THE STRONG HEART STUDY
Cardiovascular Disease in American Indians
(Phase II)

Operational Manual
Volume Four
Special Examinations

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MANUAL IV

Special Examinations

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1. ECHOCARDIOGRAPHY READING CENTER
MANUAL OF OPERATIONS

1.1 Goals of Study

Echocardiographic measurement of left ventricular (LV) mass, function and blood flow characteristics in clinical and epidemiologic studies has improved the understanding of the prevalence, demographic correlates, and prognostic significance of preclinical and clinically evident heart disease. Echocardiographic LV mass, which is increased by high blood pressure, obesity and other risk factors or life-style variables, has been shown to be an extremely strong predictor of subsequent morbidity and mortality. Genetic influences on LV mass have been suggested by family studies and by differences between African-Americans and whites in cardiac anatomy and hemodynamics. Native Americans constitute a segment of the U.S. population with high prevalences of obesity, diabetes and other risk factors and apparently rising rates of cardiovascular morbidity in which virtually nothing is known of the prevalence or correlates of structural changes of the heart and blood vessels in asymptomatic individuals that may be termed "preclinical cardiac disease." Accordingly, echocardiography will be used in American Indian participants in Exam II of the Strong Heart Study (SHS) in 3 areas (Arizona, Oklahoma and South Dakota) to answer the following questions:

1) What is the distribution of LV size, mass and function among Native Americans, and does it differ from findings in Caucasian populations?

2) What is the association of LV mass and cardiac function to prevalent, clinically recognized heart disease among Native Americans?

3) Is percent body fat and its distribution an independent predictor of LV enlargement independent of the effects of lean body mass or blood pressure?

4) What are the cardiac functional characteristics and prevalence of the cardiomyopathy of diabetes, and can its early features be detected in individuals with impaired glucose tolerance and a low likelihood of atherosclerotic disease?

5) Are circulating insulin levels associated with LV mass, independent of conventional stimuli to cardiac growth?

6) Is alcohol intake associated with LV hypertrophy and at what level of intake does LV dysfunction become evident?

7) What are the prevalence of and factors associated with valvular heart disease among Native Americans?
The populations participating in the SHS present a unique opportunity to answer these questions because of the particular mix of genetic and environmental factors and because of the relatively under-studied status of cardiovascular disease in this important ethnic group.

1.2 Background of the Study

Over the past 4 decades the understanding of cardiovascular disease has been greatly enhanced by epidemiologic studies in which risk factors have been related to prevalent (already recognized) and incident (newly occurring) cardiovascular disease. Despite its fruitfulness, this research strategy is limited by the commonly long latent period before risk factor exposure leads to morbid events, and the inconsistency with which exposure to such strong risk factors as elevated blood pressure or cholesterol levels leads to morbid events even during observation periods as long as 20 years. A series of methodologic developments have led to a conceptual advance, in which "preclinical disease" detectable by noninvasive methods has been shown to be an intermediate step between risk factor exposure and development of morbid events.

Although a number of methods may detect preclinical cardiovascular disease, including ultrasonic visualization of arterial atherosclerosis (1) and measurement of microalbuminuria (2), the measure of preclinical disease that has been most extensively validated and studied in clinical and epidemiological contexts is echocardiographic LV mass (3-5). A variety of echocardiographic methods have been shown to measure human LV mass accurately by necropsy comparison (6-10), and this measurement has been shown to be an extremely strong predictor of cardiovascular morbidity and mortality in clinical and general population samples (3-4, 11-15). The echocardiographic examination to measure LV mass can also be utilized to assess global and regional LV systolic function and blood flow, which have been shown to be related to risk factors and prognosis (16-17). Relevant background data from sources other than the Strong Heart Study or the Cornell Echocardiography Laboratory are presented in this section.

1.2.1 Distribution of Measures of LV Size in Populations and Differences by Race

The best available information concerning the distribution of measures of LV size and mass has been provided by the Framingham Heart Study. Of a total of 6,148 participants studied by 2-dimensionally (2-D) guided M-mode echocardiography 80% had technically satisfactory LV measurements; this proportion exceeded 90% in subjects under 50 years of age but fell to 52% in those 70-79, and was also diminished by chronic lung disease and male gender but not consistently by obesity (18-19). In this population, the distribution of LV mass values appeared to be unimodal but skewed toward higher values, whereas in the subset (14% of subjects) who were considered to be normal, LV mass was normally distributed (i.e., demonstrated a bell-shaped curve) (18, 20). In the entire population LV mass rose steeply with age (21), but among apparently healthy subjects LV
mass increased slightly in older women but actually fell among men (22). The difference in
the distribution of LV mass between the entire population and the normal subset reflected
the relatively high levels of LV mass in individuals with hypertension, obesity, and
prevalent coronary and valvular heart disease and the progressive increase in the prevalence
of these conditions with advancing age (21). Only in apparently healthy young men was a
weak positive relation of physical activity to LV mass observed (23). Although few non-
white subjects were studied in Framingham, other echocardiographic studies have revealed
racial differences in cardiac structure and function. Thus, Dunn et al (24) found higher LV
mass in black than white hypertensives with similar blood pressure, and Soto et al (25)
found higher peripheral resistances in black than white adolescents in Bogalusa. These
differences have been confirmed by Liebson et al (26) who found significantly higher LV
wall thicknesses in 173 black than in 671 non-black participants in the Treatment of Mild
Hypertension Study. No comparable data are currently available concerning LV size,
mass, or function in Native Americans.

1.2.2 Association of LV Mass and Function to Prevalent Heart Disease and Subsequent
Morbidity

Although numerous clinical studies have documented associations between LV
mass and both risk factors (e.g., obesity and hypertension) and overt coronary, valvular or
myocardial heart disease, these studies suffer from the common limitation of difficulty in
determining the impact of referral patterns and subject selection criteria on the observed
results. Framingham and the ongoing Cardiovascular Health Study of subjects ≥ 65 years
of age will provide increasingly complete data concerning these associations for Caucasian
subjects (who comprise about 99% and >90%, respectively, of participants) but no
comparable data are yet available for American Indians. This is unfortunate because known
divergences of patterns observed among American Indians from those in Caucasians (e.g.,
high prevalences of diabetes and obesity but low cardiovascular disease rates among Pima
Indians [27]) suggest that study of this group may clarify whether the emerging pattern of
risk factor-preclinical disease (e.g., LV hypertrophy) relations are equally observed in
groups with varied genetic and risk factor characteristics or are relatively specific to
urbanized Caucasian populations.

Echocardiographic LV mass has been related to subsequent morbidity and mortality
in both epidemiologic and clinical studies. Again, the most generalizable data come from
Framingham. Levy and colleagues (3, 13) demonstrated that baseline LV mass was a
strong predictor of cardiovascular morbid and mortal events and all-cause mortality during
4-year follow-up, and indeed that "only LV mass and age demonstrated consistent and
strong relations to all three outcome measures" (3). This predictive value of LV mass has
been confirmed in several clinical studies of Caucasian and Black patients (11-12, 14-15,
28), but no data are available concerning Native Americans.
1.2.3 **Obesity and LV Size**

Although much of the adverse effect of obesity on health is mediated through its effects on blood pressure and lipid profile, large-scale studies have demonstrated an independent relation between obesity and cardiovascular risk (29-30). Clinical studies (31-33) and data from Framingham (21) have shown positive relations between obesity and increased LV mass and have been taken to suggest that the latter may contribute to the adverse effects of obesity. However, knowledge of the relation of increased body fat to LV mass has been limited because: 1) most studies have evaluated adiposity indirectly from body proportions by calculation of body mass index (BMI=((weight in kg)/(height in m)^2)); 2) the increase in lean body mass commonly found in subjects with high BMI has generally not been taken into account; and 3) the correct method of relating LV mass to body size has been controversial, with indexation for body surface area potentially being too forgiving of obesity (20) while implicit to the alternative method of indexing LV mass by dividing it by body height is the assumption that the 3-D volume of an organ such as the heart should be linearly related to the one-dimensional measurement of height (34). To resolve these questions, data are needed in which measurements of adipose and lean body mass are related to LV mass free of the constraining assumptions implicit in conventional methods of indexation.

1.2.4 **What are the cardiac functional characteristics and prevalence of the cardiomyopathy of diabetes and can its early features be detected in individuals with impaired glucose tolerance?**

Clinically overt diabetes mellitus is a potent risk factor both for atherosclerotic cardiovascular disease and for congestive heart failure without myocardial infarction. A recent pathologic study has documented cardiac abnormalities related to diabetes in postmortem human hearts that were independent and additive to those associated with hypertension (35). Only limited data on the **in vivo** effects of spontaneous diabetes **per se** on the heart are available, due in part to 1) the low prevalence of type I ("juvenile") diabetes in the young general population, precluding assembly of adequate-sized groups of young diabetics; and 2) the relatively old age at onset and strong association between type II diabetes and large-vessel coronary artery disease in Caucasian populations, making the cause of observed cardiac abnormalities uncertain unless subjects had undergone coronary arteriography. The high prevalence of type II diabetes with a relatively young age of onset (36) and modest prevalence and incidence of coronary artery disease among diabetics (37) in full-blooded American Indians, especially the Pima, makes this ethnic group an attractive one in which to study non-coronary diabetic heart disease.

1.2.5 **Are circulating insulin levels associated with the level of left ventricular mass, independent of conventional stimuli to cardiac growth?**

The relatively weak relations between blood pressure and body build, on the one
hand, and LV mass on the other have often been taken as indirect evidence of non-hemodynamic regulation of growth of cardiac and vascular muscle (38). Although the level of volume load (i.e., the amount of blood pumped) has recently been recognized as an additional hemodynamic stimulus to increased LV mass (39-40), increasing attention is being paid to potential growth factors. Among the latter insulin merits particular consideration in view of emerging associations of glucose intolerance and insulin resistance with a spectrum of cardiovascular abnormalities (16, 41). The only available study relating insulin resistance to LV mass initially appeared to be negative (42) but had turned positive as additional cases were added before the time (11/90) the abstract was presented. The very high prevalence of abnormalities of glucose and insulin metabolism among the Pima and more moderate prevalences of these abnormalities among other Native American groups makes Strong Heart Study subjects an attractive group in which to study insulin-LV mass relations.

1.2.6 *Is increased alcohol intake associated with left ventricular hypertrophy and at what level of intake does ventricular dysfunction become evident?*

Although modest ethanol intake may have beneficial effects on lipid profile and cardiovascular morbidity, excess alcohol use leads to accelerated rates of cardiac death (43). This may be mediated by an alcoholic cardiomyopathy which is at least partially reversed by abstention. An association between alcohol intake and LV mass was reported by Manolio et al (44) based on Framingham data. To date no population-based assessment of the relation of alcohol intake to measures of LV function has been reported. The relatively high rate of excess alcohol assumption among Native Americans makes them a population in which it is practical to study alcohol-heart relationships with an adequate sample size.

1.2.7 *What is the prevalence of and factors associated with valvular heart disease in Native Americans?*

While the burden of cardiovascular disease is generally thought of in terms of coronary heart disease, it is notable that cardiac valvular surgery is undertaken annually in nearly 30,000 Americans. Reliable data on the population prevalence of significant valvular stenoses and regurgitation are not available, but are likely to emerge soon for Caucasian populations from Framingham and the CHS. Although Native Americans have commonly had limited health care, which may predispose to rheumatic fever, and have high prevalences of obesity, which appears to be associated with valvular degeneration, no data are available on the prevalence, severity, or factors associated with valvular heart disease in this population.

1.3 *Preliminary Studies*

Findings and concepts relevant to the specific questions are discussed separately.
although it is recognized that the divisions are in part artificial.

1.3.1 What is the distribution of measures of LV mass, size and function among Native Americans and does it differ from that found in Caucasians?

The Cornell laboratory has extensively validated and standardized echocardiographic measures of LV size, mass, function and hemodynamics (9, 45-53). Study of a multi-ethnic employed population in New York City revealed unimodal distributions of LV mass, LV internal dimension and wall thicknesses among normotensive adults whereas among sustained hypertensives the distribution of LV mass appeared to be bimodal with a second, higher made at about 120 g/m² (54). In this employed population LV mass was independently related to height, systolic blood pressure, body mass index, and gender (55). In the employed hypertensives and in a separate clinical population of hypertensive patients, LV wall thicknesses and mass were higher among blacks than whites (54, 56-57). This racial difference may also have contributed to slightly higher LV masses in the multi-racial Cornell normotensive group than in the overwhelmingly Caucasian normal groups studied in Framingham (18) or in Naples, Italy (58).

Left ventricular fractional shortening and fractional shortening adjusted for LV end-systolic stress also were normally distributed in the Cornell normotensives, whereas stress-adjusted fractional shortening had a bimodal distribution among hypertensives suggesting enhanced function in a subset (59). Other studies supported the usefulness of stress-adjusted fractional shortening as a simple measure of contractility (51, 60) but also suggested that this measure is partially preload sensitive (61).

Although no preliminary echocardiographic data are available on SHS participants, indirect estimates can be made from ECG findings. Physician readings of the first 1810 ECGs yielded diagnoses of LV hypertrophy in 2.2% of the population. This prevalence resembles that found by standard ECG criteria in Framingham (2.1%) (62). In view of the low sensitivity of the ECG in both Framingham (7%) and among employed hypertensives in New York (9%) and the diminished sensitivity of the ECG for increased LV mass in obese subjects (63) this suggests that the prevalence of increased LV mass in SHS subjects will approximate the 12 to 19% found in Framingham and at Cornell. The proportion of SHS subjects with increased LV mass may be even higher, however, because the presence of obesity may mask ECG recognition of LV hypertrophy in may participants.

1.3.2 What is the association of left ventricular mass and functional measures to prevalent clinical heart disease and subsequent incident mortality and morbidity?

The Cornell investigators have extensively studied the prevalence of LV hypertrophy and dysfunction in patients with various forms of cardiovascular disease. Among hypertensives, the proportion with LV mass above sex-specific upper normal limits ranged from 12 to 19% among healthy employed adults (54) to 44% among outpatients at a
referral hypertension center (47, 49) to 87% among patients hospitalized for relatively severe hypertension (47, 49). LV mass was even more consistently increased among patients with hemodynamically important aortic regurgitation (93% [64]), mitral regurgitation (84% [65]), and dilated cardiomyopathy (68% [49, 51]). LV dysfunction has been shown to be rare at rest (but relatively common during exercise [66]) in asymptomatic hypertensives, whereas it is relatively common in other forms of heart disease. Data for specific heart diseases from the SHS clinical examination reveal high prevalences of hypertension (19 to 60% among men and women with different levels of glucose tolerance in the 3 SHS regions) and at least suggestive evidence of coronary heart disease in nearly 20 percent of participants.

Research from Cornell, from Framingham and from a largely African-American population in Chicago has demonstrated the prognostic significance of echocardiographic LV mass. In initially uncomplicated essential hypertensive patients, baseline echocardiographic LV mass measurements were a stronger predictor of cardiovascular events during 10-year follow-up than any other variable except age (4). In fact, entry of age and LV mass into multivariate analyses eliminated the predictive value for morbid events or death found in univariate analyses for conventional risk factors (e.g., systolic blood pressure, cholesterol) (4). Of note, the predictive value of LV mass was greatest for cardiovascular and all-cause mortality, which would be feasible to ascertain in the future by national death Index data whether or not the SHS is continued after the present funding period. However, the Framingham and New York populations exhibit similar relations between conventional risk factors and cardiovascular events. In contrast, these relations are dramatically weaker in the Pima, who exhibit high prevalences of obesity and diabetes but low ones of clinical and ECG myocardial infarction, and to a lesser extent among other participants in the SHS. Thus, assessment of the predictive value of LV mass for subsequent events in the SHS can help determine whether or not the LV mass-morbid event relation is a fundamental one that is independent of genetic background and the mix of concomitant risk factors.

1.3.3 Is increased body fat a major stimulus to LV enlargement and hypertrophy independent of the effects of lean body mass or blood pressure?

Previous research at Cornell has demonstrated increases in LV mass and variable chamber enlargement in overweight as opposed to normal-weight hypertensive and normotensive adults (55, 58). Other analyses showed that the well-known gender difference in LV mass was proportional to differences in skeletal muscle mass estimated from 24-hour urinary creatinine excretion (45), and that obese, hypertensive men also had high skeletal-muscle masses (55). To further evaluate the relations between body proportions and LV mass, we compared echocardiographic and body habitus variables in 611 normal weight and 56 overweight-to-obese adults and children studied at Cornell and in Naples, Italy and Cincinnati, Ohio (58). In normal-weight subjects, LV mass was linearly related to body weight, but increased disproportionately with increases in body
surface area (to approximately its 1.5 power) or height (to its 2.7 power). LV mass was higher in overweight subjects but by smaller percentages than the increases in body weight or surface area, thus causing LV mass as a ratio to these measures to be reduced in overweight subjects; indexation of LV mass/height^{2.7} appeared to do slightly better than indexation by height in identifying the increase of about 14% in LV mass from values found in normal-weight subjects of the same height (58).

The SHS presents advantages for clarification of the impact of adiposity on heart size compared to existing data: 1) adipose body mass is estimated directly by bioelectric impedance (67) and 2) a higher prevalence of overweight (mean body mass index about 31 kl/m^2 with about 60% of subjects above upper normal limits) than of hypertension facilities separation of these two stimuli to myocardial growth.

1.3.4 What are the cardiac functional characteristics and prevalence of the cardiomyopathy of diabetes, and can its early features be detected in individuals with impaired glucose tolerance?

Diabetes has been an exclusion factor from normotensive and hypertensive populations studied by echocardiography at Cornell, with one small exception (68). A number of studies at Cornell have characterized the distribution of LV systolic function indices and their relation to myocardial afterload (end-systolic stress) in non-diabetic normotensive and hypertensive populations and patients with other forms of heart disease (51, 59, 66, 69-70). Results from the first SHS clinical examination indicate that sufficiently large numbers of subjects should be available for echocardiographic study in each of the 18 gender (male/female)-region (Arizona-Oklahoma-Dakota)-glucose metabolism (normal-impaired-diabetic) cells in the SHS to facilitate analyses comparing LV findings in subjects stratified by level of glucose intolerance with the capacity to control for relevant confounding variables.

1.3.5 Are circulating insulin levels associated with the level of LV mass, independent of conventional stimuli to cardiac growth?

This question has not been addressed at Cornell, or in other large-scale studies. Plasma insulin measurements obtained during the ongoing SHS clinical examination indicate that levels vary widely within and between gender-region-glucose tolerance cells, with particularly extensive overlap between subjects with normal and impaired glucose tolerance. About 1,550 SHS subjects were classified as having normal glucose tolerance, 750 as having impaired glucose tolerance, and about 2200 as having overt diabetes on the first clinical examination, providing reasonably large subject groups in which to evaluate associations of insulin levels and insulin-glucose relations to LV findings.

1.3.6 Is increased alcohol intake associated with LV hypertrophy and at what level of intake does LV dysfunction become evident?
Recognized alcoholism has also been an exclusion criteria from Cornell studies. In SHS data obtained to date, approximately 15 to 25% of women and 30 to 40% of men were classified as regular drinkers and 10 to 20% of women and 20 to 50% of men as binge drinkers. Thus, exposure to alcohol is substantial, but not uniform, in SHS participants.

1.3.7 What are the prevalence of and factors associated with valvular heart disease among Native Americans?

The Cornell laboratory has performed extensive research on echocardiographic methods to detect, identify the etiology and characterize the severity and reversibility of valvular heart diseases (64-65, 71-77). Other studies have estimated the prevalence of mitral valve prolapse at about 4% in employed subjects and clinical populations (78) and have used case-control methodology to assess the associations between mitral prolapse and infective endocarditis or severe mitral regurgitation (78-80). This extensive research experience gives the Cornell investigators a high level of expertise in detecting common forms of congenital, rheumatic and degenerative valvular heart disease.

1.4 Methods of Echocardiogram Performance, Interpretation and Analysis

The echocardiographic procedures for the Strong Heart Study have been designed with particular regard to the special difficulties of performing objective, skill-dependent cardiac tests in several variably remote sites. Procedures are presented in general outline followed by detailed description of 5 principal segments: 1) equipment to be used; 2) initial training/start-up; 3) echocardiography performance at Field Centers; 4) central coordination and echocardiogram reading at The New York Hospital-Cornell Medical Center; and 5) wrap-up/data analysis.

1.4.1 General Outline:

Echocardiograms will be performed over a 27 month period beginning in August 1993 on participants aged 47 to 78 in the Strong Heart Study (SHS). Study echocardiograms will be performed on the approximately 4,050 SHS participants returning for exam II, in addition to duplicate echocardiograms on about 200 subjects to assess reproducibility and potentially on a small number of additional subjects who were eligible for but did not participate in SHS exam I. To perform this number of echocardiograms with appropriate quality-control procedures will require one or two sonographers for each SHS region (Arizona, Oklahoma and the Dakotas). During the lead-in/training period from February through June 1993 (and thereafter as necessitated by logistical difficulties for the Dakota center) sonographers will be selected by Field and Reading Center investigators and receive initial training locally followed by intensive training in the specific study protocol at the Echocardiography Reading Center in New York.
Standardized examinations will include 2-D guided M-mode echocardiograms and selected 2-D and Doppler recordings. Studies will be sent to New York for blinded interpretation by experienced technician and physician readers. Study performance and interpretation will focus on selected measures of LV mass and geometry, global and regional systolic function and diastolic filling to maximize the yield of reliable data to answer the 7 specific questions.

Because of the long distances involved, multiple steps are planned to maximize quality control of echocardiogram performance. These include performance of preliminary measurements of LV dimensions and other variables by the examining technicians, using a standard form (Appendix I). This will increase their awareness of aspects of image orientation and definition needed for a measurable study. A copy of videotaped 2-D and M-mode views on study subjects will be returned to the Field Centers from the Reading Center with final measurements and comments and suggestions about how to enhance technical quality, for continuing education of the field technicians. Periodic site visits to Field Centers will be made by Reading Center staff. The Reading Center will use procedures adapted from those developed and refined in the Cornell laboratory over the past 12 years. Steps to assure data quality will include blinded performance of measurements, checking of initial measurements against the visual appearance of the echocardiograms, verification of technician-reader measurements by experienced investigators, and repeat verification of all measurements that fall outside expected ranges for a normal to mildly diseased population or reveal unexpected relations among variables. Computer support and assistance with data management and statistical analyses will be provided by the computer Center of the General Clinical Research Center and by the Division of biostatistics at Cornell.

1.4.2 Equipment

Echocardiograms will be performed using Acuson 128 echocardiographs equipped with 2.5/3.5 megahertz and 2.0 megaHz probes. These echocardiographs have been previously used successfully in the multi-center NHLBI-sponsored CARDIA study. The four echocardiographs will be assigned, one each to Arizona and Oklahoma and two to the Dakotas because of the long distances between study sites.

For performance of the echocardiograms, the Acuson echocardiographs will be mounted in specially-designed vans that will also be used for pulmonary function testing. As shown in Figure 1, the vans will be equipped with examining tables designed to facilitate performance of standardized, quantifiable echocardiograms.

At the Reading Center quantitative and qualitative assessment of echocardiograms will be performed using a Digisonics Cardiorevue Center.
Figure 1. Floor plan and external view of echocardiography/pulmonary function test vans for the Strong Heart Study.
1.4.3 Initial Training/Start-Up

Once selected, technicians would undergo phased training during the three months before the performance period. Pretraining will consist of a) supervised training as appropriate in echocardiogram performance in hospital or clinics in Phoenix, Lawton-Oklahoma City and elsewhere; b) study of an instructional videotape of the specific echocardiogram performance protocol for the Strong Heart Study (SHS); and c) study of other selected videotaped materials on echocardiogram performance. During this period the technicians will perform studies using locally available echocardiographs (and the study Acuson machines when available) following the SHS protocol and send the videotapes to New York by Express Mail for review and return of teaching comments, in effect constituting a "correspondence course" for the SHS study protocol.

Formal training will begin with a course in New York that will combine didactic teaching of selected general aspects of echocardiography and the specific SHS protocol and hands-on training in performing echocardiograms by the study protocol. The training course at the Reading Center will be two weeks for sonographers who are already proficient in echocardiography but not experienced with quantitative research studies. To maximize the degree of hands-on experience and the degree of individualized instruction, the training course will be conducted for one or two sonographers at a time.

After the sonographers return from New York, the Field Centers will be equipped. This will include arrival and set-up of the 4 Strong Heart Study vans equipped with Acuson echocardiographs and installation of additional low-frequency (2 megaHz) transducers on these machines. Final preparations for echocardiogram performance will also be completed, including installation of examining-table mattresses with cut-outs to facilitate access to the apical echocardiographic window and screens/shades needed to allow dim lighting for study performance. The camper trucks will be equipped with an appropriate examining table, fastening systems (both at the base and upper portion of the machines) to keep the echocardiograph in place during travel. This will provide mobility among scattered sites in South Dakota and between the examining centers in Arizona and Oklahoma and also make the addition of echocardiography possible in centers without available space for this procedure. Two units will be used in South Dakota, one at Pine Ridge and the other shared between Eagle Butte and Ft. Totten since the communities are so far apart. Oklahoma and Arizona will use one each.

With the equipment in place, a pilot/on-site-training study will be performed in each region during July 1993, after the Black Hills training course for all SHS employees. During a 2-day site visit by a member of the Reading Center staff each technician will perform echocardiograms on 4-6 subjects each day. This will permit immediate feedback to complete supervised technician training in the SHS protocol, and will also provide small-scale data on inter-technician variability. Between the training course in New York and the beginning of the performance period, technicians will perform studies on volunteers, make
preliminary measurements, and send the echocardiograms and interpretations to New York for review and feedback.

It is the principal investigator’s experience over the past 15 years that the percentage of echocardiograms that are suitable for accurate measurement is enhanced if the examining sonographer makes preliminary measurements on each study and is then provided feedback as to how to improve the suitability of the study for quantitation and the selection of interfaces to measure. To obtain reproducible M-mode measurements of LV structures dominant lines representing the necessary interfaces should be recorded, and recognized during interpretation, that exhibit continuous motion in the correct pattern for the structure for at least 0.10 second but ideally through the entire cardiac cycle (6, 48, 81).

1.4.4 Echocardiography Performance at Field Centers:

Principles: The most important primary echocardiographic measurements and derived variables to assess the heart in an epidemiologic context can be obtained from a relatively simple echo examination (50, 82). Correct orientation of the ultrasound beam and imaging planes to LV structure and blood flow is essential.

The LV resembles an ellipse of rotation that is nearly circular in short-axis views, with a long-axis about twice its minor axis. To measure the LV minor axis accurately it is necessary to orient the echocardiographic beam from the parasternal (or less commonly the subcostal) window to pass perpendicularly through the interventricular septum and posterolateral LV wall at the junction of papillary muscle tips and mitral chordae under 2-D guidance (Figure 2A). Rotation of the 2-D sector 90° to the short axis projection allows one to measure the true, maximum LV diameter (Figure 2B). If, as is common in older subjects, the best parasternal window is in a low interspace, LV minor-axis dimensions and wall thicknesses should not be measured in the usual fashion, although it may be possible to measure correctly the aortic root and left atrium (Figure 2C). Instead, a higher interspace should be used, which may image only a narrow sector that includes the LV minor axis (Figure 2D). If this is not possible, linear measurements of LV minor axis and wall thicknesses should be made at the correct level and orientation by the leading-edge method from 2-D long-axis views that maximize LV cavity size.

M-mode LV recordings taken from a low window can commonly be recognized by the appearance in systole of additional echo interfaces along the left side of the interventricular septum that was not seen during diastole (Figure 3). This occurs because segments of the septum closer to the LV base are drawn into view of the M-mode beam by LV contraction.
Figure 2. Orientation of parasternal long- and short-axis two dimensional echocardiographic imaging planes. A: Long-axis view in which the M-mode cursor would be correctly oriented to both the left ventricle and the aorta and left atrium. B: Rotation of the transducer approximately 90° results in an optimally oriented short-axis view. C: Long-axis view from a lower parasternal window in which the M-mode beam or short axis tomographic plane is obliquely oriented to the left ventricle, as is common in older individuals. D: Movement of the transducer one interspace higher than used for part C permits correctly oriented views of the left ventricle, albeit with a narrower field of vision.
Figure 4. Orientation of apical four- and two-chamber two-dimensional echocardiographic views. In optimally oriented views the left ventricular apex is centered at the top of the sector "fan" in both four-chamber (A) and two-chamber (B) projections. The left ventricular long-axis is commonly foreshortened in the four chamber view (C), as is demonstrated by protrusion of the ventricular apex out of the field of vision in the two-chamber view (D).
A major advantage of 2-D echocardiography is its ability to visualize the LV long-axis and wall segments near the apex. To accomplish this, one must obtain the true (longest) long-axis dimension and visualize the LV walls in approximately orthogonal apical 4- and 2-chamber views. The LV long-axis is commonly foreshortened in the 4-chamber view (Figure 4A), as seen when the transducer is rotated to the 2-chamber view and the LV apex is out of the field of view (Figure 4B). The transducer should then be moved inferolaterally until the LV apex is as nearly centered at the top of the image "fan" in both views as possible (Figures 4C and 4D).

The accuracy of Doppler recordings depends on the ultrasound beam being parallel to the axis of blood flow. Variants of the apical 2- and 4-chamber views should be used to sample LV inflow across the mitral anulus or valve orifice while the apical long-axis view is best to measure systolic flow across the aortic anulus to calculate stroke volume and cardiac output.

1.4.5 Protocol for Echocardiogram Performance

Standardized methods will be employed to obtain high-quality recordings. Echocardiograms will be performed in specialized vans with an area that provides room for the examining table, echocardiograph, etc., and have dimmable lighting to prevent glare on the echocardiograph screen that would interfere with study performance. Subjects will change their top for a light gown to permit discrete exposure of the chest wall overlying the parasternal and apical acoustic windows. Disposable ECG lead attachments (set of 3) will be attached to the skin to monitor a single ECG lead for timing purposes. The subject will then lie down and assume a partial left decubitus position (with pillows or a foam-rubber wedge to support the back) with the head of the examining table modestly elevated. The subjects' last name, initial, SHS study number and the date and site of recording will be entered so they will be recorded on videotape. Echocardiographic recordings will then be made using procedures outlined in Table 1. Careful performance of this protocol will require 40 minutes of subjects' time including the period required to get in and out of a gown and to step from the IHS facility to and from the adjacent van.
### TABLE 1  ECHOCARDIOGRAPHIC TECHNIQUES FOR LEFT VENTRICULAR MEASUREMENTS

<table>
<thead>
<tr>
<th>Instrument Calibration:</th>
<th>Calibrate against phantom at installation and at regular intervals thereafter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic Performance:</td>
<td>Standardize and record decubitus position. Use mattress cut-out for apical imaging. Record images in held expiration.</td>
</tr>
<tr>
<td>Location of Imaging Planes:</td>
<td></td>
</tr>
<tr>
<td>2-Dimensionally guided M-mode:</td>
<td>From short-axis view with correct angulation of short-axis plane defined in long-axis view or in long axis with maximization of left ventricular cavity diameter.</td>
</tr>
<tr>
<td>2-Dimensional Echo:</td>
<td>Define correct orientation of short-axis and apical views by use of 90 degree orthogonal planes.</td>
</tr>
<tr>
<td>Recognition of Measurable Images:</td>
<td></td>
</tr>
<tr>
<td>M-mode:</td>
<td>Dominant lines with correct motion representing interfaces for at least 0.10 seconds (5 m at standard recording speed).</td>
</tr>
<tr>
<td>2-Dimensional Echo:</td>
<td>Visualization of complete interface in motion with persistence in stop-frame mode.</td>
</tr>
<tr>
<td>Enhancement of Reproducibility:</td>
<td></td>
</tr>
<tr>
<td>Use three or more cardiac cycles.</td>
<td></td>
</tr>
<tr>
<td>Record imaging window location and patient position.</td>
<td></td>
</tr>
<tr>
<td>For research use readings by two or three investigators.</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Devereux et al (reference 50).

1.4.6  **Specific recordings will be made as outlined in Table 2 and the following text:**

**Parasternal Long-Axis 2-D recordings** will be obtained first, with the interspace and degree of left decubitus positioning chosen to allow an M-mode cursor line to traverse the interventricular septum (IVS) and LV posterior wall (PW) perpendicularly.
TABLE 2  STRONG HEART STUDY ECHO/DOPPLER SCANNING AND RECORDING SEQUENCE

I.  Parasternal Long-Axis Orientation View

A.  Two-dimensional echocardiography during quiet respiration: Maximize left ventricular and aortic diameter and record 10 beats on tape.

II.  Left Ventricular Imaging:

A.  M-mode cursor perpendicular through left ventricle just below the level of the mitral leaflet tips: Record 10 beats of 2-D update image with M-mode recording, then record at least 10 beats of full-screen M-mode during quiet respiration and attempt at least 5 beats at held-expiration; finally, record a full-screen, freeze-frame M-mode image for 5 seconds at held-expiration.

B.  Turn 90° into parasternal short-axis view.

C.  Two-dimensional echocardiography at or just above level of papillary muscle tips during quiet respiration: Record 15 beats on tape.

D.  M-mode cursor through the meridian of the left ventricle at level of papillary muscles: Record 10 beats of 2-D update image with M-mode recording and 10 beats of full-screen M-mode recording during quiet respiration on tape. Then attempt at least 5 beats at held-expiration; finally, record a full-screen, freeze-frame M-mode image for 5 seconds at held-expiration.

III.  M-mode sweep from LV through mitral valve to left atrium/aortic view recorded on videotape.

IV.  Aortic Left Atrial Imaging:

A.  Two-dimensional echocardiography in long-axis views during quiet respiration at level of aorta and left atrium with maximization of aortic diameter at the sinuses of Valsalva: 10 beats.

B.  M-mode cursor perpendicular through aorta and left atrium with maximization of aortic diameter by "tilting" medially and laterally of the 2-D imaging plane: Record 10 beats of 2-D update image with M-mode recording, then record 10 beats of full-screen M-mode during quiet respiration; finally, record a full-screen, freeze-frame M-mode image for 5 seconds at held-expiration.
C. Color Doppler will be turned on to record 10 beats of a view encompassing the left ventricular outflow tract and left atrium.

V. Apical Four-Chamber View

A. Two-dimensional echocardiography in quiet respiration. Record at least 10 beats with maximum chamber dimensions and good LV endocardial definition on tape.

B. Pulsed Doppler transmural flow recording with sample volume at the mitral anulus leaflet tips during diastole: Using a 2.5 MHz transducer, record 10 beats of 2-D update image with Doppler recording, then record 10 beats of full-screen Doppler during quiet respiration.

C. Doppler color flow mapping during quiet respiration: Using the 2.5 MHz transducer, turn on color to look for mitral regurgitation: Record 15 beats on tape while sweeping from the 4- to the 5-chamber view.

D. Turn approximately 90° into apical two-chamber view.

VI. Apical Two-Chamber and Apical Long-Axis Views

A. Two-dimensional echocardiography in the true apical two-chamber view during quiet respiration or held expiration: Record 15 beats with maximum LV chamber dimensions and good LV endocardial definition on tape.

B. Two-dimensional echocardiography in the apical long-axis view during quiet respiration or held expiration: Record 10 beats taking care to include the left ventricle, left atrium, aorta and right ventricle in the image.

C. Pulse Doppler recording in the apical long-axis view: Record 10 beats of 2-D update image with pulsed Doppler recording at the plane of the aortic valve anulus (hinging points of the aortic cusps), then record 10 beats of full-screen Doppler during quiet respiration.

**Left Ventricular Imaging:** While recording on super VHS tape, the imaging plane will be tilted medially and laterally to maximize the LV cavity area in the long-axis view. The M-mode cursor line will than be optimally oriented in the 2-D long view just basal to the level of the papillary muscle tips; at least 10 cycles of LV M-mode recordings with 2-D update and a second 10 cycles of full-screen M-mode will be made on videotape. If feasible, 5 cycles of full-screen M-mode will be recorded in held expiration and a full screen freeze-frame will be recorded on videotape. If another imaging window is subsequently recognized to be superior, the orientation and full-screen M-mode recordings
during quiet respiration will be repeated. A second 10-cycle M-mode LV recording will be made on 20% of subjects for use in assessment of measurement reproducibility. An attempt will be made to include a period of held expiration in LV recordings unless this interferes with LV visualization. The 2-D imaging plane will be rotated from the chest wall position that permitted optimal long-axis M-mode cursor orientation, approximately 90 degrees to visualize the LV short-axis view, at or just towards the LV base form the visible landmark of the papillary muscle tips. Recordings will then be made as indicated in Table 2.

An M-mode "sweep" will then be made from the LV through the mitral valve to the aorta/left atrium level. At the aorta/left atrium level, 2-D long-axis recording will be resumed, the imaging plane will be manipulated to maximize aortic diameter, the cursor beam will be oriented through the sinuses of Valsalva at their maximum diameter and M-mode recordings will be made as described in Table 2. Color Doppler will be turned on to record 10 beats of a view encompassing the LV outflow tract and left atrium.

At the completion of these recordings the transducer will be shifted to the apical window, identified by palpating the location of the LV impulse on the chest wall and then moving the transducer inferolaterally until the LV apex is visualized in both 2- and 4-chamber views. Repositioning of subjects may be needed to obtain a good apical acoustic window. When this is accomplished, the 2- and 4-chamber views that maximize LV cavity size will be recorded (at least 10 cycles of each); in the 4-chamber view pulsed Doppler recordings of blood flow velocity at the mitral annulus will be recorded (Figure 5A)(10 cycles) and then color Doppler will be turned on for another 15 cycles as the imaging plane is swept from the 4- to 5-chamber view. After completion of these recordings, the transducer will be rotated to the apical long-axis view (which visualizes the aortic valve and root as opposed to the 2-chamber view which excludes them in favor of the anterior LV wall) and pulsed Doppler recordings of blood flow at the aortic annular plane (10 cycles) will be performed (Figure 5B).
Figure 5. A: Schematic diagram showing the location of pulsed doppler sample volume for evaluation of left ventricular diastolic inflow at the level of the mitral valve orifice (◊) in an apical long-axis view oriented to maximize the diameter of the mitral annulus. B: Location of pulsed Doppler sample volume (◊) at the level of the aortic annulus in apical long-axis view. Abbreviations: AML, anterior mitral leaflet; Ao, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; PML, posterior mitral leaflet.
American Society of Echocardiography

Figure 6. Schematic depiction of M-mode echocardiographic left ventricular (LV) anatomic measurements according to the American Society of Echocardiography which recommended that end-diastolic measurements be made at the onset of the QRS complex using the leading edge of interfaces for all measurements.
At this point the subject will be returned to a supine position without turning up the lights or any other change and the blood pressure (phase 1 and 5 of the Korotkoff sounds=appearance and disappearance of sound) will be measured by appropriate-size cuff and mercury manometer. This is preferred to random-zero manometry because of documented inaccuracy of the latter (83). ECG leads will then be disconnected and the subject allowed to dress and to go to pulmonary function testing or return to the IHS clinic. The technician will then complete the logging information on the unblinded echo performance worksheet (Appendix 2) and on the "blinded" label (without identifiers that would reveal age, gender, blood pressure or body size) for videotape box (Appendix 3) that includes, the subject's last name and initial, SHS participant number, IHS number, date of performance and sonographer, and prepare the performance area for the next subject. Total technician time for echo performance (30 minutes), initial logging and area preparation will be 40 minutes per subject. With 6 subjects scheduled/day and slight inefficiency of subject flow, these activities will occupy the technician through the morning into early afternoon.

In the afternoon, Field Center technicians will continue the procedure begun during the training period of making preliminary measurements on each study of LV dimensions from 2-D guided M-mode recordings, recording the qualitative normality or abnormality of LV systolic function from 2-D recordings, and noting any clinical abnormalities. The worksheets with preliminary readings (Appendix I) will then be assembled with videotapes for shipment to the Reading Center, preparations (videocassettes, ECG electrodes, gel, etc.) for the next day completed, and the technicians will complete the day by reviewing previous studies returned from the Reading Center with teaching comments. Once a week, selected studies will be reviewed by the study personnel together.

1.4.7 Central Coordination and Echocardiogram Reading at The New York Hospital-Cornell Medical Center:

The Reading Center is responsible for design of the echocardiogram protocol, training and continuous feedback for quality control of echocardiogram performance by Field Center technicians, central reading of echocardiograms with careful procedures to assure accuracy and reproducibility of data, and on-going analyses (in appropriate conjunction with the Coordinating Center at the University of Oklahoma) to assure quality control and to test scientific hypotheses. The Center will take advantage of procedures and skills developed in this laboratory over the past 14 years in performing over 7,000 research echocardiograms in clinical patient groups, defined population samples, and large numbers of family units to study echocardiographic methodology (6, 9, 45, 49, 51), the heart in hypertension (11, 40, 46, 47, 59, 61, 66, 69-70, 84-87), heritable cardiovascular diseases (78-79, 88-95), valvular heart diseases (64-65, 72, 76-77, 96-98) and a variety of other conditions.
Measurement and qualitative interpretation of echocardiograms will be performed primarily by technician-readers (Mary Paranicis, Lily Yee and Roseanne Morris) with extensive over-reading and supervision by physician-investigators (Drs. Richard Devereux and Mary Roman). Upon receipt of studies from the Field Centers, they will be logged by the data manager (Linda Gerber, Ph.D.) into a hard-copy book and into a computer that will already contain a master file with participant last names, initials, study numbers and other demographic information needed to assure unambiguous subjects identification and enable the quality-control steps to be described below. The preliminary reading form and unblinded log sheet (Appendices I and II) will be separated from the videotape. Videotapes will be assigned to technician and physician readers who will enter name, SHS number and date to assure a match into the Revue Center. After measurements are completed and transmitted electronically to the computer center, they will be merged electronically with demographic data to facilitate checking of echocardiographic measurements against ranges of expected values for body size and gender (Appendix IV and additional nomograms derived from previous population studies done at Cornell). Random samples of studies (five percent each) will be selected for duplicate readings to assess intra- and inter-observer variability. Studies with measurements or inter-reader differences that fall outside a priori limits for further verification as well as other quality control procedures, as well as the 5% sample of "in range" studies will be re-reviewed by the physician-readers. This mix of studies for re-review has been designed to minimize any potential systematic biases in the re-review process. Procedures for computerized data tracking and management will utilize standard data bases and ASCII files with limited custom programming done in house in coordination with the SHS Coordinating Center in Oklahoma. After studies have passed the quality-control verification steps, data will be transmitted to the Coordinating Center by electronic mail with mailed backup diskettes.

Videocassettes will be received weekly from each region or field center. After the studies are logged, they will be processed by technician-readers trained in the SHS reading protocol using a commercially available computerized system (Digisonics, Inc., Houston, Texas). Super VHS video-cassettes will be placed in the VCR and advanced to the start of each 2-D study (identified by code number). Parasternal long and short-axis 2-D views will be reviewed to ascertain correct M-mode beam angulation, and scored for semiquantitative wall motion of visualized wall segments. If the M-mode beam is correctly angulated, the technician-reader will choose the visually best LV cycles (up to 3), and identify the QRS onset for each cycle on the simultaneous ECG tracing to time end-diastolic measurements of interventricular septal and posterior wall thickness and LV internal dimension by the ASE (99) convention, and at the nadir of posterior septal motion for end-systole. For each set of measurements the depth (or Doppler velocity) and time calibrations will be repeated. They will measure these cycles (and record the videotape counter units of the chosen cycles to facilitate subsequent verification by a physician-investigator), and as an immediate quality-control step compare the measurements obtained by the CardioRevue Center to the videotaped images with the use of calipers as appropriate to obtain measurements by an independent method.
Evaluation of LV Structure: M-mode LV measurements will be made by the ASE (99) method (Figure 6). The ASE recommendations, in which measurements are made from leading edge to leading edge, time end-diastolic measurements at the QRS onset. If the M-mode beam is not correctly oriented, the 2-D parasternal long-axis recordings will be played backward and forward to find the cycle or up to three cycles that maximize(s) the LV cavity area. In this view, septal and PW thicknesses and LV internal dimension will be measured by the leading-edge technique (analogous to the ASE convention) at the level of the papillary muscle tips along an axis perpendicular to the LV walls (100). This procedure has been used for the past 6 years in the Cornell laboratory, and increases the proportion of subjects with measurable LVs by about 10%. LV mass values by this technique with the ASE correction (9) have proven nearly identical to those from good quality M-mode recordings in the same research subjects in the Cornell laboratory, indicating their interchangeability.

With the parasternal long-axis 2-D view on the monitor, the cycle illustrating the largest LV outflow tract and aortic root diameter will be visualized to measure the aortic anular diameter at the QRS onset between the hinging points of the two visualized aortic cusps, a measurement needed to calculate stroke volume (52). On this same 2-D image the aortic root diameter will be measured by the leading-edge technique at the level of the sinuses of Valsalva as described by Roman et al (72, 76), and the videotape will be advanced to end-systole (end of the T wave of the ECG) for measurement of left atrial diameter by the trailing edge to leading edge technique. The choice of the trailing edge of the posterior aortic wall, rather than the leading edge, is based on the fact that a space containing loose connective tissue exists between the aortic and left atrial walls that would otherwise be included in the left atrial diameter measurement.

The videotape will then be advanced to the apical 4- and 2-chamber views and played (several times if necessary) to allow completion by the reader of semi-quantitative scoring of wall motion (from normal to aneurysmal) on the 5-step scale recommended by the ASE (100). In addition, a summary impression of global LV systolic function (normal/abnormal/severely depressed) will be made. The videotape will be advanced to the 4-chamber view recording Doppler flow across the mitral anulus. Early and late diastolic flow will be traced by the leading edge (black-white interface) method to measure peak E and A velocities and the E and A time-velocity integrals on the three cycles illustrating the highest velocity. The videotape will then be advanced to the apical long-axis view illustrating transaortic flow and the aortic flow time-velocity interval measured on three cycles by the leading-edge black-white method as described by Dubin et al (52). The recordings of color Doppler flow will be used in conjunction with imaging information to record the presence, etiology and estimated severity of valvular regurgitation or stenosis by established methods (72, 74, 91).

Calculation of Derived Variables: After the technician reader has completed
accepting or correcting the initial primary measurements of cardiac dimensions, flow patterns and grading of the motion abnormalities, the data will be transferred to the Clinical Research Center computer, where mean values for these measurements will be utilized to calculate derived variables. A second step will merge blood pressure and body size measures for further calculations before range checks and additional physician-investigator verification of primary data.

M-mode measurements at end-diastole by ASE measurements are used to calculate LV mass by the anatomically validated formula (9):

\[
\text{Left Ventricular Mass} = 0.8(1.04 [(\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3]) + 0.6g
\]

Estimates of LV mass by this method were closely related to actual LV weight at necropsy (r=0.90, p<0.001) in 52 adults.

Overall LV mass is the best measure of myocardial cell size, since the number of cardiac myocytes remains relatively constant after infancy, and is the most sensitive echocardiographic index of LV hypertrophy (46, 49). However, additional useful information is provided by the LV wall thickness/radius ratio, or "relative wall thickness" (RWT). This increases in proportion to chronic elevation of LV systolic pressure due to adaptive LV hypertrophy (101) and adds to LV mass for prediction of complications of hypertension (4). RWT is calculated from M-mode measurements as 2PWT/LVID (102); increased LV mass is classified as concentric hypertrophy if RWT is >0.41 and eccentric hypertrophy when RWT is normal (103). If LV relative wall thickness is increased but LV mass is normal, the subject is considered to have "concentric LV remodeling", an LV geometric pattern newly described from the Cornell Laboratory (4, 103).

**Evaluation of Ventricular Performance and Load:** Systolic function of a symmetrically contracting LV, such as occurs with uncomplicated hypertension, diabetes or alcoholism, can be assessed by measurement of the fractional shortening of LVID between end-diastole (d) and end-systole(s):

\[
\text{Fractional Shortening} \% = \frac{[(\text{LVIDd-LVIDs})/\text{LVIDd}] \times 100}{\text{LV ejection fraction, and is a simple substitute for it (104).}}
\]

Because ejection-phase indices of LV performance are highly dependent on afterload, measurement of myocardial afterload is helpful in determining whether or not observed ventricular function reflects normal myocardial contractility. The most direct measure of myocardial afterload is end-systolic stress (ESS), which can be measured using end-systolic LV measurements by the ASE convention and cuff blood pressure, measured with the subject on the examining table at the end of the echocardiogram, in a catheterization-
validated formula (105):

$$ESS = \frac{0.334 \times SBP \times LVIDs}{(PWTs \times (1 + PWTs/LVIDs))}$$

A close inverse relation exists between fractional shortening and ESS in both normal and hypertensive subjects (59, 69, 106-107), which becomes most linear when ESS is plotted on a logarithmic scale (ESS$_{10}$). Expression of observed fractional shortening as a percent of that predicted from end-systolic stress provides an afterload-independent measure of LV contractile performance. Afterload-corrected endocardial fractional shortening is subnormal in patients with congestive cardiomyopathy (51) and normal or elevated in patients with uncomplicated essential hypertension (59, 61). Recent research from the Cornell laboratory suggests that fractional shortening calculated at the left ventricular midwall is more appropriately matched to the mean level of end-systolic stress across the ventricular wall than is conventional endocardial fractional shortening for use in stress-shortening relations (108). This approach will also be explored.

2-D Evaluation of LV Performance will rely primarily on evaluation of LV function by the semi-quantitative scoring system recommended by the ASE (100). This system utilizes parasternal short-axis views at mitral valve and midventricular level, apical 2 and 4-chamber views, and parasternal and apical long-axis views to visualize 6 wall segments in each short-axis plane and 4 segments in the LV apical region. Careful adherence to the described protocol permits scoring of wall motion in all segments in more than 80% of subjects studied under difficult circumstances (portably in a CCU setting) and should permit at least this high a yield in SHS participants.

1.4.8 Feedback to Field Centers and Quality Control

The preliminary reports prepared by the Field Center technicians will be reviewed and comments made confirming the quality of recordings and measurements or indicating needed corrections and how to accomplish them. These comments will be returned weekly to the Field Center technicians. After the technician-reader has checked the computer print-out of primary and derived measurements for appropriate correspondence to the primary recordings from which they are derived, blinded studies will be arranged in batches for verification by a physician investigator. The M-mode stripchart recordings and print-out of measurements on all studies on a videotape will be presented in sequence.

Because of the central importance of LV mass and systolic function, LV measurements and grading of systolic LV function will be reviewed and verified or corrected by the investigators after the initial set of verified measurements have been merged by the data manager with demographic data (age, gender, height, weight and arterial pressure) to permit data-based quality control. The latter steps will include: 1) blinded re-reading by the same technician-physician pair of 5% of studies using half of the duplicate M-mode LV stripchart recording made at the field centers) to assess inter-reading
variability; 2) blinded reading of the duplicate M-mode recording and videotape of another 5% of studies by a different technician-physician pair (to assess inter-reader variability) and 3) re-review of all studies with measurements that fall outside of the normal to mildly abnormal range (based on the fact that erroneous extreme values will have the greatest impact in obscuring or distorting true biological relationships). Additional measurement sets that result from these duplicate readings will be entered into the computer under separate codes; the final physician-investigator verified data on each subject will constitute the primary data set transmitted by electronic mail with diskette backup to the Coordinating Center. To maximize feedback to technician-readers, the investigators will conduct part of their verification of measurements and the above quality-control steps, as well as final adjudication of discrepant measurements, in regular review sessions with the technician-readers.

1.4.9 Reports and Alerts

After measurements and interpretations are finalized by the Reading Center, a report including the average value of measurements on multiple cycles and clinical interpretation of the normality/abnormality of the study will be generated by the Cardiorevue Center. Copies of this will be a) returned to the Field Centers for inclusion in the subjects' IHS charts and b) sent to Dr. Oopik for the Dakotas, Dr. Ali for Oklahoma and a physician to be identified in Arizona who will determine what additional clinical feedback and follow-up should be initiated. For a limited number of potentially life-threatening tamponade or intracardiac masses) the Field Center sonographers will contact the physician to initiate an alert. Videotapes documenting these findings and others that do not trigger urgent alerts but are considered alarming by the sonographer will be sent to the Reading Center the day they are detected.

1.4.10 Wrap-Up/Data Analysis

Activities of the Echocardiography Reading Center from November 1995 to June 1996 will be devoted to final data processing and quality control and to working with the Coordinating Center for data analysis. It is planned to retain 50% effort of technician readers for the first two months of this period to assure careful processing of studies from the end of the performance period. During this period, the physician-investigators will complete verification of all echocardiographic data, and will oversee with the data manager a final step in quality control that will necessitate interaction with the Coordinating Center. Subgroups of study participants will be defined on non-echocardiographic criteria as being normal or having specific conditions (e.g., previous myocardial infarction, extreme obesity) and the distribution of measurements and qualitative/semiquantitative scoring of LV wall motion examined to determine whether they are appropriate for the group in question. Of the 4,050 subjects expected to be studied in exam II, it is anticipated that the planned strategy of echocardiographic performance and measurement will yield LV measurements and semiquantitative assessment of LV function in about 80% or 3,240,
with qualitative grading of LV function available in over 90% of SHS participants.

Once the echocardiography data set is finalized, the investigators and data manager of the Echocardiography Reading Center, in cooperation with the Coordinating Center at the University of Oklahoma, will test the following hypotheses. These hypotheses will be tested in the entire population, in subsets thereof, and in study participants who are free of prevalent myocardial infarction or clinically or echocardiographically defined valvular heart disease.

1) The distribution of measures of LV size, mass and function in SHS participants differs from that in Caucasian populations. This hypothesis is based on the high prevalence in SHS participants of obesity and diabetes, known stimuli to LV enlargement, hypertrophy and dysfunction (55, 109). Comparison groups will include a) Caucasian subjects from employed population samples studied in New York (54, 87) with proportionate sampling of hypertensive subjects to correct for their over-representation in our reported studies and b) the Framingham general population sample, which is overwhelmingly Caucasian and which was studied by echocardiographic methods that were carefully coordinated with joint echocardiogram reading by Dr. Devereux and Daniel Savage to assure comparability of measurements to those at Cornell (4, 69, 110-111). Variables to be considered are LV septal, posterior and relative wall thickness, internal dimension and mass; and LV fractional shortening. Statistical testing of between-groups differences will use Student's t-test (or Welch's approximate t for unequal variances) for normally distributed data or the Mann-Whitney test if data are not normally distributed. Because of reported differences in prevalence of diabetes and other risk factors among native Americans in different regions (Arizona, Oklahoma, South Dakota) surveyed in the SHS, findings in subjects in the three regions will be compared by one-way analysis of variance followed (if significant differences are revealed) by the Scheffe test. If homogeneity is found among SHS regions the pooled data will be compared with that from Caucasian groups; otherwise, comparison will be made using both pooled and region-specific SHS data.

2) Echocardiographic LV mass and dysfunction are strongly associated with prevalent clinical heart disease and subsequent mortality in SHS participants: This prediction is based on observed relations of LV findings to prevalent coronary, valvular and myocardial heart disease in other populations (21, 51, 69) and on the strong, independent predictive value of baseline echocardiographic LV mass for morbid and mortal events in the Framingham general population sample (3, 13), in hypertensive patients in long-term follow-up at Cornell (4, 11) and in patients undergoing coronary arteriography (15). The cohort will be divided based on clinical examination, ECG, and medical/hospitalization record data into groups a) with specific classes of disease; b) considered to be cardiovascularely normal, or c) fall in-between due to symptoms or medication use without a specific cardiac diagnosis. Echocardiographic variables will be compared among groups by ANOVA followed by the Scheffe test. In addition to testing
the applicability of previous findings to Native Americans, appropriate classification of subjects will permit comparison of the cardiac effects of preclinical conditions (diabetes, extreme obesity or alcohol excess) to those of established heart disease (e.g., myocardial infarction). To add a longitudinal aspect to this facet of SHS, follow-up for mortality can be done at relatively low cost through the National Death Index and follow-back studies beyond the duration of the present funding period; ascertainment of non-fatal morbidity events (myocardial infarction, etc.) will only be feasible over the long-term if the SHS is continued beyond the proposed period.

3) **Increased body fat mass is a strong correlate of LV enlargement and hypertrophy independent of effects of lean body mass, blood pressure or gender.** This prediction is based on studies that have used simple ratios of body proportions (body mass index) or indirect estimation from skinfold thicknesses (18, 21, 55). In SHS, percent body fat will be calculated by bioelectrical impedance, a more direct albeit still approximate method, and used with body weight to estimate adipose and non-adipose body mass. The impact of adipose body mass and its distribution on LV dimensions and functional measurements will be tested by: a) comparing LV measurements in strata of SHS men and women with normal or elevated adipose body mass by appropriate parametric or non-parametric methods, b) evaluating the independent relations of adipose and non-adipose body mass as well as blood pressure, gender and physical activity to LV mass and other LV dimensions, and c) comparing LV mass between groups of subjects in whom increased adipose mass occurs in either a gyroid or android distribution. The strength of adipose body mass as a stimulus to increased LV mass will be estimated by examining the relations of LV mass to height in normal weight and strata of increasingly overweight SHS participants. Application of this approach in a joint study at Cornell and the Universities of Naples and Cincinnati (58) has already shown that LV mass exhibited a curvilinear relation (between a second-power and a third-power one) to height in 611 normal-weight subjects; findings in 56 overweight subjects suggested that a kg of adipose body mass is associated with about half as much LV mass as a kilogram of lean body mass. The SHS cohort will provide an ideal setting in which to define more precisely these relationships, because of its population base, relative ethnic homogeneity, high prevalence of obesity and ability to estimate body fat mass and its distribution. Mr. Tarquin Collis, a Cornell University Medical College student, will perform initial analyses of this question on the first 800 subjects with LV measurements during a student research fellowship covering the 1993-1994 academic year.

4) **Impaired glucose tolerance and overt diabetes are associated with impaired LV systolic performance and abnormal diastolic filling, independent of effects of other variables:** This prediction is based on an extensive clinical, pathological, and experimental literature linking both naturally-occurring and induced forms of diabetes to evidence of cardiac dysfunction or frank cardiomyopathy. Analyses will consider glucose metabolism both as a categorical variables (normal, impaired, overt diabetes) and as a continuous variable (fasting and 2-hour post glucose-load levels of plasma glucose). Dependent variables will be measures of LV systolic performance (M-mode fractional shortening and
fractional shortening as a percent of that predicted for ESS, and 2-D semi-quantitative LV wall motion score and qualitative scoring of global LV systolic function) and of LV diastolic filling (Doppler E and A velocities and integrals and their ratios). Because of evidence from Framingham that diabetic subjects may have increased LV wall thicknesses, which may cause an overstatement of LV systolic performance when fractional shortening measured at the endocardium is related to the mean level of end-systolic stress across the LV wall (108), midwall LV fractional shortening will also be calculated. Groups categorized by normality of glucose metabolism will be compared with regard to these variables by analysis of variance followed by the Scheffe test, while relations between measures of glucose metabolism and LV function will be assessed by univariate and multivariate regression techniques, as previously described. Because of potentially important confounding effects of obesity and age, analyses will be repeated in strata of normal or increased relative body weight with adjustment or additional stratification for age.

5 and 6) Alcohol intake and fasting insulin level are positively related to LV mass, independent of body habitus or the level of resting, alcohol-free blood pressure: These predictions are based on the finding of a positive alcohol-LV mass relation in the overwhelmingly Caucasian Framingham population (44), and the recent observation of a positive relation between insulin and LV mass by Phillips et al. Primary analyses will utilize alcohol intake, insulin level and LV mass as continuous variables both in the entire population and in strata with defined ranges of relative body weight, normality of glucose metabolism, etc. Relations between variables will utilize linear (Pearson's) correlation between primary pairs of variables and multiple linear regression analyses, to determine the independence of observed relations from effects of potential confounding variables (blood pressure, gender, relative body weight, etc.). If, as expected, primary data are not normally distributed, statistically significant results of linear regression analyses will only be accepted if they are confirmed by non-parametric methods (e.g., Spearman's rank-order test).

7) Valvular heart diseases are more prevalent than in Caucasian populations, and will be related to a history of rheumatic fever and with obesity: These predictions are based on a) historic evidence of rheumatic fever outbreaks on some Indian reservations at a time when its incidence had fallen to low levels among White Americans, and b) evidence obtained at Cornell that significant valvular regurgitation due to mitral valve prolapse or idiopathic aortic root dilatation was associated with increased BMI (72, 80).
1.5 References


4. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in men and women with essential hypertension. Ann Intern Med 1991; 114:345-352.


12. Nestrova AZ, Novikov ID, Yurenev AP: Prognostic significance of blood pressure and


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51. Roman MJ, Devereux RB, Cody RJ: Ability of left ventricular stress-shortening relations, end-systolic stress/volume ratio, and indirect indices to detect severe contractile failure to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1989; 64:1338-43.


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65. Hochreiter C, Niles N, Devereux RB, Kligfield P, Borer JS: Mitral regurgitation:
Relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients. *Circulation* 1986; 73:900-12.


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APPENDIX 1  
THE STRONG HEART STUDY II  

Echocardiogram Log

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<thead>
<tr>
<th>Center:</th>
<th>Tape:</th>
<th>Log for SHS Echo Tape Box</th>
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Strong Heart Study II 7/01/93
# APPENDIX 2

## THE STRONG HEART STUDY II

Unblinded Log for Echocardiogram

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<th>SS#</th>
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<th>DBP</th>
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<th>DOB</th>
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<th>Wt.</th>
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<th>Sonographer</th>
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APPENDIX 3
THE STRONG HEART STUDY II
PRELIMINARY ECHOCARDIOGRAM INTERPRETATION

| DATE: ___________________________ | SHS#: ___________________________ |
| CENTER: __________________________ | IHS#: ___________________________ |
| TAPE: ___________________________ | Subject's Last Name: ____________ |
| COUNTER: __________________________ | Subject's Initials: _____________ |

**DIMENSIONS (cm)**

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<td></td>
<td>G_F_P_NG_</td>
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<tr>
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<td>G_F_P_NG_</td>
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<td>PWTd</td>
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<td>G_F_P_NG_</td>
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<tr>
<td>LA</td>
<td></td>
<td>G_F_P_NG_</td>
</tr>
<tr>
<td>Ao</td>
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**2-D WALL MOTION**

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<tr>
<td>Global _____ Segmental Abnl</td>
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**DOPPLER**

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<td>G_F_P_NG_</td>
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<td>G_F_P_NG_</td>
<td>G_F_P_NG_</td>
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<td>Mitral A _____</td>
<td>G_F_P_NG_</td>
<td>G_F_P_NG_</td>
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<td>MR: None_1+2+3+<em>4+</em>__</td>
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<td>G_F_P_NG_</td>
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<tr>
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**Mitral Valve:**

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</tr>
<tr>
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<td>Abnormal</td>
</tr>
<tr>
<td>Left Ventricle:</td>
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<tr>
<td>Doppler:</td>
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Study performed by: ____________

---

*Strong Heart Study II 7/01/93*

*Echocardiography*
### M - M O D E

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<th>Normal Value</th>
<th>Septum</th>
<th>LVWP</th>
<th>MV</th>
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<td>Dias Dim</td>
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<tr>
<td></td>
<td>Sys Thick</td>
<td>14.4 mm</td>
<td>Sys Dim</td>
</tr>
<tr>
<td></td>
<td>Thick Frac</td>
<td>0.42 (0.30-0.64)</td>
<td>Short Frac</td>
</tr>
<tr>
<td></td>
<td>Dias Thick</td>
<td>10.6 mm (6.0-11.0)</td>
<td>Dias Vol</td>
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<tr>
<td></td>
<td>Sys Thick</td>
<td>17.4 mm</td>
<td>Sys Vol</td>
</tr>
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<td></td>
<td>Thick Frac</td>
<td>0.64 (0.30 - 0.64)*</td>
<td>Stroke Vol</td>
</tr>
<tr>
<td></td>
<td>Dias Thick</td>
<td>11.0 mm (6.0 11.0)*</td>
<td>Eject Frac</td>
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<tr>
<td></td>
<td>Sys Thick</td>
<td>15.2 mm</td>
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<td>Thick Frac</td>
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<td>Sys Thick</td>
<td>15.2 mm</td>
<td>Dias Vol</td>
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<td>Sys Vol</td>
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</tr>
<tr>
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<td>Eject Frac</td>
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### Aorta

- **Root Diam**: 4.70 cm (2.00-3.70)*
- **Root Diam**: 4.62 cm (2.00-3.70)*
- **Root Diam**: 4.79 cm (2.00-3.70)*

### LA

- **Dimension**: 3.69 cm (1.90-4.00)
- **Dimension**: 3.81 cm (1.90-4.00)

### AV

- **Cusp Sep**: 2.6 cm (1.5-2.6)*
- **Cusp Sep**: 2.8 cm (1.5-2.6)*
- **Cusp Sep**: 2.8 cm (1.5-2.6)*
**2 - D**

<table>
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<th>Aorta - PLA</th>
<th>LVPW - PLA</th>
<th>LA - PLA</th>
<th>LV - Short Axis</th>
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<tr>
<td>Sys Dim</td>
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<td>Shrt Frac</td>
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<tr>
<td>Wall Thick</td>
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<tr>
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<tr>
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<td>Shrt Frac</td>
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<tr>
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<td>M Wall Str</td>
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**DOPPLER**

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<td>-------------</td>
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**COMMENTS**

M-MODE STUDY:

Dilated left ventricle

2-D STUDY:

Enlarged aortic root
Diastolic AMVL fluttering suggestive of AI
Normal left atrial size
Left ventricular enlargement, severe
Eccentric left ventricular hypertrophy

DOPPLER:

Severe aortic insufficiency
Mild mitral regurgitation
**Name:** SAMPLE  
**Pat #:** 111-11-11  
**Date:** 6/28/93

Parasternal Short Axis-Basal Level

Parasternal Short Axis-Mid Level

Parasternal Short Axis-Apical Level

### QUALITATIVE WALL MOTION TABLE

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Wall Motion Score Index: 1.0
APPENDIX 5
THE STRONG HEART STUDY II

Sample of Results Report for the Echocardiographic Findings

THE NEW YORK HOSPITAL - CORNELL MEDICAL CENTER
ARIZONA / DAKOTAS / OKLAHOMA
ECHOCARDIOGRAPHY REPORT

Date 01/05/1994
Study Date 09/22/1993
Reading Date 10/05/1993
Tape Number C10-93
Counter 37:25 - 47:38
Heart Rate 75 bpm
Blood Pressure 140/66 mmHg

Name xxx
SHS # xxxxxx
Age 68
Sex F
BSA 1.91 m2
Ht 160 cm
Wt 88 kg

DIMENSIONS (cm)

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<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septum (d)</td>
<td>.90</td>
<td>&lt;=1.1</td>
</tr>
<tr>
<td>Septum (s)</td>
<td>.90</td>
<td>...</td>
</tr>
<tr>
<td>LV Wall (d)</td>
<td>.80</td>
<td>&lt;=1.1</td>
</tr>
<tr>
<td>LV Wall (s)</td>
<td>1.10</td>
<td>...</td>
</tr>
<tr>
<td>LA</td>
<td>3.00</td>
<td>&lt;=3.8</td>
</tr>
<tr>
<td>Aorta</td>
<td>3.30</td>
<td>&lt;=3.6</td>
</tr>
<tr>
<td>LVID (d)</td>
<td>6.80</td>
<td>&lt;=5.4</td>
</tr>
<tr>
<td>LVID (s)</td>
<td>5.70</td>
<td>&lt;=3.9</td>
</tr>
</tbody>
</table>

DERIVED VARIABLES

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVED Volume</td>
<td>125.34</td>
<td>50-90 ml/m2</td>
</tr>
<tr>
<td>LVES Volume</td>
<td>83.85</td>
<td>15-35 ml/m2</td>
</tr>
<tr>
<td>Stroke Index</td>
<td>41.49</td>
<td>32-58 ml/m2</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>.33</td>
<td>.55-.75</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>3.11</td>
<td>liters/min</td>
</tr>
<tr>
<td>LV Mass Index</td>
<td>130.94</td>
<td>110 g/m2</td>
</tr>
<tr>
<td>RWTd</td>
<td>.24</td>
<td>&lt;.45</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>16.18</td>
<td>&gt;=26%</td>
</tr>
</tbody>
</table>

DOPPLER VELOCITIES

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVOT</td>
<td>1.25</td>
<td>&lt;=1.50 m/s</td>
</tr>
<tr>
<td>Mitral ‘E’</td>
<td>.77</td>
<td>&lt;=0.90 m/s</td>
</tr>
<tr>
<td>Mitral ‘A’</td>
<td>.97</td>
<td>&lt;=0.60 m/s</td>
</tr>
</tbody>
</table>

DIAGNOSTIC COMMENTS:

1. Dilated left ventricle
2. Eccentric left ventricular hypertrophy
3. Moderately decreased estimated ejection fraction
4. Left ventricular enlargement, moderate
5. Anterior wall hypokinesia, mild
6. Interventricular septal akinesia
7. Anterior lateral wall hypokinesia, mild
8. Apical hypokinesia, severe
9. Thickened mitral annulus
10. Doppler color flow mapping reveals mild (1+) mitral regurgitation.
11. Normal mitral valve flow pattern
12. Normal mitral valve with no evidence of rheumatic heart disease, IHSS or mitral valve prolapse.
14. Sector scan confirms the above. The aortic valve is trileaflet. The right ventricle and atrium are normal.
15. Abnormal echo exam consistent with ischemic cardiomyopathy
16. MARY PARANICAS, B.A.
17. RICHARD B. DEVEREUX, M.D.

By ____________________________