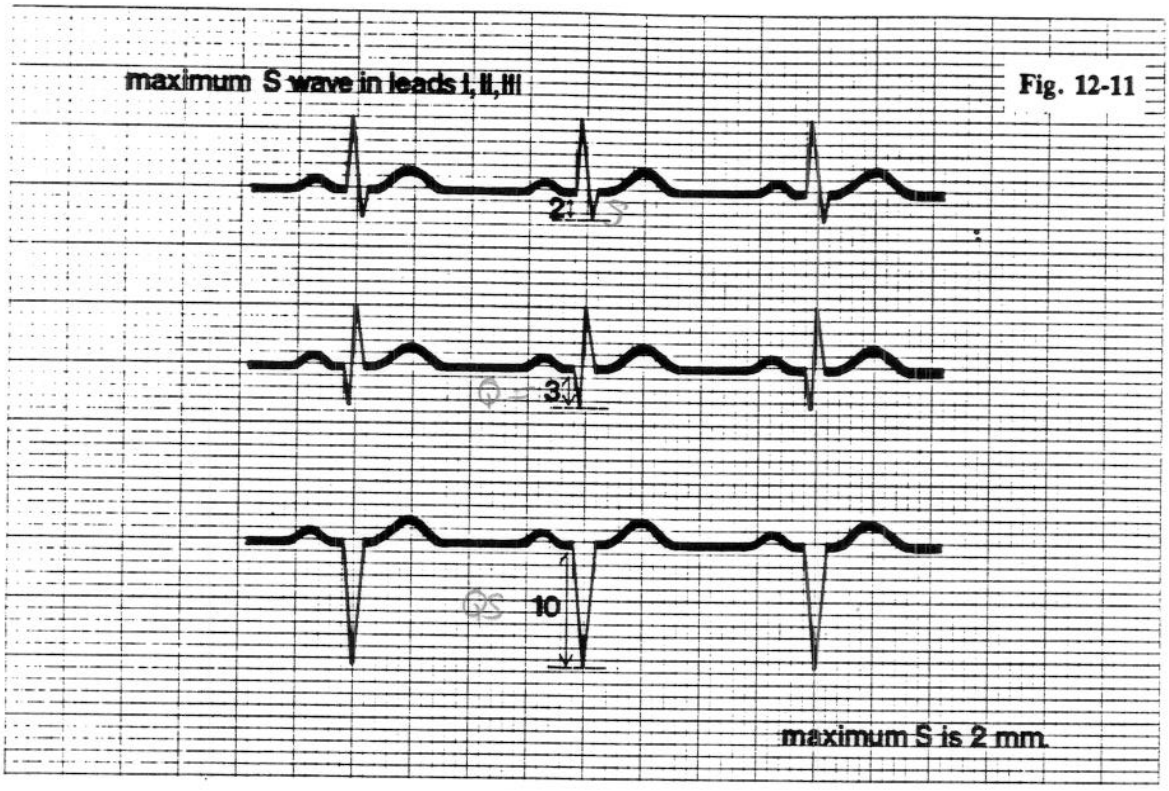
Reviewed by [illegible] Dr. Bajaj

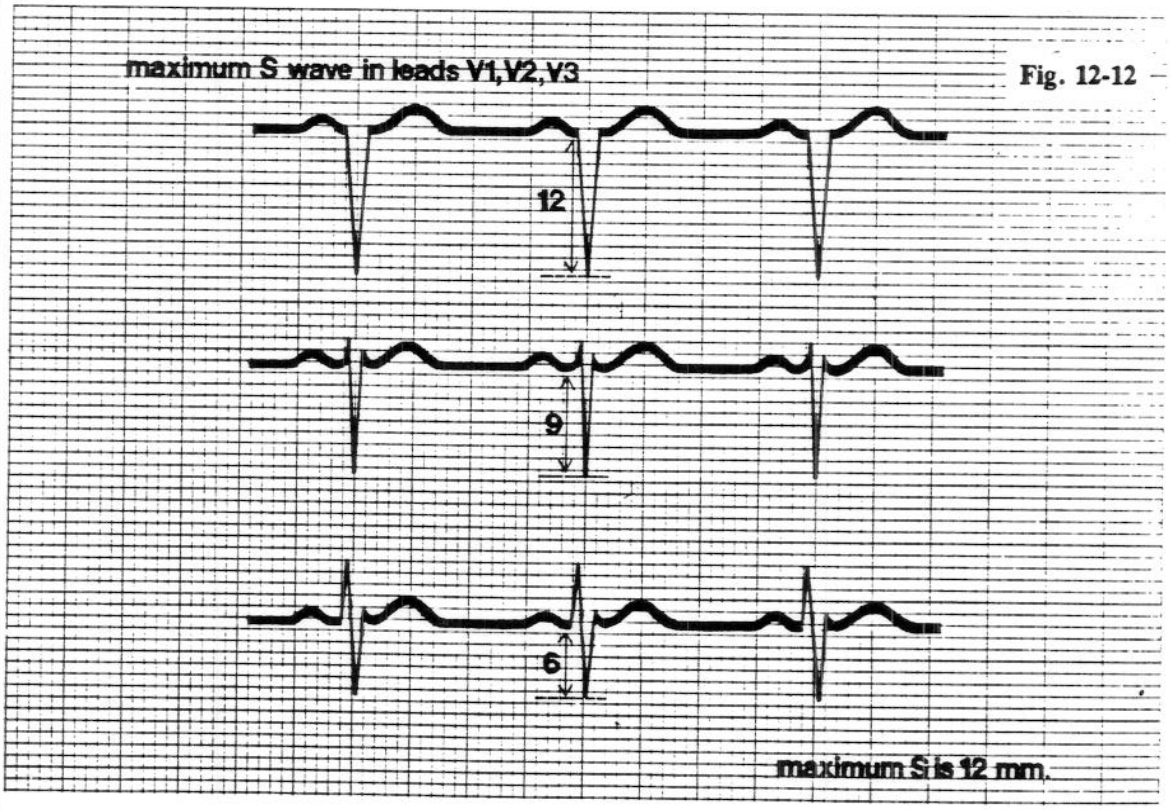






12-9,12-10. R-wave amplitude is measured to the nearest whole millimeter in the next to last complete normal beat in the appropriate leads. For example, the maximum R-wave in lead I, II and III is the highest R-wave in the next to last beat of lead I or II or III (see Figure 12-9). A similar measurement is made in V_4, V_5, and V_6 (see Figure 12-10).





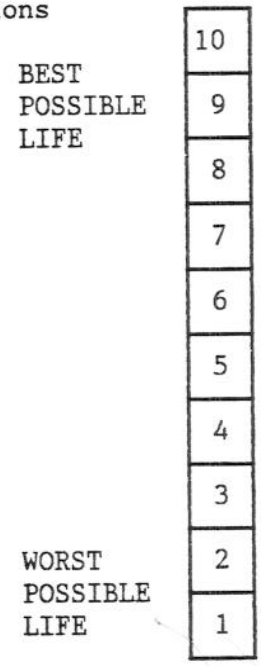
12-11,12-12. The maximum S-wave is measured in the same manner as the maximum R-wave (see Figures 12-11 and 12-12).

See file for French, Spanish versions

People's health can affect many aspects of their lives. We are interested in how your health is affecting your life. Below are a few questions about your life. Please read the question carefully and then choose the answer you agree with the most. Since there are no right or wrong answers, usually your first thought is the best. We are interested in how you feel about your life.

Patient's code number: _____

HERE IS A LADDER REPRESENTING THE "LADDER OF LIFE." THE TOP OF THE LADDER REPRESENTS THE BEST POSSIBLE LIFE FOR YOU. THE BOTTOM OF THE LADDER REPRESENTS THE WORST POSSIBLE LIFE FOR YOU. (Answer questions a through c below)



a. On which step of the ladder do you feel you are personally standing at the present time?

   PRESENT TIME (1 to 10) _____

b. On which step would you have stood five years ago?

   FIVE YEARS AGO (1 to 10) _____

c. Thinking about your future, on which step do you think you will stand about five years from now?

   FIVE YEARS FROM NOW (1 to 10) _____

Thank you very much for participating in this study. We appreciate your time.

Please turn this form in to the person who gave it to you.