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Serial echocardiographic studies of acute and chronic left ventricular volume overload

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Serial Echocardiographic Studies of Acute and Chronic Left Ventricular Volume Overload

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BA, Yale University, 1970

A thesis presented to the faculty of the School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine

Department of Internal Medicine

Yale University

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This thesis is dedicated to the four individuals whose influences on my life in Medicine have been so profound that I will carry them with me always:

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ABBREVIATIONS

A mode	-	Amplitude Modulation Mode
AC	-	Aortic Cusp
Amp	-	Amplitude
AMV	-	Anterior Mitral Valve Leaflet
Ao	-	Aorta
ASH	-	Asymmetric Septal Hypertrophy
BCG	-	Ballistocardiogram
CPK	-	Creatine Phosphokinase
CRT	-	Cathode Ray Tube
CW	-	Chest Wall
dP/dt	-	Change in Pressure/Change in Time
ds/dt	-	Change in Posterior Wall Displacement/ Change in Time
dV/dP	-	Change in End-Diastolic Volume/Change in End-Diastolic Pressure, an estimate of left ventricular compliance
ECG	-	Electrocardiogram
EF	-	Ejection Fraction
EN	-	Endocardium
Ep	-	Epicardium
f	-	Frequency, in cycles per second
Hz	-	Hertz; cycles per second
I	-	Sound Intensity, in watts per square centimeter
IHSS	-	Idiopathic Hypertrophic Subaortic Stenosis
IVS	-	Interventricular Septum
JVP	-	Jugular Venous Pulse
L	-	Left Ventricular Major Axis Length
LA	-	Left Atrium; Left Atrial Diameter
LAI	-	Left Atrial Index, LA/Ao
LBBB	-	Left Bundle Branch Block
LV	-	Left Ventricle
LVET	-	Left Ventricular Ejection Time
LVID	-	Left Ventricular Internal Diameter
LVIDd	-	Left Ventricular Internal Diameter, diastolic
LVIDs	-	Left Ventricular Internal Diameter, systolic
LVM	-	Left Ventricular Mass
LVMV	-	Left Ventricular Muscle Volume
LV_{vol-d}	-	Left Ventricular Volume, diastolic
LV_{vol-s}	-	Left Ventricular Volume, systolic
M Mode	-	Time-Motion Mode
MHz	-	Megahertz; million cycles per second
MVA	-	Mitral Valve Area
NS	-	Not Significant
p	-	Density
P	-	Pericardium
PEP	-	Pre-ejection period
PLAW	-	Posterior Left Atrial Wall
PMV	-	Posterior Mitral Valve Leaflet
PWT	-	Posterior Wall Thickening (%)

PWT_d	-	Posterior Wall Thickness, diastolic
PWT_s	-	Posterior Wall Thickness, systolic
PWV	-	Posterior Wall Velocity
PWV_{ant}	-	Posterior Wall Velocity, anteriorly
PWV_{post}	-	Posterior Wall Velocity, posteriorly
RV	-	Right Ventricle
$RVID_d$	-	Right Ventricular Internal Diameter, diastolic
SAM	-	Systolic Anterior Movement
SD	-	Standard Deviation
SEM	-	Standard Error of the Mean
ST	-	Septal Thickening (%)
STd	-	Septal Thickness, diastolic
STs	-	Septal Thickness, systolic
SV	-	Stroke Volume
v	-	Velocity
V_{ce}	-	Velocity of Contractile Element Shortening
V_{cf}	-	Velocity of Circumferential Fiber Shortening
Vmax	-	Maximum Velocity of Contractile Element Shortening, the extrapolated value of velocity at the theoretic point of zero tension
WTd	-	Wall thickness, diastolic
z	-	Acoustic Impedance
λ	-	Wave length

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INTRODUCTION

For anyone who has read a science fiction novel or watched 'Startrek' on television, the vision of medicine in the future is a characteristic one. Diagnosis is always uncomplicated. The physician of the future waves an electronic device over the patient, lights flash, and the computer provides an answer practically instantaneously. No differential diagnosis is involved, of course. Implicit in the authors' ideas are several basic goals: the procedure is simple, rapidly performed, and atraumatic. Without the constraint of technological reality, fiction writers have made tremendous advancements in medical diagnosis and treatment. Slowly the real world catches up.

Echocardiography is one of the many technological advances that has brought medicine closer to this vision of the future. Given the simplicity and safety of the procedure, the amount of useful information produced by ultrasound in medicine is unsurpassed. The widespread use of ultrasound in general and echocardiography in particular has led to improvements in equipment and techniques, and to significant advances in the understanding of physiology and pathology demonstrated by these ultrasound methods. The purpose of this investigation is to help further establish the usefulness of echocardiography in terms of its application for serial studies.

Prior to the report of the investigation undertaken, several background aspects will be reviewed. The physiologic concepts necessary for understanding the applications of echocardiographic techniques will be discussed. Included also are surveys of other invasive and non-invasive techniques and their usefulness. Finally, ultrasonic principles and the applications of ultrasound in medicine will be reviewed. The cardiologic uses will be examined in detail.

CARDIAC PHYSIOLOGY AND ITS MEASUREMENT

Volume and Function

> "An appreciation of the size of the heart as an index of diagnosis and also of prognosis is almost as old as the recognition of cardiac enlargement itself." (1)

While Woods in 1892 first recognized the physiologic application of Laplace's mechanical formulation, and Starling in 1918 concluded that the energy output of the heart was related to its diastolic volume, it was not until the 1950's with the work of Rushmer and colleagues, Burton, and others that the dynamic geometry of the left ventricle began to be well understood (1-3). Traditional concepts were based on anatomic dissections and direct measurements on open chest animal preparations (2). Further investigation awaited the technological advances that included roentgenography and the development of sensitive strain gauges necessary for a more complete understanding of length, circumference, tension, pressure, and volume relationships in the intact functioning heart. True direct measurements of ventricular volume and function are quite obviously impossible. Consequently, investigators have endeavored for years to gain more complete understanding through the use of indirect measurements including multiple angiographic studies and pressure monitoring techniques. Mathematical formulations and models have been developed so that the measurements obtained could be applied to in vivo situations in a meaningful fashion.

Fluoroscopic measurements of heart movement were described as long ago as 1898, three years after Roentgen's introduction of the X-ray (4). However, until the relatively recent development of biplane angiocardiographic techniques, accurate information was obtained primarily by the use of dimension gauges (3) and radiopaque markers (5) both requiring surgical manipulations.

Primarily through the work of Dodge and associates (6,7,8,9) and several other investigators, Wood (10) and McDonald (11) among them, biplane angiocardiography has been developed as the standard by which all other study methods are measured. With this method of volume determination the left ventricle is assumed to be ellipsoid (7). Biplane angiocardiograms, with radiopaque dye filling the ventricular cavity, are taken at a rate of 6 per second. Left ventricular margins are outlined on all films. The maximum chamber length is measured in the anterior and posterior views. Planimetered areas of theleft ventricular chamber in both views are calculated and the minor axes are derived. Volume is then determined using the formula of an ellipsoid and applying this to a previously defined (through anatomic studies) regression equation (8). In one study stroke volumes determined by this method in various cardiac patients differed by only a mean ($\pm$SD) of $+3.5 \pm 7.6$ cc. from stroke volume determined by the Fick method (8).

Subsequently, ventricular volume studies were performed to determine values for normal individuals (9) thereby establishing standards of measurement. Biplane techniques continue to be widely used in many applications, from further elucidation of dynamic geometry of the left ventricle (12,13), to validation of new techniques such as the one that is the primary subject of this report (14,15,16).

It has also been shown that the original ellipsoid model can be mathematically modified so that quantitative estimation of left ventricular volume can be made from single plane (antero-posterior) angiocardiograms (17). Using this method with sophisticated computer analyses high correlations with biplane determinations (r-0.988 for 55 subjects) were obtained (17). Thus it was concluded by this group that it is reasonable and reliable to substitute a prolate spheroid model (requiring minor axis and major axis determination in only one plane) as the reference figure for calculating left ventricular volumes. This

mathematical model development has become important for echocardiographic applications where only one plane can be examined.

There are several problems encountered in biplane determination of heart volume. A primary source of error may be that the approximation of the left ventricle to an ellipsoid is not close. It has therefore been argued that the equation used may introduce a large error (18). Additional sources of error include: difficulty in measuring the true major and minor axes, considerable observer variations in making these measurements, variations in radiographic technique, inaccurate correction for distortion introduced by X-ray tubes, disregarding image magnification, untoward effects of contrast material, and poor angiocardiographic recording techniques (18,19). Recognizing these as potential problems, however, most investigations continue to consider biplane angiography as the most accurate of all volume determining methods. All new approaches therefore must be measured against this old standard.

Most important contributions to the field of left ventricular volume quantification have employed biplane angiographic techniques. However, because of the problems noted above and the time-consuming and expense aspects of such methods, newer approaches have regularly been sought. Volume estimation by indicator dilution techniques require less complex equipment, have little direct effect on the heart, can be utilized repeatedly without hazard, and involve only simple calculations (20). In the early to mid-1960's there was much interest in thermodilution techniques (20,21,22). Of the many dilution injectates available, indocyanine green is the most widely used today (23). However, green dye was not as widely studied as thermodilution techniques in terms of validation of indicator dilution methods versus angiocardiography. In a comprehensive comparative study single plane angiocardiography, thermodilution, and direct external area and length measuring techniques were shown to correlate highly in canine hearts (24).

Determination by X-ray tended to underestimate slightly the end-diastolic volumes. Small, systematic, over-estimations were found with thermal washout recordings.

In addition to estimations of left ventricular volume, angiocardiographic techniques have proved to be useful in the determination of left ventricular mass (25,26). By biplane techniques average wall thicknesses are measured and volume of chamber plus wall thickness is determined. Left ventricular mass is then calculated by substracting chamber volume and multiplying by the specific gravity of cardiac muscle (1.050) (25). In the absence of right ventricular hypertrophy, pericardial effusion or adhesive pericarditis this method proved to be highly correlated ($r = 0.97$) with autopsy determined weights (26).

By altering filming technique to provide a more accurate study of rapid wall motion, Gorlin's group was able to describe dynamic changes in left ventricular free wall thickness (27). Accurate regional wall thickness determinations were made possible by these methods, and they could be evaluated throughout the cardiac cycle in normal and diseased states.

Evaluation of cardiac function has been a more elusive task and the results more controversial than the volume and mass studies discussed above. Accurate assessment of cardiac function is essential for a comprehensive understanding of clinical heart disease, particularly in terms of therapeutic management and prognosis. It is well known that clinical status depends on cardiac output and that this output is determined by the product of stroke volume and heart rate. Heart rate is, of course, easily measured. However, stroke volume is more complex for it depends on the interrelationship of three factors: preload, after-load, and contractility. Preload is directly related to end-diastolic volume and after-load to systemic blood pressure, thus both can readily be assessed by relatively simple techniques. The contractile state of the myocardium is, however, much more difficult to describe and estimate.

The rate of pressure development (dP/dt), readily measured in the left ventricle, has been widely used to estimate contractility. However, its quantitative usefulness is limited by its dependence on volume in addition to contractility (28). It has been suggested that normalizing dP/dt for isovolumic ventricular pressure would partially circumvent this problem (29).

By extending the principles of muscle mechanics, other parameters have been developed to assess ventricular function. The study of the instantaneous relationship between shortening velocity and wall tension has led to the proposal that the velocity of contractile element shortening (V_{CE}) might be used as a sensitive measure of contractility or the inotropic state (30). Measurements were made using radiopaque markers implanted at surgery. These measurements were then correlated with changes in left ventricular pressure and wall stress changes. Although this study was technically difficult, it was possible to accurately assess cardiac function and make quantitative comparisons among patients with and without myocardial dysfunction. This technique has been adapted so that V_{CE} could be determined indirectly from dP/dt and isovolumic intraventricular pressure (31). However, the limitations of this method are significant (32) and it is therefore not widely used.

The mean rate of circumferential fiber shortening ($V_{\overline{CF}}$) has been estimated by dilution techniques and angiocardiography (20,33). Appearing to be a most useful means of assessing ventricular function, $V_{\overline{CF}}$ has compared favorably with instantaneous rate of fiber shortening (V_{CE}) while being much more easily obtained. It is cautioned, however, that values obtained for $V_{\overline{CF}}$ may be influenced inappropriately by regional ventricular wall abnormalities (34).

Sonnenblick and colleagues (32) among others, have proposed as a measure of contractility the extrapolation of the derived velocity-tension curve to a theoretic point of zero tension (Vmax). With contractility defined as the time independent relation between force, velocity and instantaneous muscle length,

Vmax as a measure of function in unloaded muscle may well be the most independent and theoretically sound of all proposed indices.

Any one estimate of contractility is however far from being universally accepted. In a recent review of this field, Brutsaert and Sonnenblick conclude:

> "Indices of contractility in the intact heart are all partial measurements of the force-velocity-length relation. None are complete. All have limitations of either methodology, practicality or concept... Ultimately, a useful index will require the ability to distinguish a "good" and "bad" heart, independent of load and volume, which is measureable in a reliable and reproducable manner. At present, this is best done by combining methods rather than seeking unique measurement." (32).

Parameters and Indices in Cardiac Disease

Once methods for determing left ventricular chamber size, wall thickness, and mass were widely available, the next step was the study of the significance of such measurements in heart disease. Dodge and Baxley have reviewed several parameters obtained, and compared established normal values with these of patients having various types of heart disease (35). End-diastolic volume and left ventricular mass were consistantly larger in the group with myocardial disease. Stroke volume was not significantly different and ejection fraction was depressed for the patients with heart disease. More recently, biplane angiography was used to characterize the left ventricular shape in chronic heart disease (36). It was noted that the failing heart altered its shape from ellipsoid to spheroid in this study.

Assessment of ventricular function or, more basically, contractility has been of increasing interest inspite of the conceptual and methodological difficulties noted above. In general the same techniques and measures applied to isolated preparations and laboratory animals have been modified for use in patients with cardiovascular disease. Sonnenblick (37) has stressed the role of Vmax as a useful supplement to the available criteria for evaluating cardiac function. Also utilized in formulating a complete picture of cardiac function are direct pressure measurements, shunt calculations, cardiac output determinations and angiographic visualizations.

Atrial Volume in Heart Disease - Chest X-rays, ECG's and basic physical diagnosis have taught cardiologists long ago the clinical significance of left atrial volume changes. However, quantification of such changes awaited the development of suitable angiographic techniques. It was Dodge's group that was primarily responsible for the angiocardiographic elucidation of atrial

volume changes with heart disease (38). In their initial study left atrial pressures correlated well with left atrial volume in patients with aortic stenosis, idiopathic cardiomyopathy, and mitral stenosis. Patients with mitral insufficiency, however, showed no correlation between volume and left atrial pressure. In a later, more comprehensive study the same group described atrial volume changes over a wide range of physiologic and pathologic conditions (39). Atrial volume changes with mitral regurgitation, atrial fibrillation, aortic valve disease and primary cardiomyopathy were demonstrated.

Coronary Artery Disease - Ischemic heart disease has been the object of much study using volume and function indices. In a study of 20 patients with coronary artery disease it was found that even in the absence of significant ventricular dilatation, as evidenced by normal end-diastolic volumes, ejection fraction and circumferential fiber shortening were significantly lower in the diseased population when compared to normals (40). Thus abnormalities of diastolic compliance and contractile performance were demonstrated in the presence of normal values obtained for the more traditionally accepted measure of left ventricular function (end-diastolic pressure). Severe coronary artery disease was studied in 23 patients (41). The findings of dilatation, hypertrophy, mitral regurgitation and depressed myocardial performance were examined. In this group significant correlations were demonstrated between end-diastolic volume and both left ventricular mass and angiographically determined mitral regurgitation.

Congestive Heart Failure - Because of the primary myocardial factors involved, the spectrum of congestive heart failure has been widely investigated with angiographic and pressure monitoring techniques. Using pressure monitoring alone, Lassers, et al., studied 30 patients who developed failure following myocardial infarction (42). Increased pulmonary artery wedge pressure was found

to be significantly related to radiographic evidence of the pulmonary signs of failure. However the physical signs usually associated with congestive heart failure including third and fourth heart sounds and rales were not well correlated with mean pulmonary arterial wedge pressure.

The complex array of hemodynamic changes associated with congestive heart failure and its development have been investigated extensively. The findings of increased heart size, elevated left ventricular filling pressure and low cardiac output are characteristic features in congestive heart failure. Elucidation and precise definition of the course and mechanisms of cardiac decompensation have been more difficult to ascertain. The relationship between pressure overload and increasing muscle mass followed by the development of circulatory decompensation has been elucidated using angiographic techniques (43). Dodge and Baxley (44) and Mason et al., (45), have both extensively investigated and reviewed the hemodynamic changes with heart failure. Heart failure was shown to result from failure of contractile mechanisms, a large pressure-volume overload, or a combination of excess load and reduced contractility (44).

In Mason's comprehensive review article the fundamental physiologic derangements in congestive heart failure are examined in terms of these altered hemodynamic and mechanical parameters (45). The volume overload and depressed contractility aspects of failure have been precisely defined in isolated preparations and animal models. Using angiocardiography and catheter pressure monitoring these principles are extended to study the interplay of all determinants of failure in the diseased patient. It is demonstrated how evidence of decreased dP/dt, V_{CE} and Vmax all can be useful in understanding the pathophysiology and course of congestive heart failure.

More dynamic and regional aspects of failure have also been studied. Rather than focus on the "global" affection of the myocardium, Herman and colleagues studied localized disorders of contraction associated with congestive heart failure (46). Abnormalities of contraction or asynergy frequently were

found to provide angiocardiographic morphologic distinction between those individuals with coronary artery disease who developed failure and those who did not.

Cardiomyopathy - Primary cardiomyopathy (i.e., without known secondary causes such as coronary artery, valvular or congenital heart disease) has also been investigated. In a represenative study (47) the spectrum of hemodynamic abnormalities is quantitatively described. Both ejection fraction and left ventricular mass to volume ratio were found to be of prognostic value.

It is apparent then that virtually all important aspects of acquired heart disease have been studied using the previously described investigative techniques. Such techniques have been invaluable in the elucidation of pathophysiologic mechanisms and in primary investigations of the clinical course and the therapeutic management of cardiovascular disease processes. However, such methods are complex, difficult to perform and reliably interpret, expensive, time consuming, and, not infrequently, potentially hazardous to the patient. Therefore more suitable techniques continue to be sought for routine use. Several such techniques are reviewed in the next section.

Other Objective Measurements in Cardiac Disease

Perhaps the most important parameter of the circulatory system is cardiac output. Consequently many invasive and non-invasive techniques are directed at estimating cardiac output or its components. Already discussed were the most widely used and reliable techniques, those involving angiocardiography or dye dilution methods. Other invasive and non-invasive techniques are discussed below.

Measurement of the cardiac output is also widely determined by direct use of the Fick principle which states that output is equal to oxygen (O_2) consumption divided by difference in arterial and venous oxygen content. By measuring O_2 consumption by spirometry, and venous and arterial O_2 content by obtaining blood samples from a catheter in the pulmonary artery and in a peripheral artery, respectively, cardiac output can be calculated. This method is unsuitable for continuous monitoring. Significant error can occur when respiratory or circulatory changes are occurring rapidly (48).

Pressure gradient techniques have been reported for obtaining instantaneous aortic blood flow in humans (48). Based on the laws of fluid motion, an equation, dependant on the measurement of instantaneous lateral pressures at two points in the ascending aorta, is used to calculate blood flow. This method is said to correlate $\pm$20% with direct measures by the Fick principle and may be less hazardous.

Pulmonary capillary wedge and pulmonary artery pressures measured via flow directed catheters are widely used today. As a reflection of left ventricular end-diastolic pressure and therefore of volume as well, this technique is of major clinical importance in monitoring patients following acute myocardial infarction and patients in congestive heart failure (49,50). Without the addition of other procedures, direct information on cardiac output is not obtained

from such pressure monitoring. However, objective signs of early heart failure can be recognized. And, the development of rational therapeutic approaches has been aided:

> "The $\overline{PA}$ (mean pulmonary artery pressure) often provides the first warning of impending heart failure or serious arrhythmias, the usual early signs of heart failure (fourth heart sound or pulmonary venous congestion) occurring 6 to 24 hours after the $\overline{PA}$ becomes elevated. The $\overline{PA}$ appears to be a reliable index on which to base therapeutic maneuvers." (49)

Changes in central venous pressure often do not reflect left ventricular function, and in some cases are directly misleading (50). Pressure monitoring via pulmonary artery catheters seem the simplest and most reliable of available invasive techniques. Their use, unfortunately, is attended by frequent technical complications, and nearly constant nursing attention is required (51).

Measurements of cardiac output can also be obtained by recording pressure pulse contours from the aorta. When used with a small on-line computer and compared with indicator dilution measured outputs, favorable results have been produced (52). The simplicity and speed of this technique indicates its potential usefulness when compared to Fick method, but it has not gained wide acceptance or use. Variability of arterial distensibility has been pointed out is the major disadvantage in terms of accuracy (48).

Radioactive photoscanning is enjoying rapidly increasing applications in clinical cardiology (53,54). This "semi-invasive" technique requires only a venopuncture and the patient's time for scanning. Myocardial imaging is achieved through two basic approaches, one employing radioactive uptake by normal myocardium and the other using selective uptake by infarcted or ischemia muscle (53). Localization of segmental ventricular dysfunction has been successfully attempted by both "hot" and "cold" imaging of such areas. The use of an instan-

taneously sensing scintillation camera has permitted "isotope angiocardiography" which can potentially provide useful anatomic and hemodynamic information (54).

Regional abnormalities of left ventricular function often result in recordable abnormal systolic precordial movements. Such low frequency changes can be recorded by apex- and kinetocardiogram techniques (54). The former method utilizes a pick-up device fixed to the chest wall, and the latter a stationary recording device with a light metal piston interposed between patient and transducer (53). Such techniques allow accurate timing of intracardiac events and can be used to detect abnormal deviations in a semiquantitative fashion.

Various systems have been applied using X-ray tracking systems to detect heart motion and aid in the diagnosis of acquired heart disease. Roentgen-kymography and radarkymography have achieved the most attention (55,56). The former technique involves X-ray tracings of selected segments of the left heart border, while the latter is an adaptation of this method using image intensification and closed circuit television for more precise recordings. With radarkymography the heart border is tracked radiographically with the resulting voltage response being proportional to heart silhouette motion. Patients have been studied with various cardiovascular problems including mitral valve disease, aortic outflow obstruction, ventricular aneurysm and coarctation of the aorta (56). Characteristic graphic tracings were produced for each lesion. More recently, radarkymography has been successfully used to detect wall motion disorders in patients with chronic coronary artery disease (57). Although the technique is useful for the evaluation of anterior and lateral left ventricular walls, other walls (inferior and posterior) are inaccessable and therefore limit the applicability of radarkymography (54).

Ballistocardiography is a technique which records body movements produced by the forces of impact and recoil generated by cardiac contractions (53). It has been used to compute stroke volume, and cardiac output. Empiric relationships between recognizable patterns and various forms of cardiovascular disease have been established (48). Although used little today, this technique enjoyed great popularity in the past and extensive correlative work was done with patients in congestive heart failure (58), as well as in following myocardial infarction and in valvular heart disease (53).

Precise observations of the consecutive phases of the cardiac cycle have been of interest since at least 1921 with the studies of Wiggers (53). The potential use of timing cardiac events, however, was recognized nearly fifty years earlier by Garrod (59). He first described the inverse relationship between heart rate and left ventricular ejection time. Duration of ejection (LVET) is derived from external pulse recordings, and the pre-ejection period (PEP) is measured from the onset of the QRS to the onset of LVET. Other so called 'systolic time intervals' have been studied as well; but PEP, LVET and their ratio has proved most useful (53). In patients with heart failure, LVET has been shown to be decreased relative to heart rate when compared with normals (60). Prolongation of ejection time was observed with aortic regurgitation and isolated aortic stenosis. In patients with severe hypertensive cardiovascular disease LVET fell below normal (60). The ratio of PEP to LVET has been shown to be useful without correction for heart rate and sex (53). It is used merely as an adaption of LVET measurements for the purposes of standardization. Systolic time intervals are proving to be of significant value in the bedside evaluation of ventricular function.

The phonocardiogram, in addition to providing timing points for the measurement of systolic time intervals, is well known for its usefulness in the

recording of auscultatory findings. While the sounds recorded are no more useful than those heard with a stethoscope, events can be timed more accurately and confirmation of suggested findings can be obtained. External recordings of jugular venous pulse (JVP) may also aid usual physical diagnostic skills. The JVP can provide many clues in the evaluation of cardiovascular pathology. Of particular importance is the recognition of elevated right ventricular filling pressure. Also, the JVP can serve as an indicator marking various conduction and rhythm disturbances.

Cardiac output and myocardial contractility have been estimated using impedance cardiography (53). This technique involves the measurement of alterations in transthoracic electrical impedance during the cardiac cycle. Stroke volume correlations between impedance plethysmography and indicator dilution methods have been moderately high, but are inconsistant (53).

Photoelectric colorimetric oxygen detectors have been used to determine cardiac output (48). Measuring inspired air O_2 content by spirometry, and obtaining O_2 saturation levels with the photoelectric devices attached to the ear lobe has allowed computation of cardiac output by the Fick principle. Unfortunately, artifacts are great and the equipment is too cumbersome to make this technique routinely valuable.

The detection of small magnetic fields produced by cardiac electrical events has led to the development of magnetocardiography. Only a small number of subjects have been examined by this technique and its usefulness remains to be demonstrated (53).

The radiologic signs of cardiovascular disease are well known and continue to be investigated (61). Although the chest X-ray is not sensitive enough to detect regional myocardial dysfunction or accurately assess cardiac hemodynamics, its usefulness as a screening test is perhaps surpassed by only the electrocardiogram.

The applications and utility of the ECG needs no discussion here. Although ECG-anatomic relationships are not always pathologically confirmed, no other technique is as routinely useful for the detection and localization of myocardial ischemia and infarction (54). The value of serial P wave changes in association with left ventricular failure has recently been reported, adding to the long list of ECG applications (62). Vectorcardiography, high-frequency electrocardiography and isopotential mapping are all techniques derived directly from the standard ECG. In terms of expense and instrumentation they are not as widely accepted or routinely used as the ECG, however, as investigative tools they are valuable.

The clinical value of serum enzyme determination must also be mentioned for the sake of completeness. Recently, infarct size estimation from CPK serum levels has been worked out to a high degree of reliability by Sobel's group (63).

One application of ultrasound, not involving echocardiography per se, is that of the Doppler technique. This method involves recordings of the changes that ultrasound undergoes as a consequence of its reflection off moving objects (i.e., the Doppler effect). The range of applications of this technique primarily has included the timing of valvular movements with various forms of heart disease, and the recognition of myocardial events such as isometric relaxation (64). More recently, this method has been applied to the successful determination of the patency of saphenous vein coronary artery bypass grafts (65) and to the exact localization of intracardiac murmurs (66).

Still the most valuable and readily available of all techniques for cardiovascular diagnosis are the skills of physical diagnosis. However, even signs universally used and accepted continue to be appropriately investigated. As for example, the usefulness of rales as an accurate reflection of left ventricular failure has been recently questioned (67). By raising such questions and by carefully comparing time accepted physical signs with more objective measures

of heart function even the science of physical diagnosis is expanded.

Cardiac Changes with Dialysis

The hemodynamic effects of peritoneal and hemodialysis have been studied by several investigators with somewhat divergent results (68-72). Del Greco and colleagues found that following hemodialysis cardiac output, measured by a radio-iodine dilution technique, fell in 5 of 9 patients studied, and rose in the remaining 4 patients (68). Blood volume fell from a mean ($\pm$SD) of 4,400 $\pm$ 1,101 ml to 3,890 $\pm$ 990 ml with dialysis. This was directly related to the reduction in plasma volume induced by hemodialysis and was probably responsible for the increase in cardiac output when seen. It was notable that 3 of the 4 patients whose output fell had hypotensive episodes requiring pressors during dialysis. Thus, it is possible that this study detected two groups differently responsive to dialysis. The first group with well compensated cardiovascular systems was capable of responding to changes in fluid states appropriately, and the second with a poorly compensated myocardium was incapable of altering cardiac output by augmenting contractility.

In two studies concerned with effects of peritoneal dialysis, falling cardiac output was routinely detected immediately following the infusion of peritoneal dialysis fluid (69,70). This decline was probably related to impaired venous return caused by the extrinsic pressure of the dialysate on the inferior vena cava, rather than an intrinsic effect directly on the cardiovascular system. Such a suggestion was supported by the furter decrease in cardiac output induced by tilting the patients to 45°. This maneuver increased the extrinsic pressure on the inferior vena cava and further reduced venous return.

A more recent study found no change in cardiac output with hemodialysis (71). However the plasma volume of patients in this investigation was carefully maintained at a steady state. Thus sustained was the earlier suggestion that alterations in output were direct responses to the fall in plasma volume and not an

effect of the removal of some unknown "cardiodepresser" substance by dialysis.

A non-invasive approach has also been taken in an attempt to understand cardiodynamic changes with dialysis (72). By ballistocardiography (BCG) and carotid pulse tracings 12 patients were examined before and after 36 dialyses. In 8 of 36 dialyses BCG deterioration was noted, often accompanied by a fall in dP/dt as determined from the pulse wave. This was interpreted as "strong evidence that the cardiac contraction had become weak and incoordinate in these cases" (72). In the remainder of dialyses no significant changes were demonstrated. These findings are difficult to interpret. It is possible that deteriorating BCG group was equivalent to the earlier mentioned patients (68) whose cardiac output fell or remained unchanged with dialysis and who were considered to have hearts functionally incapable of responding by increasing contractility.

Ten patients undergoing peritoneal or hemodialysis have been studied with attention to the radiologic changes that occurred (73). A marked reduction in congestive changes was seen and was noted to be more pronounced in the patients who were hemodialyzed. A decrease in the cardiothoracic ratio, reduction in pulmonary engorgement (graded 0 to 4+), and the disappearance of pleural effusions were noted in most or all patients. As expected, the changes were accompanied by significant improvement of congestive symptoms.

There is a close relationship between hemodynamic changes with dialysis and those of congestive heart failure. This is evidenced by the fact that dialysis itself is not infrequently used in the therapy of severe cardiac failure (74-76). Peritoneal dialysis performed on 16 patients with refractory congestive heart failure produced a significant increase in the cardiac index from 1.4 to 1.9 liters per minute per square meter (74). A small subgroup of patients who failed to respond was noted. It was hypothesized that the cardiac

function of this group, as with those previously described, was on the descending limb of the Starling curve and that therefore they could not respond. Acute pulmonary edema, unsuccessfully treated by conventional methods, was treated successfully in two of four patients by peritoneal dialysis (75). In this small group it was concluded that the two patients survived as a direct result of the procedure. Although objective hemodynamic data was not obtained, the clinical results were significant. Among four patients with intractable failure following acute myocardial infarction, three demonstrated significant immediate benefit from peritoneal dialysis (76). In all four, loss of edema fluid, abolition of life-threatening arrhythmias, and restoration towards normal of metabolic alterations were achieved.

It is apparent, then, that dialysis significantly alters the fluid load status of the circulatory system. The indirect effects on cardiac function and specifically on contractility, although predictable, have not been specifically or completely documented. While all patients undergoing dialysis would be expected to demonstrate a decrease in the fluid overload state present initially, it might be anticipated that myocardial performance characteristics would respond with a high degree of variability. Such variability would undoubtedly be related to the underlying functional status of the myocardium.

Cardiac Changes with Postural Alterations

The effects of posture on cardiovascular function and hemodynamics has been investigated in a multiplicity of fashions using many different maneuvers to induce physiologic changes. Rushner's classic observations on canine models were among the first to clearly elucidate cardiac responses to postural changes (77,78). By means of gauges directly applied to the hearts of dogs, and by using indwelling cannulas Rushmer concluded that, "in the horizontal position, the ventricular dimensions and stroke volume are generally at or near maximum levels,... on sitting or standing ventricular size and stroke volume diminish to a new lower control level." (77). Consistant reduction in diastolic and systolic left ventricular dimensions followed passive gentle tilting of the dogs studied. Equivalent changes also occur in human subjects (79). It is interesting to note that diastolic dimensions increased to a greater extent thatn systolic ones, thereby producing changes in stroke volume as well (78). A direct infusion of blood, sufficient enough to raise filling pressures by as much as 15 mm.Hg., failed to increase diastolic dimensions. This leads to the suggestion that responses depend on more than effective blood volume alone. Such a result is at variance with earlier studies suggesting that changes in blood volume were directly paralleled by changes in heart volume (80). In that study it was concluded that readjustments following a change in postureare primarily reflected by blood drawn from "reservoirs of the first order" (i.e., heart and pulmonary circulation.) In a study of the rapid left ventricular adaptation to intravenous blood transfusion (felt to be analogous to cardiac blood volume change with postural alterations) contractility as well as ventricular volume was analysed (81). While the acute effects of increase on ventricular size were readily noted, the assessment of contractility involved the elucidation of complex interactions. Volume changes were felt to be related primarily to passive physical

mechanisms, while contractility changes represented true physiologic alterations to stress. Changes in maximal dP/dt with and without normalization for end-diastolic pressure were not consistently observed (81). This tends to rule out contractility as an explanation for adaptions to increase blood volume and thus strengthens the argument that volume changes are on a mechanical basis.

The hemodynamic response to the erect posture has been analysed in cardiac patients as well as normals (82,83). A fall in stroke volume and cardiac output was noted in both normal subjects and cardiac patients when they changed from the supine to upright position (82). In subjects with congestive heart failure, as opposed to normal controls, tilting to the upright position produced no significant changes in stroke volume, heart size or size of the right ventricle (83). Such a lack of change was attributed to preexisting underlying circulatory abnormalities including elevated plasma volume, venous distention and elevated venomotor tone. It is proposed that the net effect of these conditions minimize usual shifts of blood volume associated with postural changes (83).

Little investigative work has been done to validate the assumption that the physiologic alterations induced by leg raising perse are similar to alterations in preload produced by the tilt table or intravenous infusion. However, such an assumption is frequently made. Leg raising is often used in the cardiac catheterization laboratory to produce alterations in diastolic filling comparable to those induced in dogs by intravenous infusions. In one such study attention was focused on the effects of such a maneuver on the contractility indices of Vmax and (dP/dt)/P (84). Findings in both dogs and humans were similar in that the physiologic elevations of preload regularly were associated with reductions in the maximum (dP/dt)/P but had no effect on Vmax. Thus, they concluded that preload alone does not effect myocardial mechanics as measured by the index of Vmax but that measurements dependant on pressure appeared to vary inversely with

preload. The suggestion that leg raising acutely redistributes blood volume thereby elevating ventricular end-diastolic pressure is indirectly confirmed (84).

Thus, it can be seen that the foundations for understanding hemodynamic alterations induced by shifts of blood volume are firmly established inextensive physiologic investigations. Indirect but theoretically sound assumptions can be made for the acute affects of the leg raising maneuver. In simplest terms they include elevation of left ventricular filling pressures and consequent increases in diastolic volume as a result of this maneuver. An increase in stroke volume and varied responses of myocardial contractility depending on the underlying functional status of the muscle might also be anticipated.

DIAGNOSTIC ULTRASOUND

Principles and Engineering

A complete understanding of the use of diagnostic ultrasound, and echocardiography in particular, necessitates a minimum level of comprehension of the physical principles and engineering involved in such techniques. Consequently these aspects will be reviewed prior to further discussion of echocardiography itself.

Sound energy of any form travels through a medium as a wave. The wave exists as a periodic movement of particles of the medium in which it is travelling. The energy is transmitted through a medium without any net movement of the medium itself. Of the various types of sound waves that exist, longitudinal waves are employed in medical diagnostic techniques. These waves are propagated through media with particle motion occurring in the same direction as the flow of energy. It is this form of propagation that allows sound energy to be transmitted from one medium to the next. In addition, longitudinal waves can be well supported within a fluid medium (85). Sound waves are defined by the following parameters: wave length (λ), frequency (f, in cycles per second - cps or Hz), velocity (v), and intensity (I) or amplitude (86).

Ultrasonic waves are those with a frequency inaudible to the human ear. While this is usually 16,000 Hz for adults, and can be as high as 18,000 Hz for children; 20,000 Hz is generally accepted as the lower limit of ultrasound. Ultrasound waves generally exhibit the same properties as audible waves. They are chosen in diagnostic applications for the following reasons: 1) They are inaudible; 2) they can be directed in a beam and focused easily; 3) because of their shorter wave lengths, they are more appropriate for examination of small quantities of material or for detecting small variations in a structure; 4) they

can be used to study certain physical phenomena with very short time periods (87). The second reason, that of directional properties, is most important in medical applications.

The remainder of this discussion on ultrasound physical principles is based on the excellent and comprehensive review of ultrasound by Inge Edler and colleagues (88). This group of Swedish investigators was responsible for the growth of echocardiography from its embryonic stage to at least adolescence.

Sound intensity or I, in watts/sq. cm. is the energy passing through one sq. cm. of the sound beam's area per second. This energy is directly related to the maximum velocity attained by the moving particles in the medium and is inversely related to the density (p) of the medium and the velocity of the sound wave. The velocity of sound (which is equal to the product of frequency and wave length, $v = f \times \lambda$) in any given medium is dependant on the compressibility and density of that medium. For most fluids the velocity of sound is between 1000 and 1600 meters per second, and for soft tissue averages about 1540 meters per second.

Partial reflection of sound waves occurs at any interface between two media of dissimilar densities. At such interfaces part of the acoustic energy is reflected and progresses through the second medium. Such reflection is governed by the law: angle of incidence equals angle of reflection. Thus only if reflection occurs perpendicular to the reflecting surface will the reflection be returned directly to the source. Reflection is also governed by the difference in acoustic impedance (z) of the two media. Acoustic impedance is the product of the density of the medium and the velocity at which sound passes through it ($z = p \times v$). More sound waves will be reflected as the difference in the acoustic impedance between the two media increases. Acoustic impedance is high in muscle and low in blood, thus such an interface is ideal for ultrasound reflection.

Sound energy is progressively diminished during passage through homogenous materials. It is reduced by both absorption and scattering, the former effect being created by the viscosity or "inner friction" of the medium. Absoprtion coefficients have been derived for different media. The following are representative amplitude absorption coefficients (in cm^{-1}) for common tissue: Blood - 0.02, fat - 0.05, muscle - 0.1, and bone - 1.5. In addition to the coefficient, absorption varies with the square of the frequency. Thus higher frequencies are significantly more absorbed. Lack of homogeneity of a medium attenuates sound intensity by scatter, reflection and refraction.

Sound generated from a cylindrical generator is emitted as a round beam of approximately the same diameter as the generator. In the immediate area of the generator, referred to as the "near zone", the beam continues at the diameter of the generating surface. The length of the near zone is proportional to the square of the radius of the beam, and to the frequency. This length is inversely proportional to the wave length and velocity of the sound waves. A reduction in sound intensity per sq. cm. occurs beyond this near zone as the beam widens out to a cone. The angle of divergence of this cone is directly related to the wave length and inversely related to initial radius. Thus, the smaller the wave length (or greater the frequency) the smaller will be the divergence of sound and consequent diminution of intensity. Focusing the generating source of sound energy can be achieved so that the beam, rather than leaving its source in a parallel fashion, actually converges on itself up to a focus point. In this way sound intensity is increased at and surrounding the focus point. More importantly, the initial divergence from the near field is significantly reduced thus intensity can be maintained at greater distances.

The choice of frequency for diagnostic ultrasound must of necesssity be a compromise. This is the case because absorption is increased with higher

frequency, but resolving power and beam spreading are reduced. Maximum penetrance with highest resolution has been achieved in medical applications with frequencies of approximately 2.5 million cycles per second (MHz). In thin patients and particularly in children where absorption is less of a problem higher frequencies (3.5 MHz, 5MHz) have been used.

In 1880 the brothers Curie demonstrated that when a suitably cut crystal of quartz was caused to vibrate at a particular high frequency, electrical currents could be produced. This has become known as the piezoelectric effect and occurs with a variety of crystals. One year later the converse was demonstrated by the Curies, namely that when an alternating electric current was passed through crystals in a particular fashion the crystal vibrated at a characteristic frequency. Many years and investigations later such simple principles are now applied to the manufacture of transducers for transmission and reception of ultrasonic energy. A piezoelectric crystal is the essential element of ultrasonic transducers. Initially quartz, and later barium titanate or lead zirconate, was chosen as the substance with the most ideal characteristics for such transducers. Today's ultrasound generators are nothing more than specially built crystal holders. The maximum impulse intensity of the transducers used in diagnostic ultrasound applications is 40 watts/sq. cm. at 2.5 MHz. Transducers are available non-focused or with predetermined focal lengths (usually 5, 7.5 or 10 cm.).

The principle methods used in medial diagnostic ultrasound are analogous to techniques of more familiar radar. An electrical impulse causes a short pulse to be emitted from the transducer. Sound waves are then in part reflected directly back by structures perpendicular to the waves and strike the same transducer creating an electrical signal by causing the crystal to vibrate. Thus the same crystal transducer alternates between functioning as a transmitter and

a receiver. Suitable electronic circuitry is attached to the transducer with automatic switching so that the transmitter and receiver units function independently. Since the transducer is relatively much more efficient as a transmitter than as a receiver, equipment has been designed so that the alternating functions do not consume equal time. The duration of each transmitted impulse is usually one microsecond with a repetative rate of 1000 pulses per second. When the apparatus is not transmitting it automatically returns to the receiver mode. Thus in one second the equipment functions as a transmitter for 10^{-6} x 1000 or one millisecond, and the remainder of the time (99.9 percent of each second) it acts as a receiver. Commercially available echocardiography equipment is provided with extremely sensitive receivers. They can detect sound waves even if less than one percent of the original transmitted ultrasonic energy is reflected back (86).

By measuring the elapsed time (t) between transmission and reception of sound impulses, the distance (d) between the reflecting surface and the transducer can be determined by the following simple relationship:

$$d = v/2t$$

where v is the velocity of the sound (89). Although velocity varies in different media, as has been mentioned sound in tissue can be assumed to have a relatively constant velocity of 1540 m/sec. (90). Thus distance from the transducer to the reflecting surface is easily calculated.

By calibrating a cathode ray tube (CRT) for this velocity and attaching it to the receiver unit of the ultrasound apparatus, the conversion of time to distance can be done automatically by electronic circuitry. The reflected sound or echoes can then be displayed on the CRT at the appropriate distance from a given point of origin or reference on the tube. By convention the initial echo burst is represented by a vertical line on the left of the CRT. The electrical

impulse caused by the returning echo is displayed as another vertical line a distance away from the initial left hand line on X-axis of the oscilloscope. The distance on the X-axis is computed electronically based on the time it takes for the echo burst to leave and then, after reflection, return to the transducer. This distance on the CRT, then, is proportional to the distance from the reflecting object to the transducer. The height of the vertical lines (each representing a reflecting surface some distance away from the transducer) is electronically calibrated to be proportional to the amplitude of the sound intensity. Thus, the greater the sound energy returning to the transducer, the greater will be the height of the vertical line. This mode of oscilloscopic display is referred to as the "A" mode (for Amplitude modulation).

If the object or reflecting surface is constantly moving closer to and/or further away from the transducer, then each ultrasonic burst will catch the object at these different distances. The echoes will be displayed as a vertical line moving back and forth horizontally on the X-axis of the CRT. If, on the other hand, the object is moving laterally and the distance from the transducer does not change then the verticle line will appear stationary. In the same terms, objects at different distances from the transducer will be displayed as such, with the vertical lines in the A mode being in front and behind one another. However, objects displaced from each other laterally but each being the same distance from the transducer will be displayed as superimposed lines on the CRT and will be indistinguishable from echoes of a single object at that same distance. Thus, because of beam width, ultrasound equipment can detect objects laterally displaced, but as explained above, such lateral distance cannot be recognized, displayed or recorded.

Continuous recording of echo movements is of primary importance when ultrasound techniques are applied to the study of the cardiovascular system.

Such continuous recording is, however, impossible from the A mode because the back and forth moving echoes are constantly being superimposed on themselves. This problem necessitated the development of another display mode. The "M" (Time-Motion) mode was designed for this purpose. Adaptions for the M mode include two changes in the electronic processing of echo signals. First, the vertical lines are converted into dots. Distance continues to be displayed by displacement on the X-axis, but amplitude of the sound impulse is now proportional to intensity or brightness of the dot, rather than height of a vertical line. Second, these dots, each representing echoes from reflecting surfaces, are swept vertically up the oscilloscope screen with time being represented on the Y-axis. The time of the sweep is easily calibrated with timing of events being studied, such as the cardiac cycle. Although newer, more complex display systems are currently being developed, virtually all routine echocardiography applications today employ the M mode for display. The A mode is useful only during the echocardiographic examinations. Recognition of certain cardiac structures are facilitated by viewing the A mode prior to study of the M mode, or by viewing both modes simultaneously if two oscilloscope screens are available.

Recordings of the M mode are made in several ways. Earliest workers employed continuous photographic filming techniques by attaching a movie camera to the CRT tube. More recently Polaroid pictures have been widely used. With a Polaroid camera, photographs may be made either of the M mode from a special storage oscilloscope giving a stationary image, or by using a timed exposure to record the oscilloscope's sweep up the screen. Most recently continuous strip recordings have been obtained. Using either heat or light sensitive paper, a continuous paper strip is run across specially designed photoelectric tubes that display the M mode ultrasound image. The standard Electronics for Medicine* recorder utilized in many cardiac catheterization laboratories was

*Electronics for Medicine, 'Simultrace Recorder'
White Plains, New York

first utilized for this technique. Other recorders using similar principles have been developed as well.

For completeness, a now rarely used form of recording M mode should be mentioned. This is the "analogue gate" recording used before more sophisticated continuous strip chart recorders became available. Selected portions, usually representing the mitral valve, of the M mode seen on the CRT tube could be chosen. Impulses were applied to an analogue gating device that converted the signal to voltages that could be recorded by a standard high frequency direct-writing paper recorder such as those used in phonocardiography. Only one echo-reflecting structure could be studied at a time using this method (89). In addition, many artifacts were introduced and the technique has never enjoyed extensive utilization.

The controls on most echocardiographic equipment are relatively simple. An overall gain or attenuation control is utilized to adjust the level or intensity of ultrasound energy transmitted. A reject control similarly alters the receiver sensitivity. Both controls used in concert are necessary to produce the highest quality echocardiograms. Because of the great attenuation of echo intensity that occurs at significant distances from the transducer, all commercially available ultrasonoscopes employ some form of near gain attentuation, "time-gain-compensation," (TGC), or "depth compensation" (91). The compensation mechanism employed invariably has certain features. Near gain attenuation begins at the transducer and extends outward to a variable distance which is usually adjusted to a point close to the end of the transducer's near field. The amount of attentuation within this area is adjustable. Also controlled is the rate with which compensation is decreased. The slope of the "ramp", displayed on the CRT tube indicates whether compensation ends quickly with a steep slope or gradually with a gentle slope. Thus there are three possible alterations of the near gain attenuation apparatus:

amount of attenuation, location of the end of attenuation, and rapidity with which attenuation is ended. These are all continuously manipulated to bring out echocardiographically recordable structures as distinctly as possible.

Safety

The biological effects of ultrasound are multiple and complex. They have undergone extensive investigations (92). The generally agreed upon parameter for ultrasonic dose effects is that of energy flux density or sound intensity as previously mentioned (in watts/sq.cm.) (93). The biophysical modes of action involve thermal effects, "cavitation," and direct actions.

At high ultrasound intensities (approximately 21 watts total continuous output with an effective radiating area of 7 cm^2) heating of selected tissues has been demonstrated to be damaging (92). These heating effects are however obviated with pulsed techniques. Using 1000 impulses per second at a maximum intensity of 70 watts/sq. cm. no thermal effects could be detected in animals or man (88).

Cavitation appears in liquid media as a consequence of high alternating pressures. It can be observed in boiling water or near a ship's rotating propeller. Ultrasonic energy can also produce cavitation (94). External high ultrasonic energy is necessary to produce cavitation. Continuous ultrasound has been demonstrated as a necessary requirement for cavitation and therefore it is probably completely absent with pulsed echo techniques on a theoretic as well as an experimental basis (93).

Direct mechanisms of action imply either those that involve damage secondary to actual vibration or those due to some unknown ultrasonic action. A wide range of such effects have been reported, including the susceptibility of cells to disintegration when high amplitude continuous ultrasonic energy is applied (95). Degradation of DNA has been demonstrated with continuous energy of 30 watts/sq. cm. at 1 MHz (96). However, studies reported have all used irradiation conditions physically quite different from the beamed, pulsed techniques used in echocardiography (93).

In representative in vivo studies no untoward effects could be demonstrated using 200 watts/sq. cm. for 10 microseconds in rats (97). Despite "large" doses of ultrasonic energy to women during pregnancy no hazards have been demonstrated (98).

In diagnostic echocardiography peak intensities are no greater than 40 watt/sq.cm. Such intensities are maintained less than one tenth of the time when equipment is in use. The average intensity for ordinary transducers has been estimated at 0.003 watts/sq. cm. (88). This energy level is orders of magnitude below that used in therapeutic ultrasound and is significantly below the known biologic limits of safety. Feigenbaum has summarized the issue well:

> "As best can be determined from all available information, pulsed reflected ultrasound used in the intensity levels commonly employed for diagnostic purposes is perfectly harmless. Not a single untoward reaction has been reported despite the fact that this technique has been used on almost every part of the body for nearly 20 years." (99)

Medical Applications

Although ultrasound has been used in therapeutic and surgical applications, the discussion of such techniques is beyond the scope of this report. The equipment and energy levels used vary considerably from pulsed diagnostic ultrasound. A brief discussion of latter is however relevant. With the exception of tissues containing air or gas where the acoustical mismatch is as great as to cause essentially total reflection, most parts of the human body are accessable to diagnostic ultrasound techniques (100).

The brain received a great deal of early attention in this field. Transducers placed at both temperal areas simultaneously have been used to detect mid-line shifts with a high degree of reliability (101). However, this technique is probably of no greater utility than skull X-rays used to detect shifts of the calcified pineal gland.

Ophthalmological applications have included examination of opacities inaccessible to ophthalmoscopic visualization. Also, clarification of retinal bulges has been achieved by distinguishing between a detached retina and one protruding because of a tumor located behind it (102).

Ultrasonic analysis of soft tissue masses are now well established procedures. Such diagnostic uses require both the "A" mode and the "B" scan. In the B scan, storage of individual modified A mode tracings is accomplished on one oscilloscope screen to allow the build-up of echoes. In this way a composition representing a cross-section of the mass being examined is presented on the CRT. Such studies allow the differentiation of solid and cystic masses and can often help to decide when a palpated mass is normal organ or tumor (103).

Using combinations of A mode and B scanning, investigators have ultrasonically studied the following organs, and have often resolved clinical

questions regarding mass location and composition: liver, gall bladder, spleen, pancreas, bladder, uterus and kidneys. Retroperitoneal, pelvic, and subphrenic masses have been examined as well. Ascites is readily detected. With the aorta being the easiest of all intra-abdominal organs to demonstrate, the diagnosis of abdominal aortic aneurysm is often made ultrasonically. Finally, obstetrical applications are among the longest used and most wide-spread of diagnostic ultrasound techniques. Pregnancy can be detected as early as the fifth week post-conception. Accurate measurements of the biparietal diameter of the fetal skull have been correlated with fetal age. The latter technique is used routinely to detect fetal growth and deviations from normal development throughout pregnancy. Placental localization prior to amniocentesis and detection of molar pregnancies are further reliable and frequently used applications of diagnostic ultrasound (104).

ECHOCARDIOGRAPHY

History

Long before humans began to develop ultrasonic technology to the point of usefulness, bats, dolphins and other animals used echo soundings for measuring distances. Between 1920 and 1945 ultrasound was employed by man primarily for depth sounding and for locating submarines and schools of fish. Since approximately 1945, extensive medical and non-medical applications have been pursued (89).

Ultrasound was first used by Dussik in 1942 for diagnostic purposes, but it was not until 1950 when investigations on the heart were first reported by Keidel (88). In this work ultrasonic waves were transmitted through the thorax in an attempt to estimate fluctuations of cardiac volume. The use of pulsed reflected ultrasound to examine the heart was first described in 1953 by Hertz of Sweden; he was soon joined in his work by Edler. Together these two workers collaborated to produce the investigations that were the true beginning of ultrasound cardiography or as it is now known: echocardiography. Using relatively insensitive equipment the posterior heart wall and the mitral valve were identified ultrasonically. It is interesting that the mitral valve echoes were not initially recognized as such, and were initially interpreted as coming from the posterior left atrial wall (105). Nevertheless, particular patterns were quickly recognized as the technique was reliably applied to the diagnosis of mitral stenosis and estimations of its severity (88). The work of Edler and Hertz in Sweden was extensively duplicated with confirmatory findings in the late 1950's by Effert in Germany (105).

Ultrasound applications in cardiology were first introduced in the United States by an engineer, John Reid, who had done much of the early work in other medical uses of pulsed reflected ultrasound (105). The first extensive

work in America was done by Reid and Joyner in collaboration, and again essentially duplicated the earlier work from Sweden (106). This work was however preceeded by other American investigators using different, non-pulsed ultrasonic techniques to study the cardiovascular system. Franklin et al., reported ultrasonically determined aortic root diameters by measuring the transit time for sound to cross the root diagonally (107). Rushner and co-workers used the transit time between surgically placed ultrasonic crystals to measure ventricular diameters in dogs (108).

Segal and his associates in Philadelphia became involved with echocardiography in the mid 1960's. Although responsible for little original work, they helped produce an early comprehensive review of ultrasound cardiography published as a symposium in the American Journal of Cardiology in 1967 (109).

Feigenbaum reports that in 1963 he became dissatisfied with the shortcomings of cardiac catheterization and first became interested in echocardiography (105). His group's first important contribution, published in 1965, came with a description of a reliable technique for detecting pericardial effusions (110).

Since the late 1960's the validity and usefulness of echocardiography has been widely and extensively investigated. Feigenbaum has continued to be among the most active, but others as well have achieved widespread recognition as leaders in this field. Most notable is perhaps Popp who, beginning with his ventricular studies in 1969 (111), has continued to pursue an interest in volume and function determinations. Gramiak in Rochester has added to the anatomic-echocardiographic correlations by reliably demonstrating aortic valve echoes (112). He has also confirmed the identifications of various structures by echocardiographic visualization of cavity injections of indocyanine green (113).

The current popularity of echocardiographic techniques is evident in many ways. Echocardiographic equipment was demonstrated by five different manufacturers at the most recent (1973) meetings of the American Heart Association, while two years prior to this only two companies had such equipment available. The abstracts from these meetings in 1971 included ten reports using ultrasound techniques (114), whereas 1973 saw forty abstracts published related to echocardiography (115).

Technical Validation

Validation of echocardiographic identification of intracardiac structures was an important early step in the investigations of the Swedish workers (88). Several approaches were taken to make the necessary anatomic-echocardiographic correlations. And, in the process, mistakes were inevitably made.

As early as 1953 Hertz began to study echoes from transected, isolated human hearts (88). Intracardiac cavities were filled first with water and later with heprinized blood and the sound generating crystal was fixed to the exterior of the left ventricle. By juxtaposing a picture of the A mode echocardiogram obtained, with photographs of the heart walls cut in the same plane, interpretations of the origins of the echoes became readily apparent. In addition to measuring wall thicknesses and distances, and locating heart cavities, the fact was recognized that curvature irregularities caused break-up of echo signals. In another experiment a thrombus obtained from a surgical specimen was inserted in the left ventricle of the isolated heart. The multiple layered echoes seen were felt to represent the irregular consistency of the thrombus.

In echocardiograms obtained on normal subjects, Hertz and Edler recognized a characteristic echo easily seen with the transducer placed in the third left interspace. By correlations with the timing of intracardiac events they supposed this echo to be from the posterior wall of the left atrium. Interestingly, correlations of these tracings were made in patients with mitral stenosis still without proper identification of this intracardiac echo. Only later, after further experimental investigation, was this echo positively identified as coming from the anterior leaflet of the mitral valve. The experimental design again involved the use of an isolated heart with cow and calf hearts being utilized. Pressure variations to induce valve movement were produced

by first cannulating one pulmonary vein and tying off the others, while providing suitable left ventricular outflow and then causing pressure fluctuations with a motorized pressure system. Comparisons were made between the echocardiographic changes and films taken of the valve ostium. In such a way the ultrasound method was demonstrated to be capable of showing changes in both the mitral and aortic valve apparatus. The characteristics of these changes were recognized and accurately described for the first time (88).

Further investigations were carried out by the Swedish collaborators on autopsy specimens. Before the thoracic cavity was opened, long needles were placed along the supposed axis of the ultrasound beam. In this way the following structures were identified as being adjacent from anterior to posterior echocardiographically (3rd or 4th left interspace): anterior wall of the right ventricle, conus pulmonalis, interventricular septum, left ventricular outflow tract, mitral ostium and left atrium. By correlating direct measurements made on these specimens with relationships and measurements from ultrasoncially studied patients and normal subjects, a firm foundation for further echocardiographic identification as well as initial validation of anatomic-ultrasonic relationships was completed (88).

It was not until 1968 that further direct approaches to validation of echocardiographic studies were reported (113). Gramiak and his associates have presented a series of investigations in which contrast injections were recognized ultrasonically. Such injections were utilized to distinguish key anatomic structures and define their interrelationships. This method was dependant on the fact that rapid injection of materials via intracardiac catheters caused microbubbles which could be detected ultrasonically (116). Although indocyanine green was used most commonly, such a contrast effect could also be obtained by injection of saline, 5 percent dextrose, and blood.

Gramiak used multiple contrast injections through a catheter placed in the right heart, transseptally in the left heart, or retrograde in the ascending aorta. Four transducer positions were used to detect mitral valves, aortic root, tricuspid valves, and atrial septum. The latter involved placement on the right side of the sternum and is not commonly employed. In the mitral valve position (3rd or 4th left interspace with transducer directed posteriorly) right ventricular outflow, ventricular septum, and left ventricular outflow tract were identified anterior to the mitral valve. Posterior to the mitral valve either left ventricle or left atrium could be identified. These relationships are demonstrated in Figure 1 on the left and in the center of the figure. By angling the transducer medially from the mitral position, aortic root was detected. Its motion was described and valve cusps were frequently recognized as seen on the right in Figure 1. Intracardiac shunts and aortic insufficiency were also studied by ultrasonic visualization of contrast material.

In a similar study, positive identification of left ventricular structures has been made (117). Three echocardiographic methods of identifying structures are discussed. These include recognition of patterns of movement, location of echoes identified by their relationship to the location of other known echo-producing structures, and finally identification by observing differences in echo intensities. These methods of necessity are all based on, first, proven origin of some reference echo producing structure. Identification by the use of intracardiac indocyanine green has been a useful mode of proving such localizations. Its use, in contrast to studies of autopsy material, has had the advantage of providing positive identification of echoes in the beating heart. Verification of the source of echoes from the left ventricle substantiating previous suppositions has been reported (117). Particularly important was positive differentiation between endocardial and epicardial echoes.

In the past this had been a major source of confusion in echocardiographic interpretation. Because of different standards of interpretation, frequently this confusion between endocardial and epicardium had led to inappropriately divergent results when various investigators compared studies. The identification of intracardiac echoes produced by parts of the mitral apparatus and differentiated from posterior left ventricular wall was also aided by contrast studies. Landmarks frequently confused with the true posterior endocardial echoes have been described (117).

More recently the existance of microbubbles producing intracardiac echoes has been reported in a further application (118). Without using Doppler frequency-shift analysis, blood flow was detected by pulsed ultrasound. Because turbulent flow induces the formation of intracardiac microbubbles, echocardiography could be used to detect flow. Intracardiac echoes were influenced by respiratory changes as they induced pressure changes. Outflow tracts could be easily recognized by their echo producing turbulent flow. This study enabled echocardiographic positive localization of flow, as well as visualization of pressure differences produced at the margins of jets or vortices formed by turbulent flow. Thus flow differences with physiologic changes (respiration) and in varying anatomic locations (outflow vs. non-outflow tract) could be studied.

Various methods of indirectly proving echo origins will befurther discussed in the appropriate sections. Such methods employ either pathologic correlations with earlier obtained echocardiograms or physiologic studies such as those that compare angiographic and echocardiography volume determination.

Uses - Morphologic

The scope of diagnostic ultrasound in the recognition of cardiac disorders has increased tremendously in recent years. At the same time the validity of this well established and remarkably reliable procedure is becoming widely accepted (119,120). Recent editorials have attested to its usefulness and warned of its shortcomings (120,121). As the field of echocardiography has grown, comprehensive reviews of its applications have regularly appeared (88,106,109, 119,122). And, at this time, one excellent text has been published (86), and another is soon to be released (123). While a complete review such as those that have appeared would be impossible and inappropriate, important current applications will be discussed. This discussion will be divided between first, the uses primarily related to morphology,and second, study of applications in function and hemodynamics.

Physiology - The ability of the echocardiogram to elucidate normal and abnormal physiology has been well demonstrated. Zaky et al., studied the role of the atrium in closure of the mitral valve (124). Pressure gradients across the valve were correlated with ultrasound recordings of the anterior mitral leaflet. Atrial activity regularly preceeded movement of the valve towards closure. The mechanisms of closure were distinguished when the PR interval was long (greater than 0.18 sec.). In normals complete closure was usually recorded before the onset of ventricular systole. However, in patients with advanced heart disease, when the atrial pressure was elevated, valve closure was often delayed. It was concluded that normal mitral valve closure was associated with a "reversed" gradient after atrial activity was complete. This reverse gradient did not develop in the presence of: weak atrial activity (atrial fibrillation), increased atrial pressure (heart failure), increased blood flow (mitral regurgitation), and an initial position pressure gradient (mitral stenosis) (124).

In a more recent hemodynamic-echocardiographic correlative study it was found that opening and closing of the mitral valve as determined by pressure gradients systematically preceeded the echo signs of such movement (125). Regression equations were determined and it was concluded that such echocardiographic recordings could be applied to systolic and diastolic time interval determinations.

In patients with atrial fibrillation, the effects of cardioversion have been shown echocardiographically (126). Prominent mitral A waves were seen immediately following cardioversion as evidence of atrial systole. Echo determinations of left atrial diameters declined and those of left ventricular ejection fractions increased following cardioversion. Thus, the restoration of effective atrial contraction and the resulting hemodynamic benefits are apparent echocardiographically.

The relationship between heart sounds and valve movements has been studied as well. Simultaneously recorded phonocardiograms and echocardiograms are employed. Closure of the mitral valve has been shown to occur well before the so called "mitral" component of the first heart sound (127). It can be concluded that some later events are responsible for the generation of this sound. In patients without mitral stenosis, opening snaps have been demonstrated to occur at the point of most rapid closure of the mitral valve in diastole (128). The physiologic explanation of excessive blood flow causing opening snaps with normally mobile mitral leaflets is thus supported echocardiographically.

The physiologic events with the bundle branch blocks have been examined by several echocardiographic investigators. Septal movement with complete right bundle branch block has been described as normal (129,130). Left bundle branch block (LBBB) has been demonstrated to produce a characteristic abnormal motion of the interventricular septum (129-133). The usual echocardiographic feature of LBBB is an early abnormal systolic posterior septal wall movement.

The early sharp posterior motion is followed by a more sustained paradoxical anterior movement of the septum. Such an abnormality has been described in at least half, and usually more, of all subjects examined with LBBB. Interestingly, posterior heart wall motion is routinely found to be normal in pattern and timing. In ten patients with LBBB caused by right ventricular pacing only three had the abnormal early septal motion (132). The fact that septal asynergy was less regularly detected with artificial LBBB implies that the irregularity is related to more extensive septal and conduction system pathology. A more recent report has discussed the detection of delayed contraction of the posterior left ventricular wall in addition to the early activation of the septum (133). Echocardiographic tracings of the posterior interventricular septum and posterior left ventricular wall were compared for accuracy with tracings derived from left anterior oblique cineangiograms. This investigation enabled a most complete in vivo study of the abnormal ventricular activation sequence that occurs in LBBB.

Mitral Valve - Although recently the focus may have changed somewhat, for many years echoes from the anterior leaflet of the mitral valve were of primary interest to echocardiographers. The normal movements of this leaflet can be seen in Figure 2B. Point E represents the most anterior position attained by the leaflet and occurs at maximal valve opening. D to E represents the opening of the anterior leaflet and E to F represents movement of the leaflet toward closure, immediately after the rapid inflow of blood into the ventricle. The velocity of this closure, measured as the E to F slope, is closely related both to intrinsic valve pathology as well as to flow through the mitral orifice. Atrial systole causes a reopening of the valve to a maximum at point A. The rapid movement B to C is attributed to final closure of the mitral valve. The C to D slope represents the closed mitral valve during ventricular systole. The gradual

anterior movement of the C to D slope is explained by forward movement of the entire heart during systole. An opening snap, if heart, occurs at the E point. A third heart sound occurs during E to F closure and a fourth sound at the A point.

In mitral stenosis the anterior leaflet tracing differs from normal. The E to F slope is significantly reduced and the A wave is small or absent (134). The diastolic slope (E to F) in centimeters per second has been routinely shown to decrease as mitral valve area leasens (134-136). Severity of mitral stenosis has been reliably estimated when compared to valve areas obtained both through hemodynamic studies at cardiac catheterization and by direct surgical observations (135). Slopes were shown to be improved following valvulotomy. The groups established by Segal in 1966 although not perfectly sensitive or selective have continued to be useful; Severe: E-F slope less than3.0 cm/sec, mitral valve area (MVA) less than 1.0 cm^2; Moderate: E-F 3.0-4.5 cm/sec, MVS 1.0-1.7 cm^2; Mild: E-F 4.5-8.0 cm/sec, MVS 1.7-3.0 cm^2 (135).

Initially there was wide interest in quantitating the degree of mitral regurgitation present as well (136). Various patterns for mitral regurgitation, and combined regurgitation and stenosis were described. Since it has been realized that patterns relate more to mitral flow and to cardiac output than to regurgitation per se, these initial concepts have been disregarded (137).

With increased awareness of the relationship betweenflow and valve movement, conditions mimicking mitral stenosis have become more well recognized (138). Reduced left ventricular diastolic filling producing echocardiograms resembling mitral stenosis can be associated with the following conditions: left atrial myxoma, hypertrophic subaortic stenosis, severe left ventricular hypertrophy due to aortic stenosis, non-obstructive cardiomyopathy, and pulmonary hypertension with right ventricular overload (138).

Additional criteria have been added to that of diastolic slope for diagnosing mitral stenosis and for excluding false positives (139). Recording the motion of the posterior mitral leaflet is of great importance. In suspected mitral stenosis, if the posterior leaflet moves abnormally and parallel to, rather than opposite, the anterior leaflet, then a rigid valve structure is suggested and the diagnosis of mitral stenosis is strongly confirmed. Multiple echoes from the mitral leaflets are suggestive of thickening and calcification. Thus the diagnosis of mitral stenosis can be further confirmed if such echoes are recognized. A decreased E-F slope is unlikely to be due to alterations in flow alone if multiple echoes are present (139).

Echocardiographic recognition of mitral regurgitation and its varying etiologies has received much attention (140). Whereas quantitation of regurgitant flow and the presence of insufficiency in rheumatic disease was emphasized in earlier work (later to be found unreliable), most recent investigations have studied other causes of regurgitation.

Ruptured chordae tendineae represent one of the more common non-rheumatic causes of mitral regurgitation. Ruptured chordae to both the anterior and posterior leaflets separately and together have been diagnosed echocardiographically (141-143). Posterior rupture is associated with thin waving echoes in the left atrium during systole. The echoes are produced by the prolapsing posterior leaflet (141). Anterior rupture causes the anterior mitral leaflet to move randomly and chaotically during diastole. Such movement is often described as "coarse fluttering" likened to a sail flapping in the breeze (142). Recognition of ruptured posterior chordae can be aided by findings of increased amplitude of systolic excursion of the atrial wall in addition to the unusual echo seen within the left atrium. Posterior rupture is also suggested by increased amplitude of motion of the leaflet, failure

to coapt with the posterior leaflet in systole, and increased septal motion. With anterior rupture increased amplitude of the leaflet is seen also. In addition, the leaflet may appear to touch the septum in systole (143).

Mitral prolapse with or without mitral regurgitation has been of great interest in echocardiography. A characteristic pattern is often seen in patients with the syndrome of systolic click and late systolic murmur (149). In such cases the posterior or posterior and anterior mitral leaflets are seen to display an abrupt posterior movement coincident with the systolic click and onset of the murmur. When separation is seen between the leaflets in late systole, mitral regurgitation is strongly suggested (145). Recognition of prolapse and associated regurgitation is not confined to the click-murmur syndrome. Holosystolic posterior prolapse is seen regularly with and without mitral regurgitation (146). Such pansystolic ballooning is becoming more frequently recognized, often in asymptomatic patients (147).

Aortic Valve - The aortic valve is less easily demonstrated echocardiographically than the mitral valve. Consequently it has not been as extensively studied as the mitral apparatus. The aortic root echoes are usually obtained by locating the mitral valve first, then angling the transducer superiorly and medially. When such a scan is performed, as can be seen in Figure 1, the anterior mitral leaflet is demonstrated to be continuous with the posterior aortic root wall and the septum is continuous with the anterior wall. Echoes from two aortic cusps are frequently seen within the walls (Figure 2C). They are probably from the right-coronary cusp and non-coronary cusp, while the lateral motion of the left coronary cusp cannot be seen echocardiographically (112).

Unlike mitral stenosis, aortic stenosis cannot be diagnosed by measuring opening and closing rates of the valve. The disease process so obliterates and distorts normal landmarks that it is often impossible to make such measurements. However, the presence of calcific aortic stenosis is strongly suggested

if multiple, thick echoes are produced by the aortic root walls and by the cusps (112). The presence of multiple, linear, central, reproducible echoes within the aortic root has been correlated to cardiac catheterization findings in aortic stenosis (148). Such echoes were found to be highly specific for aortic stenosis. Their absence, associated with normal excursion of at least one aortic cusp, accurately excluded the diagnosis of aortic stenosis in 60 of 61 patients. The square of the aortic valve orifice dimension has been shown in one study to correlate highly with hemodynamically estimated aortic valve area in aortic stenosis (149). The usefulness of this finding is yet to be confirmed however.

Aortic regurgitation is echocardiographically associated with a characteristic fluttering of the anterior leaflet of the mitral valve during diastole (150). While this fluttering occurs simultaneously with the Austin Flint murmur if present, its cause is debatable (150-152). A traditional concept is that the murmur and fluttering are caused by the regurgitant jet hitting the anterior mitral leaflet. This is challenged by evidence strongly suggesting that the rumble is produced by antegrade flow across the mitral valve (151). Another group suggests that the Austin Flint murmur may arise from either a turbulant flow situation or from the diastolic oscillation of the anterior leaflet or from both (152). Rapid diastolic mitral valve closure, an absent or small A wave, and premature mitral closure in addition to the diastolic fluttering of the anterior leaflet have been described with severe aortic regurgitation (153).

Abnormal echocardiograms have been reported with dissecting aortic aneurysms (154,155). In such cases an aortic false lumen with multiple parallel echoes can often be seen in one or both aortic root walls. Aortic root diameter is increased and aortic cusps do not seem to open to the outer walls. If aortic insufficiency is present as well, the anterior mitral leaflet is seen to oscillate. Unfortunately these findings seem to be associated with many false positive diagnoses (156).

Postoperative echocardiographic evaluation of aortic valve homografts has been reported (157). Iatrogenic aortic insufficiency was easily detected. Vibrations of the homograft cusps were seen but their significance is unknown at present.

Pulmonic and Tricuspid Valves - These valves have been studied only rarely echocardiographically. Gramiak has described methods for pulmonic valve detection (158). However, the clinical usefulness of this technique has not been demonstrated. The tricuspid valve is similar to the mitral valve in all respects except location (159). Tricuspid stenosis resembles closely the pattern of the stenotic mitral valve (160). In a patient with multiple congenital defects and pulmonary regurgitation, vibrations of the tricuspid valve occurring with a "right-sided Austin Flint murmur" were demonstrated (161).

Pericardial Effusion - For the defection of pericardial effusion echocardiography is unsurpassed (162). For its speed, simplicity, sensitivity and selectivity the echocardiogram has become the routine diagnostic technique of choice for demonstrating, localizing and even quantitating pericardial effusions. Appearing as characteristic echo lucencies anteriorly and/or posteriorly the effusion can be reproducibly detected. While pleural effusions and mistakes in transducer position can confuse the diagnosis, the adoption of standard techniques has improved results over initial studies (163). The reliability and sensitivity of echocardiography in pericardial effusion has been studied by comparing echograms with findings at cardiac surgery (164). Specific patterns were described for varying amounts of fluid. Forty patients were studied, in one with a small effusion at operation three observers could not agree on whether an effusion was present echocardiographically. There were no other false positive or false negative results. Effusions as small as 16 cc. were routinely

detected in this study. Positive identification of effusion and of the pericardial sac has been obtained under experimental conditions (165). Patterns similar to in vivo situations were seen when fluid was introduced into the pericardial space in open-chest dog preparations.

Excessive cardiac motion has been demonstrated echocardiographically in some patients with large pericardial effusions (166). Electrical alteration, when present, was associated with the most marked cardiac excursions. Thus it was suggested that such alterations might be of positional etiology.

Recently the presence of subclinical pericardial effusions have been detected in patients with rheumatoid arthritis (167). In this prospective echocardiographic search, 44 percent of the patients studied showed evidence of effusions that were not evident on electrocardiogram or chest X-ray. Previously such prevalence had been demonstrated only post-mortem.

Idiopathic Hypertrophic Subaortic Stenosis - Asymmetric Septal Hypertrophy - The echocardiographic understanding of idiopathic hypertrophic subaortic stenosis (IHSS) has developed along two courses. The first has involved the recognition of a characteristic pattern of systolic motion of the anterior mitral leaflet. Second, and more recently, the disease spectrum of IHSS has been re-evaluated based on echocardiographic findings (168).

An abnormal sharp systolic anterior movement (SAM) of the anterior mitral leaflet has been described as an echocardiographic characteristic of IHSS (169). Simultaneous with the onset of SAM the systolic murmur was noted to begin. The second systolic pulse wave, a common feature of IHSS, was seen to occur with the return of the mitral leaflet to a normal position in late systole. Thus it was concluded that SAM represented obstruction of the left ventricular outflow tract by the anterior mitral leaflet. The abnormal systolic pattern was abolished when outflow obstruction was eliminated with beta-adrenergic blockage (170).

Ventriculomyotomy has also been shown to consistantly eliminate SAM (171). False-positive diagnoses have been obtained in a patient with mitral stenosis and tachycardia (170), and in another patient with an atrial septal defect (172). False-negatives are more frequent and depend largely on the experience of the echocardiographer (170).

When present, SAM has been shown to be useful in the determination of a reliable "obstructive index" (193). Epstein's group at the NIH has developed this index based on an area calculation of the left ventricular outflow tract made from the echocardiogram. A high correlation ($r = 0.95$) was obtained when this index was compared to the hemodynamic gradient. The obstructive index has also been used to estimate the hemodynamic effects of ventricular septal myectomy (174). Simultaneous hemodynamic studies confirmed the usefulness and reliability of the index determinations.

In related but separate studies the same workers who developed the obstructive index have shown an echocardiographically identifiable pathognomonic abnormality in IHSS (175). Examining the large number of patients available to them at the NIH, Henry et al., made meticulous measurements of the septal and posterior left ventricular wall thicknesses. The mean septal-free wall ratio was 1.68 in patients with IHSS, while the maximum ratio for normals and patients with other forms of heart disease was 1.03. The ratio exceeded 1.3 in all patients with IHSS. Based on this anatomic abnormality these investigators have proposed that the disease entity be more appropriately called asymmetrical septal hypertrophy (ASH). These initial results have been confirmed by others noting a septal-free wall ratio of 1.2 for normals or patients with non-IHSS left ventricular hypertrophy, and a mean of 2.2 for those with IHSS (176). False-positive diagnoses, however, have been made in patients with isolated right ventricular hypertrophy (177).

By studying the first degree relatives of all patients with IHSS the NIH group has defined the familial prevalence of this disease using echocardiography (178). Forty-six percent of the first-degree relatives studied with equal proportions of males and females had ASH. Thus these investigators were led to the conclusion that most or all cases of this disorder are inherited in an autosomal dominant manner, with a high degree of penetrance. They view IHSS as simply ASH with obstruction. Thus the entity of IHSS is regarded as a subgroup in the larger disease spectrum of ASH.

Right Ventricular Volume Overload - The echocardiographic characteristics of right ventricular volume overload have been extensively studied (179-182). Two features of this condition have been regularly assessed: right ventricular dimension, and motion of the interventricular septum. Two forms of abnormal septal motion, referred to as types A and B, have been described with conditions leading to right ventricular volume overload (179). Normally the septum moves posteriorly with ventricular systole (Figure 2A). Type A motion is manifested by both septum (or posterior septum) and posterior left ventricular wall moving in a parallel fashion. Thus, in type A motion the septum moves exactly opposite to its normal motion, exhibiting so called "paradoxical" septal motion. In the type B pattern the septum is initiailly flattened during ventricular systole with only a late, small posterior movement (179). Type A is more common than type B motion in right ventricular overload (180). Abnormal septal motion is found in as high as 95 percent of patients with conditions resulting in right sided overload (181). Right ventricular end-diastolic dimensions are regularly increased as well (181).

Of the multiple conditions that cancause right volume overload with its characteristic echocardiographic findings, atrial septal defects are by far the most common (182). Total anomalous pulmonary venous return can also produce these characteristic features (183). Partial anomalous pulmonary venous return,

tricuspid regurgitation, and a coronary artery fistula have all been reported to cause abnormal septal motion (either type A or B) and increased right ventricular diameters (184). Coronary artery disease with infarcted septums and one case of right ventricular conduction delay (possibly with an old, closed atrial septal defect) havebeen reported as false positives (184,185). Studies performed on 20 children with right volume overload have confirmed the above findings with abnormal septal motion being frequently demonstrated (186).

To evaluate the mechanism for the septal abnormalities seen on echocardiograms in right ventricular volume overload, experimental overload was created in open-chest dogs (187). With a shunt flow as low as 500 cc. per minute changes in septal motion were produced in seven of eight dogs. When the shunts were decreased or stopped, motion returned to normal. The production of left ventricular volume overload did not induce similar changes. As part of the same study 21 patients were evaluated after surgical repair of atrial septal defects (187). Sixteen had abnormal septal motion pre-operatively but only one returned to normal post-operatively. While the experimental conditions strongly suggest that right sided overload was the cause of the abnormal septal motion initially, additional factors must be involved in its persistence.

Atrial Tumors - The first report of a left atrial myxoma diagnosed by ultrasound appeared in 1959 (188). A period of nine years elapsed before one was reported in this country (189). However, since then many such diagnoses have been made echocardiographically (190-192). A report of the ultrasound diagnosis of a right atrial myxoma also has appeared (193). Most left sided intra-atrial masses prolapse into the mitral orifice during diastole. Echoes from a mass posterior to the anterior mitral leaflet are therefore seen during diastole but usually not during systole (189). Prolapse of the tumor frequently obstructs the

valve preventing normal diastolic closure and causing a reduced diastolic slope on the echogram (192). This latter condition can lead to confusion and the false diagnosis of mitral stenosis. Such confusion can frequently be avoided by careful adjustments in the gain controls to demonstrate the presence of multiple echoes behind the anterior leaflet. Although the occurrence of a false-positive diagnosis of a left atrial myxoma has not yet appeared in the literature, the description of such a case is currently in press (194). The false diagnosis of myxoma was made in a patient with a large left atrial fungal verucca.

Postoperative evaluation following removal of an atrial tumor will routinely show disappearance of the tumor mass and return of normal diastolic closure (191). Because of the simplicity of the examining technique and because of the frequently malignant course of myxomata, routine echocardiographic screening has been advised for all patients with suspected mitral stenosis (190).

Congential Heart Disease - Echocardiography has been widely applied to diagnosis in congenital heart disease. Without discussing the entities involved, the following is a list of the most important conditions that have been evaluated by ultrasound: single ventricle and hypoplastic left and right heart syndromes (195), tricuspid atresia (195), aortic atresia (196), congenital mitral stenosis (197), membranous subaortic stenosis (198), Ebstein's anomaly (198), double outlet right ventricle (199), d-transposition of the great vessels (200), and truncus arteriosus (201). Considerable attention has also been paid to the establishment of normal valves for infants (202,203). In general, work in the pediatric population has lagged somewhat behind adult investigations, probably because most early workers were adult cardiologists. Currently, however, the field is rapidly expanding with many studies now in progress.

Miscellaneous Uses - Echocardiography has been reported useful in the recognition of a left ventricular aneurysm (204). In the case discussed recordings of the

posterior ventricular wall were distinctly abnormal. A phasic movement unlike the normal posterior wall was detected at the site of the aneurysm.

Prosthetic mitral and aortic valves have been studied echocardiographically (205). While echograms of the mitral valve are easily obtained, the aortic prosthesis, because of its position is more difficult to see by ultrasound (206). Various complications of prosthetic valves have been readily detected. Fungal vegetations have been described with a Starr-Edwards prosthesis (207). Attempts at the detection of ball variance have been made by measuring ball diameters (205). In addition, thrombus formation has been echocardiographically recognized on a ball valve prosthesis (208).

Ultrasound techniques have been utilitzed in the recognition of acute rejection following cardiac transplantation. Echocardiographic measurements showed increases of both posterior wall thickness and overall heart diameter with episodes of rejection (209). As the rejection resolved these signs regularly returned towards normal. Right ventricular dilation has also been reported with rejection (210). Changes in cardiac dimensions were consistent with the known histopathological and pathophysiologic changes of cardiac graft rejection.

Echocardiography has been used in the cardiac catheterization laboratory for reliably determining left ventricular chamber position (211). Ultrasonic determination of chamber position was utilized for accurately assessing the location of the chamber in relation to the X-ray image intensifier. This enabled more precise corrections for the magnification and distortion factors necessary in left ventricular quantitative angiography.

Uses - New Techniques

B-Scan - Cross-sectional ultrasonic imaging of the heart has been performed using specially designed compound scanning techniques (212). This method, called cardiac ultrasonography or simply B-scanning, involves the recording of segmential B-scans. A B-scan is actually the M-mode without motion or time. That is, the dots representing sound reflecting structures are not swept up with the oscilliscope as in the Time-motion mode. With cardiac ultrasonography a step-action image of a cardiac cross-section is formed by a composite of B-scans recorded sequentially. The image is produced by moving the transducer along a predetermined path while multiple point echoes are obtained. The receiver and storage oscilloscope are syncronized with the electrocardiogram so that all echoes are recorded at the same point in the cardiac cycle. The final image is a stop-action picture of a cardiac cross-section at any predetermined point in the cardiac cycle. Position and angulation of the scanning transducer can be altered to produce various views of the heart.

Left ventricular volumes obtained by this technique appear to be within a clinically useful range of accuracy (213). The technique has also proved reliable in detecting various forms of congenital malformations (212). The dection of contraction abnormalities by B-scanning has been correlated closely with those diagnosed by biplane ventriculography (214). Patterns of hyperkinesis, hypokinesis and septal or posterior wall asynergy were well seen on B-scanning. In the same study ejection fractions determined from the B-scancorrelated well ($r = 0.89$) with those obtained from left anterior oblique angiograms.

An adaption of this technique allowing the study of motion has recently been reported (215). A small hand-held motorized scanner has been developed for obtaining real time two-dimensional images of the heart. Cardiac cross-sections in a 30^{o} arc can be seen at the rate of 20 frames per second, and high

sensitivity recordings have been produced. The initial experience with this technique makes it look extremely promising.

Multiscan - The use of multiple transducers has been applied to the problem of cross-sectional imaging. With a large number of transducer elements (20) positioned in a row and functioning essentially simultaneously, it is now possible to obtain instantaneous cardiac cross-sectional visualization. Such a system is known as multiscan echocardiography and has recently been developed by Hugenholtz's group (216,217). Each ultrasound crystal of the multi-element transducer functions separately with its own transmission and reception circuitry. The oscilliscope displays a separate line for each transducer with depth on the horizontal axis. Each position on the vertical axis corresponds to the position of each respective transducer element on the chest wall. Thus, a composite of 20 lines is produced displaying the cross-ectional image of the sagittal plane in which the multi-transducer is aimed. Videotape is employed to record the dynamic picture.

Several groups have had prototypes of the multiscan equipment available, and preliminary investigations show a promise of expanding capabilities. Mitral valve prolapse is easily recognized with a most distinctive picture(218). Multiscan left ventricular dimensions and derived estimates of end-diastolic and end-systolic volumes compared favorably to single plane angiographic determinations (219,220). In a cooperative evaluating study the multiscan technique produced high quality images of mitral valve, aorta, ventricular septum and posterior left ventricular wallin over 50 percent of 546 patients studied (221).

Miscellaneous - Other echocardiographic developments include the use of computers to store echo information and reprocess the data in the form of cross-sectional

images (222). A most exciting development, although at this stage only a potential one, concerns the use of computers to produce holograms from echocardiograms (223). When such techniques become available to the medical specialist it will be possible to obtain instantaneous three-dimensional images of all organs of the body.

Uses - Hemodyhamics and Function

Volume - The possibility of making quantiative determinations of cardiac dimension has attracted echocardiographers for several years. In an early investigation echoes from the mitral valve ring were used to measure left ventricular stroke volume (224). Use was made of the emperical observation that the curve inscribed by the valve ring echo closely resembled known left ventricular volume curves. It was also noted that the distance between the anterior chest wall and the posterior heart wall was roughly equal to the size of the left ventricle (225). By multiplying the amplitude of motion of the mitral valve ring times the chest wall-posterior wall dimension a rough estimate of stroke volume was obtained (224). Although the correlation coefficient was high ($r = 0.973$) when compared to Fick method determinations of stroke volume, this method was never widely accepted. A primary problem associated with this early technique of volume determination was that patients with right ventricular enlargement could not be reliably studied. Also it was quickly recognized that determinations of mitral ring amplitude were poorly reproducible making standardization quite difficult. Also since this technique was based primarily on emperical observations it was seen to be replaced by a mere logical direct method of calculating volume.

Validation of the ultrasonic left ventricular diameter measurements has been achieved in the canine model (226). By placing a transducer tipped catheter in the right ventricle measurements of left ventricular diameter at both end-systole and end-diastole were obtained and correlated highly with radiographic measurements. This technique proved useful in evaluating dimension changes with various physiologic interventions and was harmless in the intact anesthetized dog.

Reliable estimations of ventricular size in man became possible only after such experience was gained with echocardiographic techniques. Par-

ticularly important was the recognition and description of echoes from the interventricular septum (111). This provided the key for utilizing ultrasound in the measurement of right and left ventricular diameters. With well described septal echoes it became possible to measure right ventricular diameter as the distance from the anterior epicardial surface of the right ventricle to the right side of the septum (Figure 2B). Left ventricular diameter could similarly be obtained by measuring the distance between the left or posterior side of the septum and the endocardial surface of the posterior left ventricular wall as shown in Figure 2A (111).

Since the initial description of echoes from the interventricular septum, many different groups have worked at validating the echocardiographic technique of ventricular diameter and volume determination (227-232). In all studies the left ventricular chamber is considered as a prolate ellipse with minor axis being that dimension measured echocardiographically. Such a model is the same as used in angiographic studies as has been discussed previously.

Left ventricular dimensions are measured echocardiographically with a high degree of reproducibility. Echocardiograms have been recorded on the same patients at different times to test reproducibility. When measurements were made by the same observer on two echograms recorded at different times the mean difference in end-diastolic diameter was only 0.30 cm. and the difference in the end-systolic dimension was 0.34 cm (228). Observer variation was tested by comparing measurements by two investigators on the same echogram. The mean difference between end-diastolic diameters by two observers was 0.15cm. when measurements were completed (228). When echocardiographically determined dimensions were compared with angiographic data a correlation coefficient of 0.90 with a standard error of 0.45 cm. was obtained for both end-diastolic and end-systolic diameters (228). Another angiographic-echocardiographic study demonstrated slight but consistent underestimation of end-diastolic diameter

(standard error 0.57cm) and over estimation of end-systolic diameter (standard error 0.51 cm) (229). High correlations have also been demonstrated between the echographic diameter and the angiographic semi-length of the major diameter during systole and diastole (228). Two more recent studies have noted high correlations between echo and angiographically measured end-diastolic dimensions, further validating this already widely used technique (231,232).

The usefulness of such diameter determinations have primarily been in terms of the ability to calculate volumes from these measurements. The commonly used methods of ventricular volume determination from angiographic data have already been reviewed. Basically, volume is calculated from measurement of the long axis and planimetered area on one or two planes. This data is then used to calculate the volume of a prolate ellipse. Several assumptions and adaptions are made of these principles for volume calculations from echocardiographically determined ventricular dimensions (233): 1) that the separation between left ventricular walls is accurately represented in the echocardiogram, 2) that the measurement can be routinely made in a standard fashion, 3) that the measured diameter has some constant relationship, throughout the cardiac cycle, to the axes of the ventricle, 4) that there is a constant relationship between the short and long axis, and 5) that the measured dimension is equivalent to the short axis. The formula for calculation of volume of a prelate ellipse is:

$$(\pi /6)\ L \times LVID^2$$

where L is the length or major axis, and LVID is the left ventricular internal diameter or minor axis. In normal hearts the long-short axis relationships is relatively constant at 2 to 1 (233). Thus, the volume can be calculated from the echocardiographically determined LVID as $(\pi/3)\ LVID^3$, or $1.047\ LVID^3$. The stroke volume (SV) is simply the difference between the volume at end-diastole ($LVID_d^3$) and that at end-systole ($LVID_a^3$):

$$SV = LVID_d^3 - LVID_s^3$$

Correlations between echocardiographically determined SV and that measured by angiography has been good with coefficients ranging from r = 0.97 (231) to r = 0.72 (230) and most studies finding a correlation coefficient close to r = 0.83 (228).

It is well known that the left ventricle becomes more spheroid with cardiac dilation. Since this undoubtedly alters the long-short axis relationship some investigators have been led to use a regression equation for the calculation of volume (229). Their equation, although inapplicable to small ventricles, has provided reliable estimates of end-systolic, end-diastolic and stroke volumes in enlarged ventricles. It is apparent that for the most accurate measurement of cardiac volumes, different echocardiographic methods of calculation must be employed for small and large hearts. However, good "semi-quantitative" estimates are provided by simply cubing the LVID, especially in serial determination where changes, rather absolute values, are of interest (233).

It has been demonstrated that in ventricles with significant asynergy echocardiographic volume determinations are less accurate (234). In this study the L to LVID ratio varied from 1.4:1 for large ventricles, to 3:1 for small ones. The suggestion was made that a derived regression equation is more appropriate for volume determination than the cube formula and that volume cannot be calculated with confidence in the presence of asynergy. In a later study the location and extent of asynergy has been related to accuracy of echocardiographic volume determination (235). Patients with anterior abnormally contracting segments showed the poorest correlation between angiographic and echocardiographic volume calculations. Recently use has been made of the fact that asynergy lead to overestimation of echocardiographically determined volumes (236). It was shown that the difference in stroke volume between

echographic and Fick techniques was related to the size of the abnormally contracting segments. A regression equation was developed which gave close approximation of the percentage of regional asynergy.

Only one report has appeared using ultrasound to measure left atrial size by standard techniques (237). The method described used the distance between the posterior aortic root and the left atrial wall, at its greatest separation, to estimate left atrial size (Figure 2C). Left atrial dimension determined in this way correlated highly (r = 0.91) with left atrial area determined angiographically. The correlation coefficient was improved further when the left atrial dimension was normalized for body size by dividing it by the body surface area. Although confirmatory data has not been published, it has been recently suggested that the most reliable method for determining left atrial size would be to divide the left atrial dimension by the aortic root dimension (238). This would correct for perhaps the greatest source of error, transducer angulation. Since aortic root diameters are relatively constant, this measurement could provide a reference standard to compensate for inappropriately large atrial diameters if the echo beam crosses the aortic root and atrium obliquely.

Wall Thickness and Mass - Using tehcniques stemming from earlier work with pericardial effusions, Feigenbaum was the first to accurately measure ventricular wall thickness by ultrasound (239). Pericardium was clearly differentiated from posterior myocardial wall in this study. However endocardium and epicardium were not distinguished in these early investigations. Ultrasound measurements were within 0.5 cm. of measurements made at surgery in 33 patients and within 0.3 cm. in seven patients studied at autopsy.

In another, study left ventricular wall thickness determinations were made by echocardiography in 20 patients (240). The results correlated only

moderately (r = 0.77) with the angiographically measured thickness. However, it was concluded that the latter measurements were taken from different portions of the posterior left ventricular wall than the ultrasound measurements. Repeat examination in 17 patients produced almost identical results with high correlation coefficients between the first and second exams (r = 0.96) and thereby demonstrated the usefulness of the technique in longitudinal studies (240).

Similar studies have been undertaken to measure the thickness of the interventricular septum (241). Such measurements are easily obtained and it has been concluded that under normal conditions septal and posterior wall thicknesses are nearly identical.

By combining measurements of wall thickness with minor axis determinations, it has been possible to derive an estimate of ventricular mass echocardiographically (242). In one such study wall thickness correlated closely with angiographic measurements (r = 0.89) and left ventricular mass calculation was similarly related (r = 0.88). Systolic wall thickening was also measured and reliably detected subjects with ejection fraction greater or less than 0.50. This study carefully distinguished between endocardial and epicardial echoes. Determination of wall thickness in diastole (WT_d) was based upon the distance from the anterior surface of the endocardium to the anterior of epicardium of the posterior wall. Measurements for mass determinations were made at end-diastole. Left ventricular muscle volume (LVMV) was determined by the equation:

$$LVMV = 4/3 \left(\frac{LVID_d}{2} + WT_d\right)^3 - \pi/3\ LVID^3$$

Left ventricular mass in grams (LVM) was obtained by multiplying by the specific gravity of muscle:

$$LVM = LVMV \times 1.05$$

Reproducibility of the technique was confirmed by independent measurements of two observers. The study was felt to suggest high reliability for echocardiographic measurements of ventricular wall thickness and mass determination in the intact human heart. (242)

Wall Motion - With the ability to obtain discrete posterior wall echoes on most subjects, interest in posterior wall motion was initially great. Posterior wall motion is easily recorded and provides beat to beat information on ventricular position, dimension and velocity of contraction (243). Further efforts in studying posterior wall motion particularly the mean or maximum forward velocity with ventricular ejection led to the determination of standards for normal subjects at rest and with exercise (244-246). In an early study posterior wall velocity (PWV) correlated moderately well with mean circumferential shortening rate determined cineangiographically ($r = 0.76$) in normal patients but correlated poorly in patients with various forms of heart disease (244). In a subsequent investigation the effects of exercise on PWV were analysed (245). In this study changes in heart rate with exercise were found to correlate only fairly with changes in maximum PWV ($r = 0.48$) and mean PWV ($r = 0.42$). It was concluded that the significant changes in wall velocity seen with exercise reflected true alterations in contractility, inspite of the fact that some of the change occurred with increased heart rate alone (245). The suggestion that changes in posterior wall movement parallel alterations in left ventricular function was further confirmed by comparing the effects of elevated heart rate in exercise with heart rate in atrial pacing (246,247). Atrial pacing to increase hearte rate in six patients resulted in reductions of PWV in all of the patients studied. At identical rates in five patients there was a significant increase in PWV with exercise (246). Thus, the investigators conclude, PWV changes must be due to inotropic rather than chronotropic effects. The results of other

studies is, however, in conflict with this conclusion. Significantly increased mean PWV has been reported with atrial pacing in 14 patients (247). Results differed when maximal PWV was considered. Pacing in three subjects lowered maximum PWV. There seemed to be a threshold heart rate (about 110) below which PWV increased and above which it declined. These alterations appeared to be separate from inotropic influences.

Posterior wall motion has been studied in open-chest dog preparations under various physiologic conditions (248). In this study, good correlations were obtained between maximum PWV and various measures of contractility including dP/dt and (dP/dT)/peak isovolumic pressure. Conditions altering preload and afterload were found to effect PWV less than other parameters. Of note however, normal PWV was obtained despite depressed myocardial function secondary to anterior wall ischemia experimentally induced.

A more recent study has concluded that mean PWV is an unreliable index of left ventricular contractility (249). In this investigation PWV was compared to externally recorded systolic time intervals and to ejection fractions (EF) obtained from biplane left ventricular cineangiograms. Mean PWV correlated poorly with EF ($r = 0.26$), and only slightly better ($r = 0.35$) with systolic time interval contractility indices (PEP/LVET). Interestingly this study noted that echocardiographically determined EF correlated well with measures obtained by other means, but that PWV was highly unreliable.

Unfortunately at the present time there does not seem to be a clear answer to the questions of utility in measurement of posterior wall velocity. As an adjunct to most studies on wall velocity, measurements have been made on posterior wall excursion as well (245-247). The usefulness of this measure seems never to have achieved much attention, and although frequently reported is not often of significantconsideration. Many studies, however, continue to employ measurements of wall velocity as the primary means of assessing the

effects of physiologic or pharmacologic interventions, or for evaluating pathologic changes. Although these studies will continue to be of interest, their significance cannot be estimated until the usefulness of posterior wall velocity measurements is further validated in a convincing experimental fashion as well as on a primarily clinical basis.

Left Ventricular Function - Different investigators have used various methods in the evaluation of ventricular function with ultrasound. Several of these approaches will be discussed separately before concluding with a review of the more comprehensive and multi-faceted studies.

Pressure monitoring has been combined with echocardiographic volume determination to provide beat-to-beat pressure-volume plots for evaluating work of the heart (250,251). Simultaneously recorded left ventricular pressure and left ventricular wall position was recorded on magnetic tape allowing the formulation of instantaneous pressure-dimension loops. Significant alterations in area and systolic contraction velocity were induced by interventions including pacing and infusion of isoproterenol (250). Pressure-volume plots were noted to have characteristic shapes for various states studied (251). The curves were noted to be quite similar to previously derived plots using quantitative angiography. The area inscribed by the plot could be integrated to accurately measure left ventricular stroke work. Study of the diastolic filling phase of the loop allowed left ventricular compliance to be assessed. Valvular regurgitant flow could be evaluated by study of the pressure-volume plot as well (251). Classical differences have been observed between the pressure-volume plots of normals and those of patients with pressure or volume overload states (252).

Left ventricular minor axis circumference at end-systole and end-diastole can be easily calculated from echocardiographically measured dimensions. Since the duration of minor axis shortening (LVET) can be measured from the echogram

as well, the contractility index of mean velocity of circumferential fiber shortening ($V_{\overline{CF}}$) is readily obtainable by ultrasound alone (253). The $V_{\overline{CF}}$ can be then normalized for the initial internal circumference during ejection and expressed as circumferences per second; completely reduced the equation is:

$$V_{\overline{CF}} = LVID_d - LVID_s \,/\, LVID_d \times LVET. \quad (254)$$

In studies using $V_{\overline{CF}}$ determinations it has generally been found that patients with normal ventricular function can be distinguished from those with impaired function, especially if patients with left ventricular asynergy and severe mitral regurgitation are excluded (252,254,255). Removal of these latter two groups is necessitated because changes in their minor axis dimensions alone do not reliably give an accurate picture of myocardial performance as a whole. This consideration has greatly diminished the usefulness of $V_{\overline{CF}}$ calculation as a clinical tool (233). While $V_{\overline{CF}}$ by echocardiography has correlated well with angiographically determined $V_{\overline{CF}}$ and ejection fraction, it has correlated poorly with other possible measures of ventricular function such as posterior wall velocity and excusion (254). Similar results were obtained in a related study although $V_{\overline{CF}}$ was normalized for average, rather than initial, circumference (255). By combining measurements of circumferences with end-diastolic and end-systolic pressures, estimation in terms of circumferential wall stress have been made for preload and afterload (256). The correlation between echocardiographic and angiographic measurements was high ($r = 0.86$ and 0.96 for afterload and preload respectively). While calculation of $V_{\overline{CF}}$ is clearly limited as a strictly diagnostic tool, its utility is exemplified by the following conclusion of Paraskes et al. (255):

"The major usefulness of this technique will reside in the serial study of left ventricular performance in a given patient. The ability to detect early deterioration of myocardial function in patients with myocardial infarction, chronic valvular disease, etc., without the need for repeated cardiac catheterization, may prove to be of value in guiding therapy for these patients."

Recognizing the postential criticisms of using posterior wall velocity to estimate contractility, a Danish group has recently undertaken a series of investigations to adapt and validate measurements of posterior wall movement for such a purpose (257,258). In these studies the critical view point was taken that prior methods of posterior wall movement determination might be invalidated by changes of the location of the heart itself inside the thorax. A method was developed for recording ventricular wall motion in fractions of the cardiac cycle by connecting ultrasound equipment to 'on-line' computer facilities (257). Changes in movement with time (velocity) closely resembled the pressure relationship dP/dt. If wall movement was recorded and information stored as in these studies, it was concluded that similar use might be made of the first derivative of posterior wall displacement (ds/dt) as has been made of dP/dt determinations. In subjects examined at rest and with exercise, displacement of the posterior wall of the left ventricle and its derivatives (velocity and acceleration) were analysed. It appeared that heart movements other than actual contraction and relaxation contributed little to the data obtained. Thus, true myocardial activity was being measured. Displacement, maximum velocity and acceleration all were noted to rise proportionally with increasing cardiac work. Cardiac function could be estimated during different phases of a single heart cycle as well (258). While the sophisticated methodology of these investigations is currently beyond the capabilities of most workers today, these studies are significant for at least two reasons. First, prior work using mean or maximum posterior wall velocity is demonstrated to be theoretically, if not technically, valid. And second, as facilities are

expanded and as computer technology becomes more widely available similar reliable techniques may become more useful on a routine basis.

It has been suggested from studies of mitral stenosis that the rate of left ventricular filling is related to the initial diastolic slope of the mitral valve (233). This association has led to attempts at estimating left ventricular end-diastolic pressure and compliance by measuring this early closure slope (259). With decreased mitral valve slopes accurately predicting elevations in end-diastolic pressure, investigators were led to conclude that a decreased slope did, in fact, reflect impaired left ventricular filling and, in the absence of mitral stenosis, this was evidence of elevated left ventricular compliance as well. A similar linear relationship between diastolic mitral valve closure rate and left ventricular filling pressure has recently been reported (260). It has been concluded that diastolic closure rate reflects the height of the left atrial pressure and left ventricular stroke volume as well (261). These findings have been questioned by a recent study that found while diastolic closure velocity did reflect an abnormality in early diastolic left ventricular filling it was a most insensitive and unreliable measure (262). There was no relationship between slow diastolic closure and the presence or absence of congestive heart failure and only fair correlations with left ventricular end-diastolic pressure and left ventricular dP/dt in this investigation.

An emperical observation has been made regarding late mitral valve closure and its relationship to left atrial pressure (263,264). In five patients with elevated left ventricular end-diastolic pressures, final valve closure was delayed and was characterized by a prominent notch in the A to C portion of valve closure on the echogram (263). It was demonstrated that final closure of the mitral valve was interrupted as a result of an elevated atrial component to the left ventricular diastolic pressure. In a later confirmatory study it

was suggested that the A-C interval, when subtracted from the PR interval on the electrocardiogram, could serve as an accurate predictor of elevated end-diastolic pressure (264). In all 19 patients with left ventricular pressures less than 20 mm.Hg. the PR-AC interval was greater than 0.06 seconds. Conversely all 14 patients with pressures 20 mm.Hg. or greater and with an elevated atrial component of left ventricular pressure had a PR-AC interval of 0.06 seconds or less. In three patients with elevated left ventricular end-diastolic pressures but with normal or only slightly elevated atrial component pressures (normal A wave on pressure tracing) PR-AC intervals were in the range of normal. In this study various patterns of mitral valve closure and different configurations of the echogram A wave are emperically related to differing pressure situations (264). While these observations remain interesting, their usefulness has not yet been demonstrated by work in other laboratories.

No less than five different investigative groups have made comprehensive attempts to evaluate cardiac pump function and have extensively compared results with angiographically measured indices (228,231,265-267). In general, studies evaluated ventricular dimension, pump performance and myocardial function more or less separately. The usefulness and validity of dimension and volume studies have already been reviewed. Most groups examined pump function by analysing echocardiographically determined ejection fraction (EF). Statistically significant correlations between echocardiographic and angiographic EF were obtained with coefficients ranging from 0.69 (231) to 0.80 (228). In addition to EF and stroke volume, the percent change in the minor axis with systole has been considered as estimate of pump performance (265). Percent systolic change of this axis allowed excellent separation of patients with clinically normal ventricular function from those with obvious heart failure. Calculation of EF afforded no advantage over precent systolic change in separating groups of patients.

Developing reliable indices of myocardial performance has been perhaps the major goal in recent investigations. A most frequently used parameter is $V_{\overline{CF}}$. This index proved of significant usefulness in distinguishing patients with normal myocardial function from those with abnormal function (265). In general $V_{\overline{CF}}$ provided the same separation of groups as EF. However, because the dimension of time is added to the other indicators of shortening, $V_{\overline{CF}}$ differed somewhat from EF in individual cases. In particular, in two patients with signs of circulatory congestion and depressed EF the values obtained for $V_{\overline{CF}}$ were in the normal range. It was suggested that muscle function was better in these patients than could have been expected from signs alone. Conversely, several well compensated patients had low values of $V_{\overline{CF}}$. These patients may have had depressed myocardial contractility in spite of their compensated state (265). Throughout, the findings of $V_{\overline{CF}}$ echocardiographically have agreed well with $V_{\overline{CF}}$ observed under various experimental and pathologic conditions when the parameter had been determined angiographically.

Unfortunately, after $V_{\overline{CF}}$, there has been little standardization of the indices considered to evaluate myocardial function. An incomplete list of various measures studied follows: extent of shortening of LVID during ejection, total systolic shortening, shortening during ejection divided by ejection time, shortening during ejection divided by ejection time and normalized for initial diameter, mean shortening velocity of internal diameter, mean shortening velocity of internal diameter normalized for end-diastolic diameter, and percent thickening of posterior wall (266,267). Although many of these indices are very closely related to those previously mentioned such as $V_{\overline{CF}}$, EF, and percent systolic change, the calculations are altered by measuring slightly different intervals or by normalizing differently so that the values are not strictly comparable.

The clinical usefulness of a single left ventricular echocardiographic study currently appears of limited value for the functional classification of individual patients. The ability to distinguish objectively among groups of patients with clinically obvious differences has been adequately demonstrated however (265-276). As such, echocardiographic data can only provide useful additional information in the assessment of left ventricular function when integrated with other clinical and hemodynamic data. Such a use of ultrasound does not seem adequate to justify the intensive investigative efforts currently being devoted. The technique would hardly be worthwhile if it merely confirmed routine findings in physical diagnosis. Its usefulness, however, is not confined to single left ventricular studies. The future importance of ultrasound studies is emphasized in the conclusion of a recent echocardiographic function investigation:

> "The results of other investigators and our own observations suggest that a major role of echocardiography in clinical cardiology may be the monitoring of left ventricular function indexes and chamber dimensions by serial studies rather than by a single echocardiographic study. Sequential changes in these variables may provide a sensitive, non-invasive method of detecting cardiac enlargement, ventricular dysfunction or a functional response to therapeutic interventions in the individual patients." (267)

Clinical Applications of Volume and Function Studies

The advantages of using reliable non-invasive techniques for the evaluation of cardiac function in seriously ill patients are obvious. Such techniques are particularly valuable for patients with acute myocardial infarction where the performance of elaborate diagnostic techniques would be of significant stress to the individual. Thus the use of echocardiography in myocardial infarction has received such attention.

Early echocardiographic studies of acute myocardial infarction employed techniques of posterior wall motion analysis. In one study groups of patients with transmural and non-transmural infarction, examined on the first day of hospitalization, had values significantly lower than normals for posterior wall excursion and mean and maximum posterior wall velocity (268). In another hospital a prospective investigation was carried out on patients admitted to a coronary care unit with chest pain (269). Using amplitude of posterior wall excursion and mean posterior wall velocity patients with acute myocardial infarction could be distinguished from those with old but not acute infarctions, from patients with chest pain of miscellaneous origin, and from normal subjects. Patients without an acute infarction did not have values statistically different from the normal group. Alterations in the configuration of posterior wall echoes were detected in 10 of 11 patients with acute myocardial infarction. These abnormalities, consisting of mid-systolic "bulges" and unusual diastolic waves, were attributed to distortions of ventricular motion with asynergy (269). Serial changes of posterior wall motion following acute myocardial infarction have been studied as well (270). In most patients maximum posterior wall velocity fell during the first 36 hour period following infarction. A return toward normal was universally noted 24 hours later. In two patients pulmonary artery end-diastolic pressure was raised when wall velocity was depressed and both

reverted to normal levels relatively simultaneously. In a study comparing acute myocardial infarction of different locations, posterior wall velocities were noted to be lower in patients with inferior infarctions than in these patients with primarily anterior processes (271). Evidence concerning the etiology of posterior wall motion changes with myocardial infarction has been obtained in an experimental study in open-chest dogs (272). Coronary artery ligation was used to create either apical (group1) posterior wall (group 2) infarctions. Post infarct echograms in group 1 showed no significant changes in posterior wall velocities or excursion. However, striking reductions were seen in the group 2 dogs. While it remained possible that the specific contour of posterior wall motion might be of diagnostic value the following statement was made:

> "We conclude that the marked changes in posterior wall motion following posterior infarction were due to echocardiographic detection of dyskinesis in the infarcted area rather than to generalized changes in ventricular function. Posterior wall velocities are not a reliable index of left ventricular performance when localized dyskinesis, as indicated by abnormal posterior wall motion, is present." (272).

Mitral valve motion following acute infarction has been serially studied (273). Significant variations in the diastolic slopes were noted in only 24 percent of patients studied. When such abnormalities were present, however, the serial changes correlated well with clinical status. In particular, alterations in slope were associated with changes in the intensity of the murmur of mitral regurgitation due to papillary muscle dysfunction. In a more recent study the temporal pattern of mitral valve velocity changes was studied (274). In patients admitted to a coronary care unit with acute myocardial infarction echocardiograms were obtained daily for three days then at three day intervals for the remainder of the hospitalization. A basic triphasic response of diastolic valve velocities was noted with a transient increase, followed by a fall below initial values, and then a gradual rise in velocity. Biphasic

and monophasic responses were also noted. It was concluded that the temporal pattern reflected alterations in myocardial function and compliance that occurred during the recovery phase of myocardial infarction.

Changes in stroke volume and cardiac output occurring with acute myocardial infarction have been detected echocardiographically (271,275,276). In one study the stroke volume values obtained correlated highly (r = 0.90) with dye-dilution determinations on the same patients (275). Although serial measurements did not demonstrate trends in stroke volume, in one patient depression of stroke index and cardiac index occurred shortly before death (271). Following infarction, patients with elevated pulmonary artery end-diastolic pressures (greater than 15 mm.Hg) were noted to have significantly increased en-diastolic volumes echocardiographically (276). Ejection fraction was depressed in this group as well.

One study was undertaken to study changes in left atrial size following acute myocardial infarction (277). Echocardiographic determination of left atrial size correlated poorly with mean left atrial pressure determined from pulmonary artery wedge catheters. Increased left atrial diameter was detected in only two of 13 patients with elevated left atrial pressures.

Patients with coronary artery disease but without acute myocardial infarction have also been of interest to echocardiographers. Mean and maximum systolic and diastolic posterior endocardial wall velocities were analysed in a group of patients during angina pectoris (278). Studies of diastolic posterior wall motion have not been otherwise routinely reported. Findings during exercise but before angina were similar to results of other studies (245) in that systolic wall velocity significantly increased. Diastolic velocity did not change

under these conditions. During angina, however, there was a remarkably consistent slowing of the maximum and mean diastolic endocardial wall velocity while systolic velocity and excursion responded variably. Diastolic velocities returned to normal as S-T segment depression disappeared. The authors suggest that this "echocardiographic stress test" might be useful in the further study and detection of ischemic heart disease (278).

Regional left ventricular asynergy has been reliably detected echocardiographically (279). Forty-eight patients underwent left ventricular angiography and selective coronary arteriography. In 10 patients without evidence of coronary artery disease, normal echocardiograms were obtained. In 38 patients with significant obstructive coronary artery disease 25 were seen to have left ventricular asynergy on angiography. In all but one of these 25 patients echocardiograms demonstrated abnormal motion of portions of the interventricular septum and/or abnormalities of the posterior left ventricular wall. In the 17 patients with significant coronary artery disease but without apparent contraction abnormalities angiographically, eight showed abnormal echocardiograms. In addition, the location of demonstrated echocardiographic abnormalities correlated well with asynergy seen on angiography and with the location of the coronary artery obstructions. Poorest agreement occurred in lesions of the left anterior descending artery. While the results of this study are quite promising, confirmatory investigations in other's hands are of great necessity. Since this report comes from the laboratory with perhaps the greatest echocardiographic experience in this country, duplication of their results may prove difficult at the present time.

It is well known that myocardial ischemic is associated with abnormalities of left ventricular end-diastolic pressure. This association led to a study comparing left ventricular pressure with ultrasonically measured left ventricular volume during pacing induced angina (280). In normal subjects a decrease in

end-diastolic volume during pacing was associated with a significant decrease in left ventricular end-diastolic volume. Following atrial pacing, the predicted increase in end-diastolic pressure (dP) occurred with an increase in left ventricular end-diastolic volume (dV) and a mean of 24 percent above control values. End-systolic volume increased similarly with angina. Analysis of their data led the authors to conclude that the pressure elevations during ischemia were related to increased left ventricular volume and not to a decrease in compliance (280). While changes in complicance could not be excluded, the individual values for dV/dP (used to estimate compliance changes) did not appear to be related to abnormal inventricular contraction.

Ultrasound has been used in the assessment of left ventricular function following surgery for coronary artery disease (281). Post-operative echocardiographic examinations were performed both immediately and six weeks after aortocoronary saphenous vein bypass grafting. The indices of maximum posterior wall velocity, amplitude of posterior wall excursion, and ejection fraction were improved in the post-operative studies. The study therefore confirmed data of others suggesting improvement in myocardial function following bypass surgery.

It is somewhat surprising the comprehensive longitudinal studies of functional changes with congestive heart failure have not yet appeared in the echocardiographic literature. There have, however, been several non-serial studies. Twenty-four patients were examined echocardiographically seen after admission for decompensated left ventricular failure and results were compared with echocardiograms taken later, after clinical improvement (282). Posterior wall velocity, systolic and diastolic, were the only indices measured. Most patients showed increased velocities of systolic and diastolic motion following clinical improvement. Decreased diastolic mitral valve closing has been noted to be reduced in congestive cardiomyopathy, and was used to reliably distinguish

between this latter group and patients with chronic rheumatic mitral regurgitation (283). As would be expected, left ventricular volume overload of various causes are regularly associated with increased echocardiographically measured internal diameters (284,285). End-diastolic volume, in particular, has been shown to be significantly increased in patients with congestive cardiomyopathies (285). Ejection fraction in these circumstances is depressed as well (285). The sum of the amplitude of septal motion and posterior endocardial motion has been reported to be a sensitive measure in differentiating patients with congestive cardiomyopathies from normals and patients with other forms of heart disease (286). The value of echocardiography in detecting subclinical cardiomyopathy has been stressed as well (287). Echographic determination of ejection fraction and $V_{\overline{CF}}$ were found to reliably distinguish patients with myocardial dysfunction due to primary muscle disease and results were well correlated to systolic time interval determinations (287).

The serial evaluation of left ventricular performance in aortic insufficiency is a clinicall difficult problem. The question of when to perform valve surgery is a difficult one for the cardiac diagnostician unless repeated cardiac catheterizations are performed. Therefore, the potential usefulness of echocardiography with such patients is clear. Diastolic mitral valve closure rate has been found to be distinctly elevated in patients with aortic regurgitation with a return to normal noted soon after valve replacement (261). Application of this parameter or others would seem useful in studying patients with aortic insufficiency to detect the point at which serious decompensation begins. In another investigation, several indices have been examined in patients with aortic insufficiency for the purpose of evaluating the hemodynamic effects of this lesion (288). Aortic valvular flow was estimated from left ventricular cavity minor axis changes. This was compared to mitral valvular flows estimated from

the opening velocity of the mitral valve. The difference in estimated flows provided a measure of regurgitant flow. Also studied was left ventricular performance by measuring the velocity and amplitude of systolic posterior wall excursions and by computing V_{CF}. The above flow calculations were based on many unproven assumptions and provided rough estimates at best. However, the data presented appeared to support the usefulness of such simple non-invasive methods for serial observation of the hemodynamics and function in patients with chronic aortic regurgitation.

Various ultrasound methods have been applied to the evaluation of the effect of pharmacologic and physiologic interventions potentially altering cardiac function. Left ventricular posterior wall motion was analysed in 19 patients given vasoactive drugs at the time of cardiac catheterization (289). Isoproterenol produced significant changes in systolic posterior wall excursion (16 percent), mean posterior wall velocity (54 percent), and maximal posterior wall velocity (73 percent). Atropine produced equivalent changes in two patients studied except for a slight fall in wall excursion. Demonstration of isoproterenol's positive inotropic effects were produced by plotting maximal posterior wall velocity against essentially simultaneous left ventricular systolic pressure changes. Methoxamine produced slight decreases in all posterior wall motion parameters.

Reuctions in left ventricular volume have been demonstrated following the administration of amyl nitrite and nitroglycerin (290). With both drugs end-systolic volume fell to a greater extent than end-diastolic volume. It was concluded that volume changes with these vasodilators may contribute to their beneficial effects in myocardial ischemia. Another study has confirmed these volume changes and noted an increase in V_{CF} as well with nitroglycerin (291).

The effect of isometric handgrip on left ventricular size and function has been evaluated echocardiographically (292). Significantly increased cardiac index was observed, without significant changes in end-diastolic volume or stroke index. Thus it was concluded that the response to handgrip was through tachycardia with significant volume changes not being detected in the normal heart.

Echocardiographic studies of altering posture to the upright position has been reported in six normal subjects (291). Tilting significantly reduced end-diastolic and end-systolic dimensions. Myocardial performance as estimated by $V_{\overline{CF}}$ was unaltered.

In general, the detection of anticipated changes in left ventricular volume and function has been easily and reliably accomplished by echocardiography. It may be expected that ultrasound methods will frequently be used in similar future investigations.

CURRENT STUDY

The preceeding pages present two points of overall importance which provide background as well as impetus for the current study. The first is that most facets of cardiovascular disease including diagnosis, treatment and pathophysiologic understanding, depend on the recognition and elucidation of hemodynamic status and myocardial performance. The foundation of investigations of such status and performance clearly lie in the field of invasive cardiology and, specifically, cardiac catheterization. The second point of significance is that today echocardiography has become firmly established as a reliable and safe non-invasive investigative technique. It is apparent from the preceeding discussions that the acceptance of the usefulness of echocardiography extends beyond the recognition and assessment of cardiac lesions such as mitral stenosis. Echocardiographic measurements of function and volume status are now frequently employed.

The importance of evaluating hemodynamics and myocardial performance, coupled with the attractive possibility of doing so non-invasively led to the initiation of this study. The usefulness of echocardiographic techniques has been limited when applied to the serial study of clinical states. Most accepted are the multiple, short term follow-up studies for pericardial effusions (162). Serial echocardiograms were also reported recently in a study of papillary muscle dysfunction following acute myocardial infarction (273). Other workers have begun to examine different parameters following myocardial infarction serially. This has most recently been done by studying the changes in mitral valve opening velocity (274). Changes with physiologic (exercise) on pharmacologic (isoproterenol, amyl nitrite, and nitroglycerin) interventions continue to be studied (289,290,292). Echocardiographic examinations pre- and post- operatively

represent another aspect of usefulness serially. Surgery for rheumatic heart disease, coronary artery disease, and idiopathic hypertrophic subaortic stenosis have all been studied longitudinally (135,171,281). It is obvious then, that, as echocardiographic techniques for the study of ventricular performance have been more meaningfully and reliably worked out, it has become clear that such methods would be extremely useful in serial studies. This is particularly true in terms of the ability to detect changing myocardial status and pump function without the need to perform repeated cardiac catheterizations.

Such a possibility is the basis for this research. To be considered are physiologic and pathologic states of "fluid overload." Clinically the most important fluid overload condition is that which involves congestive heart failure.

Based on the principle that hemodynamic and myocardial changes associated with heart failure are relatively constant, despite the varying causes or initiating events, it is anticipated that echocardiography might be useful in the assessment of failure. These changes might not be quantitatively recognizable on a single examination because of the technical difficulties associated with reliably measuring hemodynamic and contractility parameters. However, approaching the problem in a serial study fashion might be expected to give quantifiable information on patients changing status. Echocardiography, then, as a non-invasive but direct way of looking at functioning heart chambers and wall movements, potentially can provide valuable information regarding the state of congestive heart failure and its progressive changes with treatment. The existing body of echocardiographic investigations shows ample justification of the validity of volume and function study. Non-serial investigations of congestive cardiomyopathy have already been undertaken (282-286). Evidence

correlating clinical findings with echo results must be shown to demonstrate the diagnostic and therapeutic usefulness over time of this new tool.

Presently, however, there are methodological problems involved with the study of patients with congestive heart failure. Results from the serial study of two such patients are included here. However, because of difficulties in communication, constraints of time, and consideration of patient care priorities a series of patients in severe congestive heart failure large enough to attempt statistically significant analyses has not been accumulated.

A twofold approach was taken to make up for the deficit of direct information on patients with severe congestive heart failure. First, to validate the reproducability of serial echocardiographic examinations, data is presented from normal controls studied on consecutive days or at time intervals. Second, other conditions of fluid overload were examined. Specifically, patients undergoing hemodialysis or peritoneal dialysis were studied at points in their routine course. Included are data obtained at the initiation of dialysis, immediately prior to the finish of dialysis, and at the initiation of the next dialysis. Also, groups of normal subjects and patients with coronary artery disease were examined prior to and during a leg raising maneuver.

Dialysis was chosen because of the dramatic volume changes associated with the procedure. It is assumed that the volume changes with dialysis are well correlated in echocardiographic terms with the volume changes of congestive heart failure. In fact, successful treatment of intractable failure by peritoneal dialysis has been well reported (74,76). By examining these dialysis patients, rapidly changing fluid states were able to be studied in the non-acute medical setting.

Straight leg raising is well known as a physiologic intervention to increase venous return. As has been discussed, it is assumed that this maneuver

results in an "auto-transfusion" of approximately 300-600 ml (80). Thus, another easily accessable group of subjects were studied in whom the true volume and function changes were expected to be reflected in the echocardiographic evaluations.

In summary the aims of this study were twofold:

1. Echocardiographic analysis of serial volume and function changes occurring in conditions of acute or chronic volume overload states including a) dialysis; b) straight leg raising; and c) congestive heart failure.

2. Validation of serial study echocardiographic techniques in normal individuals examined at 15 minute and 24 hour intervals.

METHODS

Population

Normal Subjects - Control subjects consisted of seven normal volunteers. All were males between the ages of 22 and 26, and all were in good health without a history of severe illness or cardiovascular disease. Complete echocardiographic examinations were performed on six subjects on five consecutive days for each. They were examined at the same time of day, were requested to eat a consistent diet prior to examination, and were asked not to perform strenuous exercise preceeding the study. The daily routine was nearly the same for each control on each day. All normals were medical students or technicians and most were examined at mid-day before lunch. The seventh normal control was subjected to complete echocardiographic examainations at fifteen minute intervals over a two hour period, with a total of eight studies being performed. During the intervals when not being examined the subject rested quietly.

Dialysis Patients - Five patients admitted to the Yale-New Haven Hospital Renal Service for chronic hemodialysis and four undergoing chronic peritoneal dialysis were studied. The hemodialysis patients were selected on the basis of three criteria. First, their condition had to have been chronic, without a superimposed acute process and without serious cardiovascular disease (one patient was excluded because of the presence of a surigcally placed pericardial window, two patients had long standing hypertension with moderate left ventricular hypertrophy but were not excluded). Second, attention was directed to the usual weight loss during dialysis and patients whose dialysis goal was to remove as little fluid as possible were excluded. All hemodialysis patients lost between two and six and a quarter pounds during dialysis (mean $\pm$ SD : 3.7 $\pm$ 1.1 lbs.) Peritoneal dialysis patients' weight decreased between three and nine pounds (5.3 $\pm$ 2.3 lbs.)

All patients routinely loosing greater than two pounds were studied. The final criteria was patient acceptance of the procedure. The purpose and details of the echocardiographic study were explained to each subject and permission to perform the examination was requested. No patient refused initially and thus none were excluded. However, when nausea and vomiting occurred during the course of one patient's hemodialysis he requested not to be re-examined at the conclusion of dialysis and his initial data are not included.

All dialysis patients (nine) were examined just after dialysis had begun and immediately prior to the conclusion of the procedure. Care was taken with peritoneal dialysis patients to make sure that each was examined between exchanges so that the abdomen was empty of dialysate during echocardiography. Four of the five hemodialysis patients were studied on two different occasions. Combining all pre- and post-dialysis studies, a total of 13 pairs of studies were obtained.

Following hemodialysis approximately 400 ml. of blood remains in the dialysis apparatus; this is slowly (five minutes) reinfused back into the patient at the conclusion of the procedure. Serial examinations were performed before and after this infusion a total of five times in three separate patients.

Four hemodialysis patients were examined at the conclusion of one dialysis and at the start of the next. The interval between dialyses was two or three days in all cases. It was felt that this group would potentially present the reverse of those changes seen with dialysis, only under more chronic conditions (48-72 hours instead of 6-24 hours.)

Hemodialysis patients were younger than peritoneal dialysis patients (Hemodialysis: 27 years, mean; 18-35 years, range.) In general, except for their chronic renal failure, the hemodialysis group was in better health than the older, more chronically ill peritoneal dialysis group. No patient studied was acutely ill.

Leg Raising Subjects - Two groups of subjects were studied before and during a straight leg raising maneuver. The first group was made up of five normal subjects. A second group consisting of five patients with ischemic heart disease and without clinically detectable valvular pathology was examined. Procedures were identical for all ten subjects. The first echocardiographic examination was performed after subjects had rested for ten minutes in the supine position with their legs dangling over the end of the examaination table. This was done so that an initial stable state was assured. Subjects' legs were then raised to an upright position. Leg support was provided to prevent the performance of an involuntary Valsalva maneuver. The second echocardiography examination was performed with subjects resting in the leg up position.

Congestive Heart Failure Patients - Two patients in severe decompensated congestive heart failure admitted to the coronary care unit at Yale-New Haven Hospital were studied as well. The first patient (#1, Figure 9) was a 55-year-old man who had been hospitalized on several previous occasions for congestive heart failure. The etiology of his congestive failure was uncertain, but was presumed to be on the basis of an alcoholic cardiomyopathy. He was discharged from the hospital after five days of diuresis and rest. The second patient (#2, Figure 11) was hospitalized for a total of eight days. He was a 78-year-old man with a history of an anterior myocardial infarction one year prior to this hospitalization. He had had a six month history of moderate shortness of breath which became acutely worse the day of hospitalization. The patient was admitted in pulmonary edema. The suspected diagnosis of a second myocardial infarction was not confirmed by enzymes or ECG changes. He was discharged following diuresis and symptomatic improvement. Both patients had been digitalized and given diuretics prior to their current admission. Neither patient had a history of hypertension or evidence of valvular cardiovascular disease. Complete echocardiographic examainations were performed daily on both patients.

Equipment

Echocardiographic examinations were performed using a commercially available ultrasonoscope (Unirad Series "C" Echocardiography System with Tectronix continuous hard copy strip recorder.) The system utilizes pulsed ultrasound with a repetitive rate of 1000 impulses per second, and 1/2 inch, 2.25 MHz. crystal transducers focused at 5, 7.5, or 10 cms. Theoretically, the longer focal length transducers should be more appropriate for thick chested or obese individuals and the choice of transducer for each subject was based upon this principle. However, there existed no objective or subjective difference in signal image in this study, regardless of the transducer selected. Echocardiograms were displayed simultaneously in the "A" (Amplitude Modulation) mode on one oscilloscope and in the "M" (Time-Motion) mode on another oscilloscope with storage capabilities. They were recorded on the strip recorder (black on white) at 50 mm./sec., or on Polaroid film pictures taken of the "M" mode displayed on the storage oscilloscope. A simultaneous ECG was also recorded in most cases.

Examination Techniques

The echocardiographic technique for visualizing cardiac structures, although standardized, varies with each patient examined. Patient position, signal intensity and transducer location are slightly different in each subject. The following discussion relates the standardized approach for each echocardiographic examination used in this study. The constant goal of optimal visualization served as the end point for adjustments in positioning, echo gain and transducer angle. Initially all subjects were examined in the semi-recumbent position at approximately 30-45^{o}. Later, subject position was adjusted to a partial or complete left lateral decubitus if good quality echoes were not otherwise obtained. A small quantity of water soluble "Aquasonic" transmission gel was placed on the transducer tip, with more gel added later in the examination

if extensive transducer manipulation and alternate placements had been necessary. This gel produces airless contact between transducer and chest, facilitating the transmission of ultrasonic impulses.

The transducer was first placed in the third intercostal space as near to the left sternal border as possible. In some subjects, usually small individuals with normal cardiovascular systems, good quality echograms could be obtained in this interspace. However, most required repositioning of the transducer in the fourth or fifth interspace before intercardiac structures could be recognized. The transducer was directed posteriorly, slightly medially, and slightly superiorly until well defined echoes characteristic of the anterior leaflet of the mitral valve were visualized (Figure 2B). For a complete echocardiographic study, strip chart recordings were made with several different transducer angulations from this initial position (Figures 2A,C). These recordings were taken following angulation only. Once the best transducer position was determined at the outset, it was not moved from that point on the chest wall, but simply angled in various directions. The one exception occurred during examination of the aortic root region and will be descrobed below. The examination consisted of three segments. 1) The transducer was angled to provide maximum anterior mitral valve excursion and diastolic slope (Figure 2B). Also a view of the valve was recorded so that echoes from the anterior leaflet could be seen throughout systole and diastole. This was usually obtained at an angle slightly inferior to that used for maximum valve excursion. 2) The transducer was then directed laterally and inferiorly until optimal echoes from the septum and posterior left ventricular wall could be observed simultaneously (Figure 2A). As part of the standard technique, echoes from this position were recorded only if inferior portions of the mitral valve apparatus were visible. This was done, as it is by most other investigators, to insure that interventricular measurements are taken from a reasonably standardized location. It is of importance that both

endocardial and epicardial echoes be visible in this position. A sudden gain attenuation at this point in the examination aided in the identification of such posterior heart wall echoes (Figure 10B) The interventricular septum was also visualized in this position. Once left ventricular echoes were well seen, minor adjustments in the gain controls and very slight angling of the transducer invariably produced a visible band of nearly parallel echoes approximately 3 to 6 cms. anterior to the left ventricular wall echo and 1 to 4 cms. posterior to the broad band of chest wall echoes. This band of echoes represented the septum. Left ventricular (LV) cavity echoes were obtained by the "T-scan method" (175). Acquired by this method were optimal "major sweeps" (to obtain maximum LV diameter in the superior-inferior axis) and "minor-sweeps" (to obtain maximum LV diameter in the medial-lateral or short axis once the best major sweep has been determined.) 3) The final segment of the echocardiographic examination involved superior and medial angulation of the transducer from the initial position. This maneuver usually produced easily definable echoes from the aortic root, often with two of the three aortic cusps visible in portions of systole and diastole (Figure 2C). If a good quality echogram could not be obtained by such angulation, then the transducer was repositioned an interspace higher, where invariably aortic root echoes could be obtained. This was the only time that the transducer was moved, rather than angled, once the initial optimal position was located. Aortic root to mitral valve scans were obtained in all patients to demonstrate aorto-mitral continuity (Figure 1). This was done simply by angling the transducer between the two positions while strip chart recordings or polaroid pictures were being obtained.

The ultrasound controls were adjusted constantly during the course of an examination. The time gain compensation controls or "ramp" was adjusted so that the slope was maximal and the initial point of deflection was located at the anterior margin of the septum. The amount of near field attenuation was

varied so that the right side of the interventricular septum could be identified and, if there was a definable right ventricular (RV) cavity, so that anterior RV wall could be visualized. The main attenuation control and reject control were manipulated so that clearly visible left interventricular septum, endocardium and epicardium could be recorded. When necessary, the main attenuation was further reduced to view the mitral valve throughout systole and diastole.

Electrocardiogram gain and position controls were varied so that the ECG could be seen during the echocardiographic recordings.

Echocardiographic Measurements

Each echocardiogram contains time and distance calibration points as shown in Figure 2A. Diastolic opening velocity and initial diastolic closing velocity of the anterior mitral leaflet were measured by calculating the slope, in centimeters per second, of tangents to the valve echo during the appropriate period. Opening velocity is therefore equivalent to the D-E slope, and closing to the E-F slope. The tangent lines for these slopes can be seen in Figure 2B. Amplitude of opening in centimeters was measured from the same echocardiogram, as indicated. The A to C interval was measured in seconds and was subtracted from the PR interval obtained from the simultaneous ECG. Height in centimeters of the A wave was also measured. This measurement was made twice, using both the F point and C point for reference.

Diastolic left ventricular diameter ($LVID_d$) was measured at end diastole as determined from the initial QRS deflection of the ECG. If the ECG was unavailable, $LVID_d$ was then taken at the point just prior to the small posterior notch in the posterior left ventricular wall, known to occur at the onset of electrical systole (Figure 2A). Left ventricular internal diameter in systole ($LVID_s$) was measured from the most posterior point of the interventricular septum. This usually occurred just before the most anterior excursion of the posterior left ventricular wall. It has been established (266) that in systole, during the interval between the most posterior excursion of septum and the most anterior of LV wall, the septum and posterior wall move in a parallel fashion and diameter does not change. Therefore, $LVID_s$ taken any time during this interval would be reliable. Right ventricular diameter ($RVID_d$) was measured at end-diastole as determined from the ECG also.

Maximum posterior LV endocardial wall velocities were measured in centimeters per second with both contraction during systole (PWVant) and relaxation during diastole (PWVpost) as shown by the tangents drawn in Figure 2A. Posterior

LV wall (PWT_d, PWT_s) and septal (ST_d, ST_s) thicknesses were measured at end-diastole and at the point of maximal systolic thickening. These can been seen in Figures 2A and 2B respectively. The amplitude of endocardial excursion was measured as well (Figure 2A).

Left ventricular ejection time (LVET) was also determined directly from the echocardiogram. As is shown in Figure 2A, LVET was measured from the point of posterior deflection of endocardium at end-diastole (or from the ECG if available) to the point of maximum systolic endocardial excursion.

Finally, measurements were made of left atrial and aortic root size. The aortic width was measured at end-diastole. The maximum diameter seen was used as an estimate of left atrial size. These parameters were obtained with the transducer in the aortic position and can be seen in Figure 2C.

Additional derived data was calculated from measurements taken directly from the echocardiogram as indicated above. Diastolic volume (LV_{vol-d}) was calculated as the cube of $LVID_d$, and systolic volume (LV_{vol-s}) as $LVID_s^3$. For stroke volume (SV), end-systolic volume was subtracted from end-diastolic volume ($LV_{vol-d} - LV_{vol-s}$); and for ejection fraction the SV was divided by LV_{vol-d}. Percent systolic thickening for both the septum (ST) and the posterior LV wall (PWT) was calculated as the difference between systolic and diastolic thicknesses, divided by the diastolic thickness, and multiplied by 100 (i.e., $ST = (ST_s - ST_d / ST_d) \times 100$). As a reliable index of left atrial size (LAI), to compensate for changes with angulation, the atrial-aortic root diameter ratio (LA/Ao) was calculated. Finally, the mean velocity of circumferential fiber shortening in circumferences per second was calculated as follows:

$$V_{CF} = LVID_d - LVID_s \; / \; LVID_d \times LVET.$$

Clinical Information

Brief physical examinations were performed on all normal subjects to detect significant, particularly valvular, cardiovascular pathology. The dialysis patients and the five patients with ischemic heart disease were examined as well. Weight loss was recorded for all dialysis patients. In those being dialysed peritoneally, records were kept of fluid loss.

Extensive daily physical examinations were performed on the two hospitalized patients with decompensated congestive heart failure. Evidence was recorded of changing physical signs reflecting changing fluid overload status. In addition, records were kept of relevant laboratory data, serial weight changes, daily diuresis, and alterations in the cardiao-thoracic ratio as determined from routine chest X-rays. Therapeutic regimens were noted.

Statistical Analysis

Analysing the data from the normal control subjects examined serially was an awkward task. In a sense this part of the study was done to demonstrate lack of significant differences on daily examinations to thereby validate the reliability of echocardiographic techniques for serial purposes. Such validation was attempted in two ways. First, daily values of all subjects were tested for significant differences with the values of the subsequent and the preceeding day. All values from day one were matched with day two and tested, then day two with day three and so on. The student's T test for paired observations was used (293). Thus, p values were obtained for all adjacent pairs of days. A high or non-significant p value was interpreted as evidence for the lack of significant daily variation. Although day-to-day correlations could have been obtained, this was felt not to be relevant, for it was not correlation that was sought as would be appropriate for two measures of the same parameter (e.g., echocardiographic volume with angiocardiographic volume.) Also calculated were the mean, standard deviation, and standard error of the mean for each subject over the five days tested. A mean of the six subjects' means, standard deviations, and standard errors was computed as well. Small standard deviations and standard errors for each subject, as well as for all together, could then be cited as further evidence for lack of high variability.

Since T testing could obviously not be performed on the one subject examined at fifteen minute intervals, one additional calculation was made (beyond obtaining mean, standard deviation and standard error of the mean.) Size of the standard deviation in terms of the mean (SD/mean x 100 = % SD of the mean) was calculated for each echocardiographic measure in this subject.

The remainder of values to be statistically tested all involved the comparison between two states for groups of subjects. Thus, a simple T test

for paired observations could be performed, with a p value obtained to demonstrate statistical significance. Means and standard errors of the mean were also computed.

As previously mentioned the data accumulated on patients with congestive heart failure was insufficient for statistical analyses.

RESULTS

Complete echocardiographic studies were obtained in 27 individuals for this report. A total of 105 examinations were performed in these subjects. In some hemodialysis patients a single study was often used in two different comparison categories (e.g., a final dialysis echocardiographic study was used for the pre-, post- comparison, and for the post-, post infusion comparison.) Thus Tables 3-5 which report the data on these patients containe some overlap. The usual time necessary for a complete study, including analysis of data averaged approximately one hour, but varied considerably. Particularly on examinations subsequent to the first, the time required was much less than one hour and, rarely, as little as twenty minutes was necessary. On several patients encountered, good quality echocardiograms were most difficult to obtain and significantly more than the usual hour of study time was required. Such patients tended to be obese or to have respiratory difficulties. Respiration problems affected the study in two ways. In patients with chronic obstructive lung disease, good quality echoes are difficult to obtain because of the attenuation of the ultrasonic energy caused by absorption in an increased amount of air containing tissue. Also, patients in respiratory distress tend to breath rapidly and vigorously creating an excess of artifactual movement which temporarily obscurs echoes of intracardiac structures.

The selection process for patients has already been discussed. No patient was excluded from the study once the echocardiograph examination was undertaken. This is unusual, for most authors report a 10 to 15 percent incidence of patients in whom echocardiograms are unobtainable. A lack of such patients in this study can be attributed to the careful selection process, which undoubtedly excluded those patients in whom there existed a high probability of obtaining poor echocardiograms.

As is apparent from previous discussions, the echocardiographic field is repleat with investigators studying and searching for new and better measures of hemodynamic status and myocardial function. Therefore, from the outset all conceivable data was recorded from each subject's echocardiogram. Simple scanning of the echogram and the data revealed several of these measurements or calculations to be unreliable. When three different complexes from the same echocardiogram could be analysed for a particular index and was found to vary by as much a 100 percent from one beat to the next, such indices were excluded from further analysis. These included measurements of the amplitudes of the posterior LV wall, mitral valve excursion and A wave height. Also excluded on this basis were measures of the AC interval, and PR minus AC interval. Right ventricular internal diameter, although important in certain circumstances, was likewise of no value in this study. Of the 18 remaining measures or indices all but four are reported for normal controls studied. These include: $LVID_d$, $LVID_s$, LV_{vol-d}, LV_{vol-s}, SV, PWV_{ant}, PWV_{post}, % PWT, % ST, D-E slope, E-F slope, EF, $V_{\overline{CF}}$, and LAI. Not reported are ST_d, ST_s, PWT_d and PWT_s. Internal variance appeared great for these latter four parameters, and if significant information were to be obtained it should have been available from percent ST and PWT alone. Posterior wall thickness itself is, of course important in certain disease states such as IHSS, but was not relevant to the results of this study.

Based on the results with normal controls the indices for systolic septal and left ventricular posterior wall thickening were clearly unreliable in this study, and were therefore excluded from further analyses. For each study state comparison, six categories of values (direct measures or derived indices) are represented graphically (Figures: 3, 5, 6, 7, 8.) Those chosen were the most reliable values or were ones frequently reported in other studies; they include: LV_{vol-d}, SV, PWV_{ant}, E-F slope, $V_{\overline{CF}}$ and LAI. For the two patients in congestive

heart failure, four of the above six values were chosen to be represented graphically with the clinical data from those patients (Figures 9, 11). Two function measures, $V_{\overline{CF}}$ and LAI, and two volume parameters LV_{vol-d} and SV are recorded in these figures.

Figures 1 and 2 show echocardiograms that together comprise a complete ultrasound study. Equivalent pictures were obtained for each subject on each occasion examined. Figure 1 is a complete mitral-aortic scan as was performed on each subject. All significant intracardiac structures appear in this echogram and are appropriately labelled. The portion of this strip chart recording on the left was obtained with the transducer aimed posteriorly and slightly inferiorly and laterally. Sharp echoes from both mitral leaflets as well as from the endocardium and epicardium are well seen. As the transducer was gradually angled superiorly and medially continuity was demonstrated between the interventricular septum and the anterior aortic root, and between the anterior mitral leaflet and the posterior aortic root. At the far right of Figure 1 the aortic root is visualized, with echoes appearing from two aortic cusps and the left atrium posteriorly. Figure 2 demonstrates the three echocardiographic angulations that are standard and have been described above, with A being from the most inferior-lateral transducer angulation, B from mid-ventricle with the transducer directed posteriorly, and C from the superior-medial angulation.

Normal Controls - Daily Examinations - Reproducedin Table 1 are the individual values, means, standard deviations (SD), and standard errors of the mean (SEM) for all subjects for the 14 echocardiographic measures and calculated indices. The direct measurements of internal diameter showed little day-to-day variation in different individuals. This was evidenced by the average SD for $LVID_d$ of 0.4 cm, and for $LVID_s$ of 0.2, both quite small. The average of the means for $LIVD_d$ (thus the mean of a total of 30 determinations of $LVID_d$) was 4.8 cm. This

is close to the normal adult value reported in Feigenbaum's text (294) of 4.6 cm. The overall range of $LVID_d$ was 4.0 - 5.8 cm. which is also close to Feigenbaum's range of 3.5 - 5.6 cm. None of the interval diameter measures or the indices derived directly from these measures (LV_{vol-d}, LV_{vol-s}, SV, EF) showed day to day statistically significant differences. However variability was greatly increased when the diameters were cubed. Standard deviations went from being approximately eight percent of the mean with diameter measurements, to greater than 20 percent for stroke volume. The daily variability for these above values appeared consistent within different categories. That is, all subjects showed a small SD and thus low variability for $LVID_d$, while all demonstrated a consistently higher SD for SV.

Measures of posterior wall velocity, while not as consistent as $LVID_d$ and $LVID_s$ were also clearly reproducable on daily examination. Although minor statistical significance ($p < 0.2$) was demonstrated between day one and day two for PWV_{ant}, overall the values were quite consistent with a mean SD of 1.0 cm/sec for an overall mean of 7.6 cm/sec. While this mean resting PWV_{ant} is greater than the values of 4.1 and 3.7 cm/sec. reported for normal resting individuals previously (245,246), other investigators were most probably measuring epicardial wall velocity and not endocardial velocity as was studied in this work. PWV_{post} with a mean SD of 3.9 cm/sec. for an overall mean of 18.0 cm/sec. showed much greater day-to-day change and was often inconsistent with the PWV_{ant} changes.

Changes in systolic thickening of the septum and posterior wall were grossly unreproducable. Posterior wall thickening for one patient varied by greater than 300 percent of the original value going from 57 percent to 200 percent in three days. In spite of the fact that statistically significant daily differences were not demonstrated the SD was always quite high for both PWT and ST. In one subject (no. 6) the SD of PWT (68%) was greater than half of the mean itself (113%). Variability was high for all subjects for both ST and PWT.

Mitral valve opening velocity demonstrated moderately high reproducibility while initial closing velocity showed consistency of a lesser degree. Overall mean for D-E slope was 38.4 cm/sec. (mean SD was 5.2 cm/sec) and for E-F slope was 15.2 cm/sec (mean SD was 2.7 cm/sec.) In making the calculations of slope it was noted that beat-to-beat variability (not shown in Table 1) was great for D-E slope but if care was taken to always choose the steepest slope seen, these internal variations could be significantly reducted. There was less internal inconsistency when calculating E-F slope, but the same principle for slope selection was followed. Although standard deviations were moderatly low for three subjects E-F slope (1.6 - 1.9 cm/sec), the other three had a much greater SD (3.2 -4.3 cm/sec) all with comparable means (15.2 $\pm$ 0.5 SEM). Half of the subjects, then, demonstrated low variability while the remainder showed high variability for this measure. Also, statistical significance, though small, was demonstrated between days one and two. Therefore, although E-F slope appeared more reliable than D-E slope, its overall reproducibility remains questionable.

Ejection fraction proved to be one of the most reliable of all indices with an average mean of 0.67 and an average SD of 0.06 (SD less than 10 percent of the mean.) Mean velocity of circumferential fiber shortening was less consistent. However reliability was impossible to evaluate since this sensitive index may have been accurately reflecting normal physiologic changes in contractility that were clinically unrecognizable and that were not seen in changes of other indices. Suggestive of this was the fact that $V_{\overline{CF}}$ for subject no. 1 was highly consistent with an SD of 0.02 circ./sec. for a mean of 1.22 circ./sec. On the other hand, subject no. 5 demonstrated great variability (mean 1.22, SD 0.37 circ./sec.). It seems unlikely that the index would be reliable in one patient and not in another. More probable is that the patient with a variable $V_{\overline{CF}}$ was undergoing dynamic changes in inotrope state while the other

patient was stable. The mean of all values was 1.14 circ./sec. and the mean SD was 0.15 circ./sec. LAI appeared to be highly reproducible as an index as well, with an overall mean of 1.06 and a low average SD of 0.08.

Normal Control - Quarter Hour Examinations - The results of serial echocardiographic examinations performed at 15 minute intervals on a single subject are shown in Table 2. The values closely parallel those obtained on the six controls examined daily (Table 1). For each echocardiographic measure or index, percent SD of the mean is reported with the lowest (therefore most consistent values) found for EF (2.8%) and the highest (least consistent) for PWT (30.6%). Again, internal diameters and indices obtained from them were highly reproducible in serial studies, with SD/mean X 100 being quite low for $LVID_d$ in particular (4.1%). The mean ($\pm$SD) $LVID_d$ was 4.9 $\pm$ 0.2 cm. and the mean SV was 85.7 $\pm$ 13.3 ml. The values for PWV_{ant} (7.9 $\pm$ 1.0 cm/sec) were slightly more consistent than for PWV_{post} (15.8 $\pm$ 2.4 cm/sec.). Systolic thickening percentages were unacceptably variable, with percent SD of the mean nearly 30% for both ST and PWT. Based on the overall poor reproducibility of the systolic thickening values, these two indices were excluded from further analyses. Ejection fraction (0.71 $\pm$ 0.02) was again more consistent than $V_{\overline{CF}}$ (1.34 $\pm$ 0.11 circ./sec.) as a function index. Only D-E slope was found to demonstrate much greater variance than that seen with six control subjects. For D-E slope the percentage SD of the mean was 23.3% for this single control subject but was 13.5% for the six subjects overall. The E-F slope however proved to be more reproducible in the single subject, with a percent SD of 11.4% and 17.8% for the six normal controls.

Pre-Dialysis - Post-Dialysis - The echocardiographic changes recorded with dialysis are included in Table 3. Results are presented on nine patients studied a total of 13 times (subject numbers 2 - 5 were studied on two occasions each).

Significant changes (with p values at least <0.05) were demonstrated for the following: $LVID_d$, $LVID_s$, LV_{vol-d}, LV_{vol-s}, PWV_{ant}, E-F slope, and LAI. There were no significant changes among PWV_{post}, D-E slope, EF, or $V_{\overline{CF}}$. As expected, diameters and volumes decreased with the change in $LVID_d$ being highly significant ($p<0.0005$) and going from a mean ($\pm$SEM) before dialysis of 5.0 ± 0.2 cm. to 4.4 ± 0.1 cm. after dialysis. Initial posterior wall velocity increased significantly ($p<0.025$) from 8.0 ± 0.7 cm/sec. to 9.8 ± 0.9 cm/sec. Also impressible was the fall in LAI from 1.16 ± 0.05 to 1.05 ± 0.03 ($p<0.025$). The changes in six selected measures and indices are represented in Figure 3, with the fall in LV_{vol-d}, in the upper left corner, seen most dramatically. The change in left ventricular internal diameter can be readily appreciated from the representative echocardiograms shown in Figure 4 (from patient no. 2, examination b). The significant change from the pre-dialysis state (A) to the post dialysis state (B) is apparent even without noting the measurements as indicated. The increase in PWV_{ant} can also be seen by observing how much steeper the initial systolic endocardial slope is in B than in A.

Post-Dialysis - Post-Dialysis Plus Infusion - Data is shown in Table 4 from three patients with a total of five pairs of studies comparing echocardiographic findings at the end of dialysis with values obtained following the 300-500 ml. infusion from the hemodialysis apparatus. Significance could be demonstrated for three parameters only: $LVID_s$ increased from 2.9 ± 0.2 cm. to 3.1 ± 0.2 cm. ($p<0.10$), LV_{vol-s} went up from $25/3 \pm 4.5$ ml. to 30.8 ± 5.2 ($p<0.025$), and D-E slope rose from 40.9 ± 12.4 cm./sec. to 51.0 ± 3.9 cm./sec. ($p<0.01$). As can be seen in Figure 5 which graphically represents the six chosen measures and indices, most values showed little or no change. As can be appreciated from Figure 5, it was this lack of change rather than variable changes in different directions among subjects that contributed to the lack of statistically

significant alterations for this group. It should be noted that LAI did rise slightly, as would be expected, but the change was not significant.

Post-Dialysis - Pre-Next Dialysis - Table 5 contains the data from this group of four patients studied at the conclusion of dialysis and at the start of their subsequent dialysis. Significant changes were demonstrated in all volume categories including $LVID_d$, $LVID_s$, LV_{vol-d}, SV and LAI, but in none of the other categories. Greatest changes were seen in $LVID_d$ which increased from 4.2 ± 0.2 cm. to 5.0 ± 0.3 ($p<0.01$). As can be appreciated from Figure 6, for at least E-F slope (9.4 ± 0.6 cm./sec. to 13.2 ± 2.9 cm./sec.) and $V_{\underline{\quad}CF}$ (1.23 ± 0.08 circ./sec. to 1.13 ± 0.15 circ./sec.) the lack of significant change (p = NS for both) can probably be explained by the variable course of change among subjects with one patient changing opposite to the remaining three. In general, the changes seen between dialyses were reciprocal to those with dialysis as is clear by comparing Figures 3 and 6.

Leg Raising - Normals and Patients - The results of serial echocardiograms done before and during straight leg raising are shown in Tables 6 and 7 for normals and patients with ischemic heart disease respectively. Diastolic diameter and volume increased significantly in both normals and patients with LV_{vol-d} in the normals going from 84.6 ± 6.2 ml. to 96.8 ± 7.2 ml. ($p<0.05$), and $LVID_d$ in patients increasing from 4.2 ± 0.3 cm. to 4.7 ± 0.4 cm. ($p<0.025$). Interestingly systolic diameters and therefore volume did not significantly increase in either group. Stroke volume did, as expected, increase, in the patients going from 5.2 ± 8.2 ml. to 67.6 ± 8.4 ml. ($p<0.025$), and in normals from 56.7 ± 3.3 ml. to 71.3 ± 7.15 ml. ($p<0.05$). Velocities and function indices were not, however, significantly altered by the leg raising maneuver in either normals or patients. With minor variations, most measures and indices did not respond differently in the normal versus the patient group. Most apparent from Figures 7 and 8 was

the fact that patients with coronary artery disease displayed a wider range of values for all categories than the more tightly grouped normals.

Congestive Heart Failure - Figure 9 displays the clinical course and serial echocardiographic changes in the first patient with congestive heart failure. Two echocardiographic volume measures, SV and LV_{vol-d}, and two function indices $V_{\overline{CF}}$ and LAI are shown over the patient's five day course. The echocardiographic values from the first day were obtained after the patient had been digitalized and given diuretics in the emergency room. Diuresis had begun at this point and if earlier studies could have been obtained LV_{vol-d} would have most probably been seen to be higher than the initial values shown. On the second day the patient improved clinically, and function indices reflected this improvement. But, diuresis was practially zero (45 ml.) and SV and LV_{vol-d} both increased significantly with the LV_{vol-d} going up from 188 ml., on day one, to 252 ml. on day two. They continued to rise on day three, LV_{vol-d} going to 286 ml., and accompanied by a net fluid gain that day of 70 ml. On the fourth day diuresis again was significant and the LV_{vol-d} precipitously fell to 196 ml. However, the patient subjectively felt much worse, was anxious, diaphoretic, and noted increasing shortness of breath. This was reflected clinically by the detection of increasing rales and of slight peripheral edema for the first time. Interestingly $V_{\overline{CF}}$ was lowest on this day. Values remained nearly constant on the fifth and final day of hospitalization. Figure 10 shows three representative echocardiograms taken from this patient on days one, two, and five of hospitalization. Of particular note are the mitral valve patterns in each. While the heart has dilated on the second day, the mitral valve opening slope, closing slope, and excursion have all increased suggesting an elevated cardiac output when compared to day one. However by the fifth

day, when intracardiac diameters are seen to have decreased, the mitral pattern had reverted to that of day one suggesting less cardiac dilation, but lower cardiac output as well. Also of note is the appearance of the posterior left ventricular wall by the final day. It seemed to be contracting more vigorously than on days one or two.

The clinical and echocardiographic data on the second congestive heart failure patient are shown in Figure 11. Volume and function studies followed a more usual course in this patient. There was an 810 ml. diuresis on the first day, and the LV_{vol-d} decreased appropriately by 65 ml. from day one to day two. Left atrial index also dropped rapidly and continued to drop on day three. The patient diuresed little on day two and LV_{vol-d} increased slightly, while SV dropped, and $V_{\overline{CF}}$ fell significantly. As diuresis continued on days four and five, SV increased as did $V_{\overline{CF}}$, and LV_{vol-d} remained stable. The patient noted much symptomatic improvement during this period. Echocardiograms taken on the first and fifth days are shown in Figure 12. While $LVID_d$ was almost unchanged, $LVID_s$ decreased from 5.7 cm. to 5.2 cm. resulting in the calculated increase in SV. It can be appreciated by comparing posterior wall endocardium in 12A and 12B that the increased SV and therefore elevated cardiac output with consequent symptomatic improvement was associated with, and possibly a result of, the increased excurison of the posterior myocardium. Such changes are reflected in increased PWV_{ant}, PWT, and posterior wall amplitude all of which can be compared in two echocardiograms of Figure 12. On day seven the patient complained of malaise and increasing fatigue, and rales reappeared. With the clinical worsening SV, LAI and $V_{\overline{CF}}$ all fell, while the heart dilated as was evidenced by an increase in LV_{vol-d}. The clinical decline was felt by the house staff to be related to inadequate rest (the patient was in a noisy four bed room) and anxiety about further hospitalization. Therefore, he was discharged, as previously planned, on the eighth day. The change in echocardiographic values

during the last two days of hospitalization were much more dramatic than the clinical worsening. In spite of the reappearance of rales the patient was sent home on clinical grounds. The echocardiographic signs might have been taken as indications of inadequate treatment or incomplete resolution of the course of failure, for the patient was readmitted with the same problem three weeks later.

DISCUSSION

The goals of this investigation have been twofold. The first was to gain an understanding of both the echocardiographic changes in states of cardiovascular fluid overload and the echocardiographic reflection of the progression of these states as influenced by therapy and natural course. An the second was to produce further evidence of the usefulness of echocardiography in serial studies. Since accomplishment of this latter purpose is relevant to the former it is necessary that the establishment of echocardiography's utility be understood and accepted before considering longitudinal changes with fluid overload.

The process of proving echocardiography's serial usefulness is a multi-facted problem. Demonstration and acceptance of the following aspects are necessary: validity, accuracy, reliability, and consistancy. Anatomic validity has been adequately proven, as discussed, by work ranging from Edler's pathologic studies (88) to Gramiak's dye injection investigations (113). Today the anatomic-echocardiographic correlations are widely accepted and there is little argument over the source of various echoes seen on standard tracings. This has not always been the case. It is interesting that for several years Inge Edler, one of the field's first pioneers, incorrectly identified echoes from what is now the most easily recognized of all intracardiac structures: the mitral valve. Primarily through systematic anatomic studies and later by confirmatory investigations using ultrasound visualized dye injections, the origins of intracardiac echoes have become well established. There is little doubt then to the technique's validity.

The accuracy of echocardiography in terms correctly displaying and allowing measurement of intracardiac structures has been attested to by the multitude of studies demonstrating high echocardiographic - angiocardiographic correlations. Data on wall thickness, chamber diameter and valve and wall movement velocities

all are obtainable to a high level of accuracy with ultrasound equipment. Interpretation regarding the meaning of this echocardiographic data is often, however,unresolved. The questionable significance of posterior endocardial wall velocity is a case in point. Elaborate studies have determined that wall velocity as measured echocardiographically is in fact closely comparable to sensitive measures of dP/dt (257,258). Nevertheless clinical studies, particularly those in patients with coronary artery disease (235), continue to show that posterior wall velocity is an unreliable index of left ventricular contractility. Thus, while there can be no doubt that posterior wall velocity can be accurately measured, the significance of this determination is unclear.

While posterior wall velocity is not the most reliable of echocardiographic indices, there is wide acceptance of the technique's reliability when other measures or function parameters are considered. There is no question that once the diagnosis of mitral stenosis is made, the severity of the lesion can be surely predicted by measuring the E-F slope in the mitral valve (135). Dependability has been demonstrated in many studies where echocardiography has been used to clearly distinguish among cardiac patients with various disease processes. Burgess' review of the ultrasound assessment in mitral regurgitation points out at least seven causes of insufficiency that can be regularly recognized echocardiographically (140). In the preceeding review of clinical applications (page 76) numerous studies are mentioned where echocardiography's diagnostic reliability has been demonstrated. Thus while ultrasound techniques may be clearly unreliable in certain applications their usefulness in others is widely accepted.

The first step in allowing for reproducible echocardiographic results was brought about by the use of standardized examination techniques repeatedly emphasized by leading workers in the field. Once clear that valid and accurate echograms were being obtained by standard techniques, the next logical step

was to demonstrate that observer variation or error was low in standard interpretation. Pombo et al., compared measurements made by two observers on the same echogram of 27 different patients (228). The values obtained rarely differed by more than five percent in this study. Most frequently, agreement was within one percent. Also in Pombo's study, for eleven patients measurements were made by two observers from two different echograms taken one hour to 30 days apart (mean = 4 days). Values again compared closely, with mean differences being about twice that of the different observer, same echogram,comparison mentioned previously. It is quite possible that the additional variation occurring when patients were studied at separate times was due to real changes in the parameters measured.

In spite of the data produced in the studies of Pombo, aspects of reproducibility or consistency remain unproven. While observer variations are widely accepted as insignificant, day-to-day reproducibility has yet to be demonstrated. Prior to this study attempts at showing low daily variability in normal subjects had not been undertaken. Data is presented here showing a consistent inability to demonstrate statistically significant changes when comparing mean values from one day to those of the next. This is strong evidence that echocardiographic measurements are reproducible on a daily basis. For most parameters the regularly low standard deviations for the mean of each subject over five days is further confirmatory evidence of this low day-to-day variability. If additional consideration is given to the fact that the human cardiovascular system is never in a totally steady state, and it is realized that some variability must be due to changes that are real, then the low standard deviations and standard errors appear even more significant. Approximately the same consistency was noted in the one subject examined at fifteen minute intervals, as was found in the pooled data of six subjects examined daily. This suggests that quarter-hour variability is as low as day-to-day variability.

Once daily consistency was established for several primary parameters such as internal diameter and ejection fraction, other data obtained simultaneously could be approached critically. Thus, the serial studies in normals were used first to demonstrate reproducibility, then to select which measurements were most reproducible. For the parameters or indices that demonstrated consistently higher variability two possible explanations can be offered. The first is that this variability is real. Measures such as posterior wall velocity and velocity of circumferential fiber shortening may simply vary to within a greater "normal" range during steady state conditions than measures such as end-diastolic diameter or ejection fraction. Studies of Paulev (257, 258) on posterior wall motion, and Gault et al. (30) on fiber shortening velocity would tend to support this possibility. Since both posterior wall motion and V_{CF} appear to accurately reflect the true contractile state of the myocardium, such an explanation seems probable. Minor beat-to-beat changes undoubtedly occur as the heart adapts to the slight variations in afterload and preload that occur with respirations and body movement. Left ventricular volume on the other hand is most probably more resistant to change with such minor physiologic alterations.

A second possible explanation for variability among different echocardiographic measures is that somehow the changes being measured are not real. This is undoubtedly the case for two indices, posterior wall thickening and septal thickening. Although these measures have correlated highly with angiographic determinations in the hands of other investigators (266) this could not be the case in the current work. In the study of one subject over a period of two hours, and in six normals studied daily, these two measures of thickening had greater standard deviations relative to their means than all other parameters

or indices recorded. And it is certainly difficult to believe that changes in posterior wall thickening of over 300 percent could occur without concomitant changes in ejection fraction occurring simultaneously (Subject 1, day 1 - day 3 for example, Table 1 (H)).

Measures of mitral valve slope might conceivably vary based on both above explanations. Particularly for the D-E slope, significant beat-to-beat changes were frequently apparent. Occurring at a time when the individuals were at quite steady states, it is tempting to conclude that such changes were not real. Yet, as has been previously discussed, these slopes appear to reflect ventricular compliance and they may be capable of detecting subclinical changes that occur with, for example, respiratory alterations in preload. While it is impossible to resolve such a question with the data obtained, Table 1 (J) and (K) contain information arguing for the reality of measured changes. Great differences in standard deviation are seen among several but not all subjects for D-E and E-F slopes. This suggests that daily these slopes change more for some people than for others. If the measure itself was inaccurate the latter would probably not be the case, and all subjects would uniformly show high standard deviations. However, it is more likely that the echocardiographic measure is real and that some subjects vary more on a day-to-day basis. It is interesting to note that for a clearly unreliable measure such as septal thickening (Table 1 (I)), the standard deviations are consistently high.

Thus, this study has shown that certain echocardiographically determined parameters and indices are consistently reproducible. This observation, when added to those regarding the technique's validity, accuracy and reliability helps complete the picture of usefulness for this simple non-invasive procedure. Data has been presented that supports the contention of many authors that echocardiography's most promising applications are to be found in the performance of serial studies.

While such serial techniques have already been widely applied in the study of ischemic heart disease (270,271,273,274) little data concerning the course of fluid overload have been obtained. This is somewhat surprising given the proven accuracy of ventricular diameter and volume determinations, particularly compared to the controversial measures of function that are available and used in the studies on myocardial infarction. The implied goal of these serial studies is the detection of deterioration in functional status before the onset of clinical signs. Presumably an observation of falling contractility might warrant more aggressive therapy. Certainly the chances of benefit from such therapy would be greater if it was initiated before decompensation to an irreversible state. Similar logic can be applied to the serial study of fluid overload conditions. While evaluation of functional status in terms of contractility is important in these circumstances as well, it would be most valuable to assess the more reliable measures of left ventricular volume. The clinician would be provided with an objective parameter which could aid in the making of decisions.

The results of this study clearly demonstrate that known alterations in fluid status are closely reflected in echocardiographic measures. In only one patient (no. 1, Table 3) was dialysis associated with anything less than a 25 ml. (more than 20 percent) fall in end-diastolic volume. (The patient whose ventricular volumes rose was acutely ill, and great difficulty was experienced in getting adequate flow during hemodialysis.) This fall in ventricular volume must be related to the removal of plasma volume and consequent reduction in pre-load. Although a fall in stroke volume occurred regularly as well, changes in function parameters (wall velocity, ejection fraction, and velocity of circumferential fiber shortening) were less consistent. The presence of diverse responses agrees with other studies of dialysis patients

which have noted changes in cardiac output in some, but not all, subjects studied (68,72). While all patients examined underwent similar falls in plasma volume, the myocardial responses to such alterations seemed to vary depending on the underlying functional status. Since the group studied was heterogeneous in terms of age, duration of renal failure, degree of hypertension, and, therefore, degree of cardiovascular compensation, it is reasonable to expect variable inotropic responses to a reduced plasma volume. Unfortunately, trends or particular subsets of responses cannot be determined from the data obtained. Further study of more patients with attention to prior inotropic state is necessary for this latter end.

The demonstration of nearly opposite results in patients studied at the end of one dialysis and prior to the next (Table 5) again demonstrates the reliable echocardiographic detection of fluid change in the presence of variable myocardial responses. Changes in posterior wall velocity, mitral valve diastolic closing velocity, and mean velocity of circumferential fiber shortening are clearly variable as can be appreciated from Figure 6. While the range of responses in end-diastolic left ventricle volume is great as well, the direction and magnitude of responses is quite consistent. Thus, the changes in left ventricular diameter and derived left ventricular volume are easily demonstrated following therapeutically induced fluctuations in plasma volume. The sensitivity of echocardiography in such conditions is apparent and leads to the conclusion that similar alterations should be detectable under other conditions of fluid overload.

The responses to post-dialysis infusions and to leg raising are more difficult to understand. These situations are physiologically analogous. The post-dialysis infusion and the "auto-transfusion" with leg raising both occur rapidly and both involve an effective blood volume increase of approximately 400 cc. Significant changes were demonstrated in diastolic volume with leg

raising, and in systolic volume with infusion. However, the increases in volume were not large and the consistency of change did not compare with that seen before and after dialysis. Changes in contractility parameters were irregular in all three groups (Tables 4,6,7). These findings are in contrast to other studies of the effects of postural change on contractility (82,84), however they are consistent with the observation that in congestive heart failure, patients' stroke volumes and ventricular size does not change with postural alterations (83). Although the patients were not in congestive heart failure, the possibility exists that underlying myocardial dysfunction in dialysis patients and certainly in patients with coronary artery disease may be responsible for these individual responses. It also should be pointed out that the three groups considered in Tables 4, 6 and 7 are all made up of onlyfive comparison studies. Changes would of necessity have to be great to attain statistical significance in groups of this small size. It is disappointing however that more significant change were not noted in the normal leg raising group. Physiologically, these normal subjects should have been quite homogenous. That fact remains that changes in diastolic, systolic and stroke volume known to occur angiographically (78,79) with tilting could not be well recognized echocardiographically. Small acute volume changes do not seem to be recognizable in terms of change in the echocardiographically measured left ventricular internal diameter. The lack of change in contractility could be related to echocardiographic insensitivity as well. However, another study has noted that preload independent measurement of contractility (Vmax) did not change with leg raising (84). Echocardiographically determined posterior wall velocity or mean velocity of circumferential fiber shortening may be likewise unrelated to acute volume change. It is interesting also that no readily apparent differences could be ascertained between the normal and coronary artery disease groups studied with leg raising.

This further emphasized that echocardiography's greatest utility will not be in single examinations for the purpose of distinguishing among similar populations, but more likely will come in terms of its usefulness for serial studies on single patients.

Several incongruities are present in the echocardiographic study of congestive heart failure patient no. 1 (Figure 9). First, why did the patient's left ventricular volume increase initially with therapy? Second, why did volume then decrease when the patient suddenly felt worse and developed further signs of decompensation? And, finally, how is the patient's rise in ventricular contractility, as measured by $V_{\overline{CF}}$, explained when symptomatically he was improved? Ignoring the possibility that the echocardiographic measures simply were wrong, several explanations can be offered. It is probable that the initial fall in volume with therapy and diuresis was not detected since the patient was first studied echocardiographically after these changes could have occurred. The patient decompensated at home where diet and activity were poorly restricted. Thus his subjective feelings of malaise and fatigue, and perhaps resultant shortness of breath, quickly abated with an initial diuresis, and more importantly with bedrest in the hospital. While this bedrest resulted in subjective improvement on days two and three, diuresis was small and fluid was probably being reaccumulated. This accumulation was not reflected clincally in terms of signs or symptoms until day four, but was readily apparent echocardiographically while it occurred during days two and three. Although the patient actually felt worse on day four, diuresis had begun again and was reflected in the measurement of a decreased end-diastolic volume. The initial improvement in $V_{\overline{CF}}$ is difficult to explain and, although it may be spurious, it probably was related to the initial therapeutic intervention which included digitalis and furosomide. The elevation was associated with increased mitral valve velocity and excursion as can be seen in Figure 10 by comparing the value pattern in (A) with (B). By

day five, when the ventricular volumes had fallen, the mitral valve pattern again looked less dynamic, suggesting a fall in ventricular compliance coincident with the patient's subjective complaints.

The echocardiographic changes with the other congestive heart failure patient studied followed a more predictable and readily explained course. It is interesting that in both patients if attention had been paid to echocardiographic signs, then their respective clinical courses might have been favorably altered. In patient no. 1, the late decompensation might have been avoided had the increases in left ventricular volume been treated on day two or day three. The other patient might have been spared such an early rehospitalization had his further decompensation been recognized at the time of discharge.

Any conclusions reached on the use of echocardiography in serial studies of congestive heart failure in this investigation are necessarily based on "anecdotal" rather than on statistically significant data. However, with the knowledge from other investigations that this technique can be accurate, reliable and reproducible, its utility is strongly confirmed by the data presented on the two patients studied. Probably through combining aspects of both pattern recognition or morphologic description (e.g., mitral valve appearance) and objective data accumulation (e.g, PWV_{ant}, $V_{\overline{CF}}$) echocardiography will, in the future, provide useful information in the evaluation of the course of congestive heart failure. Most importantly, this information will be obtainable rapidly, safely, and without inconvenience or stress to the critically ill patient.

In this investigation the initial approach to gathering echocardiographic data was somewhat of a "shotgun" method. All possible measurements were made and collected. Final selection of measures and indices for statistical consideration was based upon either the widespread use of the parameter in other studies, or the appearance of reasonable consistency in the current studies on

normal subjects. This method, though cumbersome, proved useful in sorting out among the many different measures being reported in the current literature. Certain parameters such as ventricular diameter or ejection fraction, for example, had to be chosen for review because most other studies report them. However, ones of questionable utility such as systolic wall thickening, although reported by other groups (242), clearly were unreliable (see Table 1,2) in this study and could be easily discarded.

One parameter, that of left atrial index (LAI) was retained and analysed in spite of the lack of prior information regarding its usefulness. Atrial diameters determined echocardiographically have been shown to be reasonably accurate, with the reliability increased when the diameter was divided by the subject's total body surface area (237). However, untested experimentally is the more recent suggestion that left atrial diameter divided by aortic root diameter would provide an even better estimate of atrial dimension, particularly in terms of technical standardization (238). In this study the daily consistency of LAI is apparent from the data in Table 1 (N). The finding that days two and three are statistically different is acceptable. The level of significance is only $p<0.2$, which indicates that there is a 20 percent chance that such a difference was due to random distribution and not a significant difference. That measure of consistency aside then, it is clear that LAI is quite reproducible. The mean standard deviation (0.08) is a smaller percentage(7.5%) of the mean (1.06) than any other mean standard deviation compiled, with the exception of that for systolic left ventricular internal diameter (6.1%). In the subject examined at 15 minute intervals (Table 2 (N)) LAI was slightly less consistent yet still quite reproducible, with variations averaging about 10 percent of the mean. It is reasonable that LAI be quite reproducible. The potential for error in left atrial diameter is primarily related to the possibility that the transducer beam intersects the atrium obliquely. To do this, the beam would intersect the aortic root obliquely as well. An assumption is made that the

aortic root is of consistent diameter. Thus, consideration of the atrial diameter relative to the aortic root width should compensate for any error introduced by varying transducer angle.

Review of Figures 3, 5, 6, 7 and 8 demonstrates that LAI consistently undergoes alterations similar and equivalent to changes in end-diastolic volume, stroke volume, and changes in mitral closing velocity. Agreement with $V_{\overline{CF}}$ is more variable. Left atrial index is probably a complex function of myocardial compliance and end-diastolic volume. Since changes in either are reflected in left atrial pressures, atrial volume must respond similarly. Left atrial index, then, clearly is related to ventricular volume. To the extent that this volume reflects performance (just as left ventricular end-diastolic pressure reflects performance) LAI should provide an estimate of myocardial function as well. As such it has much potential as a single, simple parameter for objective assessment of cardiovascular status. Specific investigations need to be undertaken before the validity of this suggestion can be accepted. Nevertheless, LAI was included as a "function" parameter for following the patients in congestive heart failure. Interestingly in patient no. 1 (Figure 9) LAI seemed to reflect the volume indices, where as in patient no. 2 (Figure 11) $V_{\overline{CF}}$ was closely paralleled by LAI. Other than noting these interesting findings, no interpretation can be offered without additional objective information on cardiac performance, and without proof of the validity of LAI as a measure of cardiac function.

It is hoped that these investigations have contributed to the long range goal concerning the future usefulness of echocardiography. The anticipation is that ultrasound equipment may some day be available and useful on a routine basis in the acute medical setting. The ability to obtain accurate objective data quickly and non-invasively will hopefully make diagnostic and therapeutic decisions far easier in the intensive care units of the future.

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APPENDIX

Tables 1 through 7

Figures 1 through 12

TABLE LEGEND

$LVID_d$ - Left Ventricular Internal Diameter, diastolic

$LVID_s$ - Left Ventricular Internal Diameter, systolic

LV_{vol-d} - Left Ventricular Volume, diastolic

LV_{vol-s} - Left Ventricular Volume, systolic

SV - Stroke Volume

PWV_{ant} - Posterior Wall Velocity, anteriorly

PWV_{post} - Posterior Wall Velocity, posteriorly

PWT - Systolic Posterior Wall Thickening

ST - Systolic Septal Thickening

D-E - Initial Mitral Valve Opening Velocity

E-F - Initial Mitral Valve Closure Velocity

EF - Ejection Fraction

$\overline{V_{CF}}$ - Mean Velocity of Circumferential Fiber Shortening

LAI - Left Atrial Index

NS - Not Significant

SD - Standard Deviation

SEM - Standard Error of the Mean

TABLE I

Normal Controls - Daily Measurements

(A) Left Ventricular Internal Diameter, diastolic - LVIDd (cm)

Day -	1	2	3	4	5	Mean	±SD	±SEM
Subject # 1	4.2	4.7	4.8	4.3	4.4	4.5	0.3	0.1
2	5.0	4.0	4.9	4.8	4.8	4.7	0.6	0.2
3	4.4	4.4	4.3	4.8	4.9	4.7	0.3	0.1
4	5.1	5.0	5.3	4.8	4.7	5.0	0.2	0.1
5	4.7	5.8	5.0	4.8	4.9	5.0	0.4	0.2
6	5.2	5.0	5.0	4.9	4.3	4.9	0.3	0.2
P value	NS	NS	NS	NS	Mean	4.8	0.4	0.2
					±SEM	0.1		

(B) Left Ventricular Internal Diameter, systolic - LVIDs (cm)

Day -	1	2	3	4	5	Mean	±SD	±SEM
Subject # 1	2.9	3.4	3.5	2.9	2.9	3.1	0.3	0.1
2	3.3	2.8	3.5	3.5	3.3	3.3	0.3	0.1
3	3.3	3.0	3.2	3.3	3.3	3.2	0.1	0.1
4	3.4	3.6	4.0	3.4	3.6	3.6	0.2	0.1
5	2.8	3.8	3.3	3.5	3.8	3.4	0.4	0.2
6	3.1	3.2	2.9	3.1	2.8	3.0	0.2	0.1
P value	NS	NS	NS	NS	Mean	3.3	0.2	0.1
					±SEM	0.1		

TABLE I (Cont.)

(C) Left Ventricular Volume, diastolic - LV_{vol-d} (ml)

Day -	1	2	3	4	5	Mean	±SD	±SEM
1	74.1	103.8	110.6	79.5	85.2	90.6	15.8	7.1
2	125.0	64.0	117.6	110.6	110.6	105.6	24.0	10.7
Subject # 3	85.2	85.2	79.5	110.6	117.6	95.6	17.2	7.7
4	132.6	125.0	148.9	110.6	103.8	124.2	17.9	8.0
5	103.8	195.1	125.0	110.6	117.6	130.4	37.0	16.6
6	140.6	125.0	125.0	117.6	79.5	117.6	22.8	10.2
P value	NS	NS	NS	NS	Mean	110.7	22.4	10.0
					±SEM	6.5		

(D) Left Ventricular Volume, systolic - LV_{vol-s} (ml)

Day -	1	2	3	4	5	Mean	±SD	±SEM
1	24.4	39.3	42.9	24.4	24.4	31.1	9.2	4.1
2	35.9	22.0	42.9	42.9	35.9	35.9	8.5	3.8
Subject # 3	35.9	27.0	32.8	35.9	35.9	33.5	3.9	1.7
4	39.3	46.7	64.0	39.3	46.7	47.2	10.1	4.5
5	22.0	54.9	35.9	42.9	54.9	42.1	13.9	6.2
6	29.8	32.8	24.4	29.8	22.0	27.7	4.4	2.0
P value	NS	NS	NS	NS	Mean	36.2	8.3	3.7
					±SEM	3.0		

TABLE I (Cont.)

(E) Stroke Volume - SV (ml)

Day -	1	2	3	4	5	Mean	±SD	±SEM
Subject # 1	49.7	64.5	67.7	55.1	60.8	59.6	7.2	3.2
2	89.1	42.0	74.8	67.7	74.7	69.6	17.3	7.7
3	49.2	58.2	46.7	74.7	81.7	62.1	15.5	6.9
4	93.4	78.3	84.9	71.3	57.2	77.0	13.8	6.2
5	81.9	140.2	89.1	67.7	62.8	88.3	30.9	13.8
6	110.8	92.2	100.6	87.9	57.6	89.8	20.0	9.0
P value	NS	NS	NS	NS	Mean	74.4	17.4	7.8
					±SEM	5.3		

(F) Posterior Wall Velocity, anteriorly - PWV ant (cm/sec)

Day -	1	2	3	4	5	Mean	±SD	±SEM
Subject # 1	10.0	7.4	9.0	7.0	8.2	8.3	1.2	0.5
2	6.4	6.5	5.8	5.8	6.0	6.0	0.5	0.2
3	9.2	8.8	7.2	6.1	8.2	7.9	1.2	0.6
4	6.8	7.5	9.2	7.9	7.7	7.8	0.8	0.3
5	9.1	6.4	7.5	7.8	5.4	7.2	1.4	0.6
6	9.3	7.8	8.4	9.0	7.7	8.4	0.7	0.3
P value	< 0.2	NS	NS	NS	Mean	7.6	1.0	0.4
					±SEM	0.4		

TABLE I (Cont.)

(G) Posterior Wall Velocity, posteriorly - PWV post (cm/sec)

Day -	1	2	3	4	5		Mean	±SD	±SEM
Subject # 1	14.8	18.4	24.8	23.6	19.6		20.2	4.0	1.8
2	14.0	18.6	34.0	16.4	20.2		20.6	7.8	3.5
3	18.1	15.2	12.7	19.8	23.0		16.2	5.2	2.3
4	14.8	19.6	20.6	15.0	16.0		17.2	2.7	1.2
5	18.6	17.6	14.0	13.2	13.6		14.6	1.8	0.8
6	18.2	21.6	17.0	20.4	19.4		19.3	1.8	0.8
P value	< 0.2	NS	NS	NS		Mean	18.0	3.9	1.7
						±SEM	1.0		

(H) Systolic Posterior Wall Thickening - PWT (%)

Day -	1	2	3	4	5		Mean	±SD	±SEM
Subject # 1	57	125	200	125	125		126	51	22
2	125	150	150	80	125		126	29	13
3	66	43	100	60	100		74	25	11
4	28	33	80	50	57		50	21	9
5	88	89	57	67	44		69	20	9
6	128	88	62	225	62		113	68	30
P value	NS	NS	NS	NS		Mean	93	36	16
						±SEM	13		

TABLE I (Cont.)

(I) Systolic Septal Thickening - ST (%)

Day -		1	2	3	4	5		Mean	±SD	±SEM
Subject #	1	40	40	71	30	50		46	16	7
	2	44	67	67	40	62		56	13	6
	3	71	43	33	62	33		48	17	8
	4	40	44	25	40	36		37	7	3
	5	33	54	62	80	50		56	17	8
	6	27	62	33	60	54		47	16	7
P value		NS	NS	NS	NS		Mean	48	14	6
							±SEM	3		

(J) Initial Mitral Valve Opening Velocity - D-E (cm/sec)

Day -		1	2	3	4	5		Mean	±SD	±SEM
Subject #	1	40.0	34.0	40.4	35.2	39.2		37.8	2.9	1.3
	2	47.2	36.8	48.8	46.0	44.4		44.6	4.7	2.1
	3	36.8	52.8	40.4	46.8	45.2		44.4	6.1	2.7
	4	33.2	29.6	31.4	33.6	42.5		34.1	5.0	2.2
	5	20.2	22.6	21.6	28.6	20.0		22.6	3.5	1.6
	6	52.4	35.2	58.4	46.4	41.6		46.8	9.0	4.0
P value		NS	NS	NS	NS		Mean	38.4	5.2	2.3
							±SEM	3.7		

TABLE I (Cont.)

(K) Initial Mitral Valve Closing Velocity - E-F (cm/sec)

Day -		1	2	3	4	5		Mean	±SD	±SEM
Subject #	1	13.5	14.0	15.8	16.2	18.4		15.6	1.9	0.9
	2	16.4	16.8	13.0	16.6	16.2		15.8	1.6	0.7
	3	12.4	14.0	16.8	14.2	14.6		14.4	1.6	0.7
	4	8.7	18.8	12.3	15.2	15.0		14.0	3.8	1.7
	5	11.8	14.4	13.8	19.4	11.6		14.2	3.2	1.4
	6	12.9	24.4	15.2	16.8	16.2		17.1	4.3	1.9
P value		< 0.1	NS	< 0.2	NS		Mean	15.2	2.7	1.2
							±SEM	0.5		

(L) Ejection Fraction - EF

Day -		1	2	3	4	5		Mean	±SD	±SEM
Subject #	1	0.67	0.62	0.61	0.69	0.71		0.66	0.04	0.02
	2	0.71	0.66	0.64	0.61	0.68		0.66	0.04	0.02
	3	0.58	0.68	0.59	0.68	0.69		0.64	0.06	0.02
	4	0.70	0.63	0.57	0.64	0.55		0.62	0.06	0.03
	5	0.79	0.72	0.71	0.61	0.53		0.67	0.10	0.04
	6	0.79	0.74	0.80	0.75	0.72		0.76	0.03	0.02
P value		NS	NS	NS	NS		Mean	0.67	0.06	0.02
							±SEM	0.02		

TABLE I (Cont.)

(M) Mean Velocity of Circumferential Fiber Shortening -V_{CF} (circ/sec)

Day -	1	2	3	4	5		Mean	±SD	±SEM
Subject # 1	1.19	1.20	1.23	1.25	1.21		1.22	0.02	0.01
2	1.06	0.96	0.92	0.87	1.00		0.96	0.07	0.03
3	0.92	1.17	0.82	1.04	1.16		1.02	0.15	0.07
4	1.23	1.00	0.94	1.08	0.78		1.01	0.17	0.07
5	1.68	1.49	1.21	0.96	0.77		1.22	0.37	0.17
6	1.61	1.44	1.50	1.41	1.24		1.44	0.14	0.06
P value		NS	< 0.2	NS	NS	Mean	1.14	0.15	0.07
						±SEM	0.07		

(N) Left Atrial Index (LA diameter/Ao diameter) - LAI

Day -	1	2	3	4	5		Mean	±SD	±SEM
Subject # 1	1.15	1.14	1.23	1.20	1.21		1.19	0.04	0.02
2	0.93	0.86	0.85	0.96	0.92		0.90	0.05	0.02
3	1.12	1.00	1.12	1.17	1.18		1.12	0.07	0.03
4	1.03	1.07	0.96	1.07	1.12		1.05	0.06	0.03
5	1.05	0.96	1.12	0.88	0.65		0.93	0.18	0.08
6	1.11	1.15	1.28	1.25	1.15		1.19	0.07	0.03
P value		NS	< 0.2	NS	NS	Mean	1.06	0.08	0.04
						±SEM	0.05		

Table 2

Normal Control - Quarter Hour Measurements

Time (min) :	0	15	30	45	60	75	90	105	Mean	±SD	±SEM	SD/mean(%)
(A) LVIDd (cm)	4.9	4.5	5.0	4.8	5.4	5.0	4.8	5.0	4.9	0.2	0.1	4.1
(B) LVIDs (cm)	3.2	3.0	3.3	3.1	3.6	3.4	3.2	3.2	3.2	0.2	0.1	6.2
(C) LVvol-d (ml)	117.6	91.1	125.0	110.6	157.5	125.0	110.6	125.0	120.3	18.9	6.7	15.7
(D) LVvol-s (ml)	32.8	27.0	35.9	29.8	46.7	39.3	32.8	32.8	34.6	6.1	2.2	17.6
(E) SV (ml)	84.8	64.1	89.1	80.8	110.8	85.7	77.8	92.2	85.7	13.3	4.7	15.5
(F) PWVant (cm/sec)	6.6	8.2	7.4	9.2	8.9	6.8	9.0	7.2	7.9	1.0	0.4	12.6
(G) PWVpost (cm/sec)	19.8	16.8	16.6	17.8	13.3	13.0	14.2	14.8	15.8	2.4	0.8	15.2
(H) PWT (%)	167	89	86	78	100	67	100	100	98	30	11	30.6
(I) ST (%)	100	75	62	67	50	36	87	60	67	20	7	29.8
(J) D-E (cm/sec)	22.8	37.4	28.8	34.4	42.0	29.8	22.4	40.0	32.2	7.5	2.7	23.3
(K) E-F (cm/sec)	14.2	13.8	14.2	13.6	14.6	15.2	14.8	18.8	14.9	1.7	0.6	11.4
(L) EF	0.72	0.70	0.71	0.73	0.70	0.69	0.70	0.74	0.71	0.02	0.01	2.8
(M) $V_{\overline{CF}}$ (circ/sec)	1.44	1.38	1.21	1.36	1.19	1.33	1.28	1.50	1.34	0.11	0.04	8.2
(N) LAI (LA/Ao)	0.77	0.90	0.93	0.88	1.10	0.90	1.03	0.89	0.92	0.10	0.04	10.9

Table 3

Pre-Dialysis - Post Dialysis

Patient #	$LVID_d$ (cm)		$LVID_s$ (cm)		LV_{vol-d} (ml)		LV_{vol-s} (ml)		SV (ml)		PWV_{ant} (cm/sec)		PWV_{post} (cm/sec)		E-F (cm/sec)		D-E (cm/sec)		EF		$V_{\overline{CF}}$ (circ/sec)		LAI (LA/Ao)	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1	4.9	5.2	3.1	3.3	117.6	140.6	29.8	35.9	87.8	104.7	10.0	14.6	17.2	29.8	10.6	6.4	54.0	34.0	0.75	0.74	1.22	1.52	1.30	0.96
2a	4.8	4.4	3.8	3.5	110.6	85.2	54.9	42.9	55.7	42.3	7.4	9.3	12.5	15.2	10.6	11.2	31.2	50.8	0.50	0.50	0.71	0.75	1.16	1.03
b	4.6	4.1	3.6	2.6	97.3	68.9	46.6	68.9	50.7	51.3	8.4	10.2	9.2	19.8	10.5	12.8	52.0	53.6	0.52	0.74	0.70	1.40	1.08	0.88
3a	5.9	5.1	3.3	2.9	205.4	132.6	35.9	24.4	169.4	54.4	7.8	14.4	20.4	20.8	9.2	8.9	31.6	26.4	0.82	0.82	1.33	1.87	1.50	1.11
b	4.8	4.2	2.9	2.7	110.6	74.1	24.4	19.7	86.2	108.3	7.0	9.4	11.4	14.6	7.4	9.8	17.4	23.4	0.86	0.73	1.41	1.27	1.07	1.22
4a	6.1	4.7	3.9	3.1	227.0	103.8	59.3	29.8	167.7	167.7	6.4	11.6	12.7	17.0	20.2	10.8	37.2	36.0	0.74	0.71	1.28	1.41	1.02	1.02
b	5.9	4.4	3.8	3.0	205.4	85.2	54.9	27.0	150.5	58.2	11.8	10.6	16.8	13.2	21.2	17.4	38.6	32.2	0.73	0.68	1.31	1.27	1.00	1.02
5a	4.4	4.0	3.0	2.5	85.2	64.0	27.0	15.6	58.2	48.4	8.6	10.6	17.4	15.4	10.8	8.7	34.8	33.4	0.68	0.76	1.22	1.22	0.92	1.00
b	4.6	4.1	2.9	2.8	97.3	68.9	24.4	22.0	72.9	47.0	12.2	8.8	16.2	12.7	13.6	11.6	30.4	42.8	0.75	0.68	1.31	1.21	1.07	1.03
6	4.5	4.1	4.0	3.8	91.1	68.9	64.0	54.9	27.1	14.0	2.9	4.2	5.0	6.7	17.8	15.8	43.6	62.2	0.30	0.20	0.54	0.34	1.36	1.12
7	4.6	4.3	3.3	3.0	97.3	79.5	35.9	27.0	61.4	52.5	5.0	5.2	6.5	6.2	13.6	7.4	44.0	38.8	0.63	0.66	0.80	0.77	1.40	1.19
8	5.3	4.7	3.2	2.6	148.9	103.8	32.8	17.6	116.1	86.2	6.7	5.4	8.2	6.8	3.7	2.4	36.0	28.6	0.78	0.83	1.07	1.14	1.20	1.11
9	5.0	3.9	3.3	3.0	125.0	59.3	35.9	27.0	89.1	32.3	9.9	13.8	20.0	12.2	6.2	6.4	20.6	36.8	0.71	0.54	1.30	1.04	1.00	0.92
Mean	5.0	4.4	3.4	3.0	132.2	87.3	40.4	31.7	91.8	62.6	8.0	9.8	13.4	14.6	12.0	10.0	36.3	38.4	0.68	0.66	1.08	1.16	1.16	1.05
±SEM	0.2	0.1	0.1	0.1	13.6	7.2	3.8	4.3	12.8	12.3	0.7	0.9	1.4	1.8	1.4	1.1	3.0	3.1	0.04	0.05	0.09	0.11	0.05	0.03
P value	< 0.0005		< 0.0005		< 0.005		< 0.025		< 0.025		< 0.025		NS		< 0.05		NS		NS		NS		< 0.025	

Table 4

Post Dialysis (A) - Post Dialysis Plus Infusion (B)

Patient #	$LVID_d$ (cm)		$LVID_s$ (cm)		LV_{vol-d} (ml)		LV_{vol-s} (ml)		SV (ml)		PWV_{ant} (cm/sec)		PWV_{post} (cm/sec)		D-E (cm/sec)		E-F (cm/sec)		EF		$V_{\overline{CF}}$ (circ/sec)		LAI (LA/Ao)	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
1a	4.4	4.8	3.5	3.7	85.2	110.6	42.9	50.6	42.3	59.9	9.3	7.6	15.2	16.0	50.8	54.8	11.2	11.8	0.50	0.54	0.76	0.85	1.04	1.12
b	4.1	4.8	2.6	3.0	68.9	110.6	17.6	27.0	51.3	83.6	10.2	9.1	19.8	12.4	53.6	55.6	12.8	11.9	0.74	0.76	1.41	1.34	0.88	0.96
2	4.2	4.4	2.7	3.1	74.1	85.2	19.7	29.8	54.4	55.4	9.4	9.2	14.6	18.2	23.8	41.2	9.8	8.4	0.73	0.65	1.28	1.02	0.70	0.86
3a	3.9	3.6	2.9	2.7	59.3	46.7	24.4	19.7	34.9	27.0	10.6	12.2	15.4	14.8	33.4	42.4	8.7	11.0	0.59	0.58	1.07	1.14	0.81	1.08
b	4.1	4.1	2.8	3.0	68.9	68.9	22.0	27.0	47.0	41.9	8.8	11.6	12.7	15.8	42.8	60.8	11.6	13.2	0.68	0.61	1.22	1.07	1.04	0.92
Mean	4.1	4.3	2.9	3.1	71.3	84.4	25.3	30.8	46.0	53.6	9.7	9.9	15.5	15.4	40.9	51.0	10.8	11.3	0.65	0.63	1.15	1.08	0.89	0.99
±SEM	0.1	0.2	0.2	0.2	4.2	12.3	4.5	5.2	3.4	9.5	0.3	0.8	1.2	0.9	12.4	3.9	0.7	0.8	0.05	0.04	0.11	0.08	0.06	0.04
P value	NS		< 0.10		NS		< 0.025		NS		NS		NS		< 0.01		NS		NS		NS		NS	

Table 5

Post Dialysis (A) - Pre Next Dialysis (B)

Patient #	$LVID_d$ (cm)		$LVID_s$ (cm)		LV_{vol-d} (ml)		LV_{vol-s} (ml)		SV (ml)		PWV_{ant} (cm/sec)		PWV_{post} (cm/sec)		D-E (cm/sec)		E-F (cm/sec)		EF		$V_{\overline{CF}}$ (circ/sec)		LAI (LA/Ao)	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
1	4.2	4.6	3.0	3.6	74.1	97.3	27.0	46.7	47.1	50.7	8.2	8.4	10.6	9.2	49.4	52.0	8.3	10.5	0.64	0.52	1.14	0.70	0.96	1.09
2	4.2	5.1	2.7	3.4	74.1	132.6	19.7	39.3	54.4	93.4	9.4	7.2	14.6	17.6	23.8	20.6	9.8	7.6	0.73	0.70	1.28	1.19	0.70	1.04
3	4.7	5.9	3.1	3.8	103.8	205.4	29.8	54.9	74.0	150.5	11.6	11.8	17.0	16.8	36.0	38.6	10.8	21.2	0.71	0.73	1.42	1.32	1.03	1.00
4	3.9	4.6	2.9	2.9	59.3	97.3	24.4	24.4	34.9	73.0	10.6	12.2	15.4	16.2	33.4	30.4	8.7	13.6	0.59	0.75	1.07	1.32	0.81	1.07
Mean	4.2	5.0	2.9	3.4	77.8	133.2	25.2	41.3	52.6	91.9	10.0	9.9	14.4	15.0	35.6	35.4	9.4	13.2	0.67	0.68	1.23	1.13	0.88	1.05
±SEM	0.2	0.3	0.2	0.2	9.3	25.5	2.1	6.5	8.2	21.4	0.7	1.2	1.4	1.9	5.3	6.6	0.6	2.9	0.03	0.05	0.08	0.15	0.07	0.02
P value	<0.01		<0.025		<0.025		<0.025		<0.05		NS		NS		NS		NS		NS		NS		<0.10	

Table 6

Leg Raising - Normals

Subject #	$LVID_d$ (cm)		$LVID_s$ (cm)		LV_{vol-d} (ml)		LV_{vol-s} (ml)		SV (ml)		PWV_{ant} (cm/sec)		PWV_{post} (cm/sec)		D-E (cm/sec)		E-F (cm/sec)		EF		$V_{\overline{CF}}$ (circ/sec)		LAI (LA/Ao)	
	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during
1	4.2	4.6	2.8	3.0	74.1	97.3	22.0	27.0	52.1	70.3	6.7	5.7	20.8	18.8	42.4	37.6	16.4	18.2	0.70	0.72	1.19	1.20	1.00	1.07
2	4.1	4.2	2.8	2.9	68.9	74.1	22.0	24.4	47.0	49.7	6.3	6.8	13.8	18.8	40.4	42.0	12.2	16.4	0.68	0.67	1.32	1.19	0.95	0.95
3	4.5	4.9	3.0	3.8	91.1	117.6	27.0	54.9	64.1	62.8	6.3	5.3	28.2	20.6	32.4	30.0	7.7	12.9	0.70	0.53	1.04	0.72	0.83	1.04
4	4.4	4.5	2.8	3.0	85.2	91.1	22.0	27.0	63.2	94.1	4.9	6.0	12.3	15.6	61.6	48.4	11.0	12.3	0.74	0.70	1.21	1.08	1.08	1.22
5	4.7	4.7	3.6	2.9	103.8	103.8	46.6	24.4	57.2	79.4	7.9	7.7	16.0	22.0	42.5	48.8	15.0	15.4	0.55	0.76	0.78	1.24	1.12	1.11
Mean	4.4	4.6	3.0	3.1	84.6	96.8	28.0	31.5	56.7	71.3	6.4	6.3	18.2	19.2	43.9	41.4	12.5	15.0	0.68	0.68	1.11	1.09	1.00	1.08
±SEM	0.1	0.1	0.2	0.2	6.2	7.2	4.8	5.9	3.3	7.5	0.5	0.4	2.9	1.1	4.8	3.5	1.5	1.1	0.03	0.04	0.09	0.10	0.05	0.04
P value	< 0.05		NS		< 0.05		NS		< 0.05		NS		NS		NS		< 0.025		NS		NS		< 0.10	

Table 7

Leg Raising - Coronary Artery Disease Patients

Patient #	$LVID_d$ (cm)		$LVID_s$ (cm)		LV_{vol-d} (ml)		LV_{vol-s} (ml)		SV (ml)		PWV_{ant} (cm/sec)		PWV_{post} (cm/sec)		D-E (cm/sec)		E-F (cm/sec)		EF		$V_{\overline{CF}}$ (circ/sec)		LAI (LA/Ao)	
	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during	pre	during
1	4.8	4.9	3.3	3.0	110.6	117.6	35.9	27.0	74.6	90.6	7.8	7.4	21.0	12.2	44.8	44.0	13.2	13.4	0.68	0.77	1.11	1.33	1.23	1.42
2	3.7	4.1	2.6	2.7	50.6	68.9	17.6	19.7	33.1	49.2	7.1	5.7	16.0	17.4	30.8	34.4	8.3	18.2	0.65	0.71	1.06	1.17	1.04	1.08
3	4.3	5.0	3.0	3.5	79.5	125.0	27.0	42.9	52.5	82.1	5.8	4.6	11.2	11.4	31.2	41.4	5.1	6.7	0.66	0.66	1.07	0.96	1.40	1.30
4	5.0	5.2	3.9	4.2	59.3	140.6	59.3	74.1	65.7	66.5	11.4	13.4	22.7	28.2	47.8	57.6	8.9	10.1	0.52	0.47	0.75	0.68	0.94	1.10
5	3.9	4.4	2.9	3.3	59.3	85.2	24.4	35.9	34.9	49.2	6.3	5.7	15.6	17.4	22.8	24.2	13.2	16.4	0.59	0.58	0.98	0.96	1.03	1.11
Mean	4.2	4.7	3.1	3.3	71.9	107.5	32.8	39.9	52.2	67.6	7.7	7.4	17.3	17.3	35.5	40.3	9.7	13.0	0.62	0.64	0.99	1.02	1.13	1.20
±SEM	0.3	0.4	0.2	0.2	10.8	13.2	7.2	9.4	8.2	8.4	1.0	1.6	2.0	3.0	4.7	5.5	1.6	2.1	0.06	0.05	0.06	0.11	0.08	0.07
P value	< 0.025		NS		< 0.05		NS		< 0.025		NS		NS		< 0.05		< 0.10		NS		NS		NS	

FIGURE 1

ECHOCARDIOGRAPHIC SCAN:

Left Ventricular (Left) - Mitral (Left,Center -

Aortic (Right) Regions

Legend

En - Endocardium

Ep - Epicardium

AMV - Anterior Mitral Valve Leaflet

PMV - Posterior Mitral Valve Leaflet

LV - Left Ventricular Cavity

RV - Right Ventricular Cavity

IVS - Interventricular Septum

CW - Chest Wall

PLAW - Posterior Left Atrial Wall

AC - Aortic Cusps

LA - Left Atrium

AO - Aortic Root

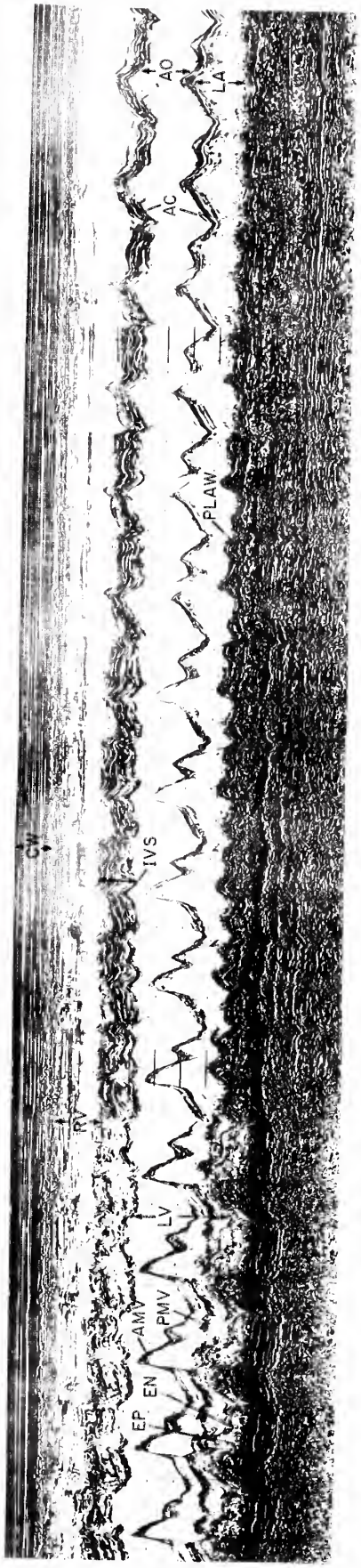


Figure 1

FIGURE 2

Normal Echocardiographic Study

(A) Left Ventricular Cavity

(B) Mitral Valve Region

(C) Aortic Root - Left Atrium

Legend

$LVID_d$ - Left Ventricular Internal Diameter, diastolic

$LVID_s$ - Left Ventricular Internal Diameter, systolic

PWV_{ant} - Posterior Wall Velocity, anteriorly

PWV_{post} - Posterior Wall Velocity, posteriorly

PWT_s - Posterior Wall Thickness, systolic

PWT_d - Posterior Wall Thickness, diastolic

Amp - Amplitude

LVET - Left Ventricular Ejection Time

IVS - Interventricular Septum

AMV - Anterior Mitral Valve Leaflet

En - Endocardium

$RVID_d$ - Right Ventricular Internal Diameter, diastolic

ST_d - Interventricular Septal Thickness, diastolic

ST_s - Interventricular Septal Thickness, systolic

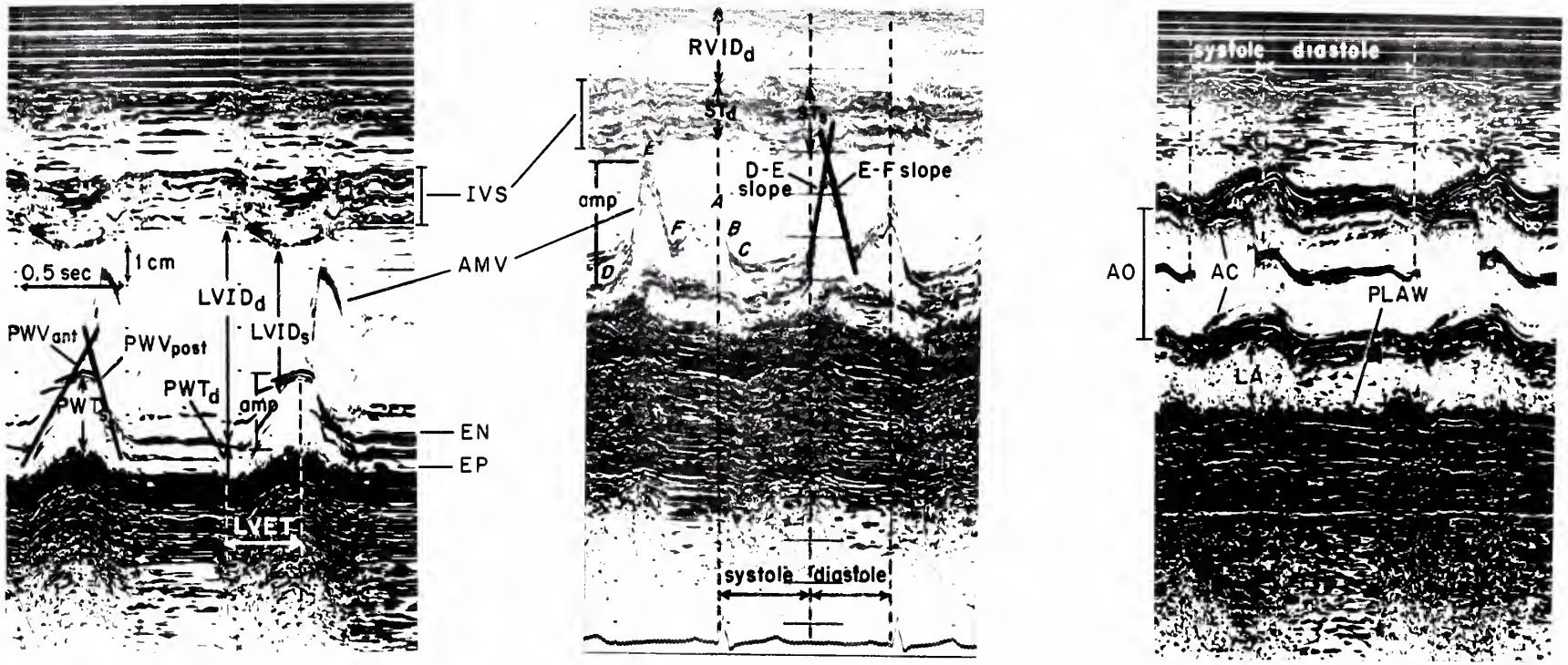
D-E slope - Mitral Valve Opening

E-F slope - Mitral Valve Closure

AO - Aortic Root Diameter

PLAW - Posterior Left Atrial Wall

AC - Left Atrial Diameter


IVS
AMV
0.5 sec
1 cm
LVIDd
LVIDs
PWVant
PWVpost
PWTd
PWT
amp
EN
EP
LVET
RVIDd
STd
amp
D-E slope
E-F slope
A
B
C
D
E
F
systole
diastole
systole
diastole
AO
AC
PLAW
LA

(A) (B) (C)

Figure 2

Figure 3

Echocardiographic Changes: Pre-Dialysis - Post-Dialysis

Legend

Heavy Black Line	-	Mean Change
Brackets	-	$\pm$ Standard Deviation
N.S.	-	Not Significant

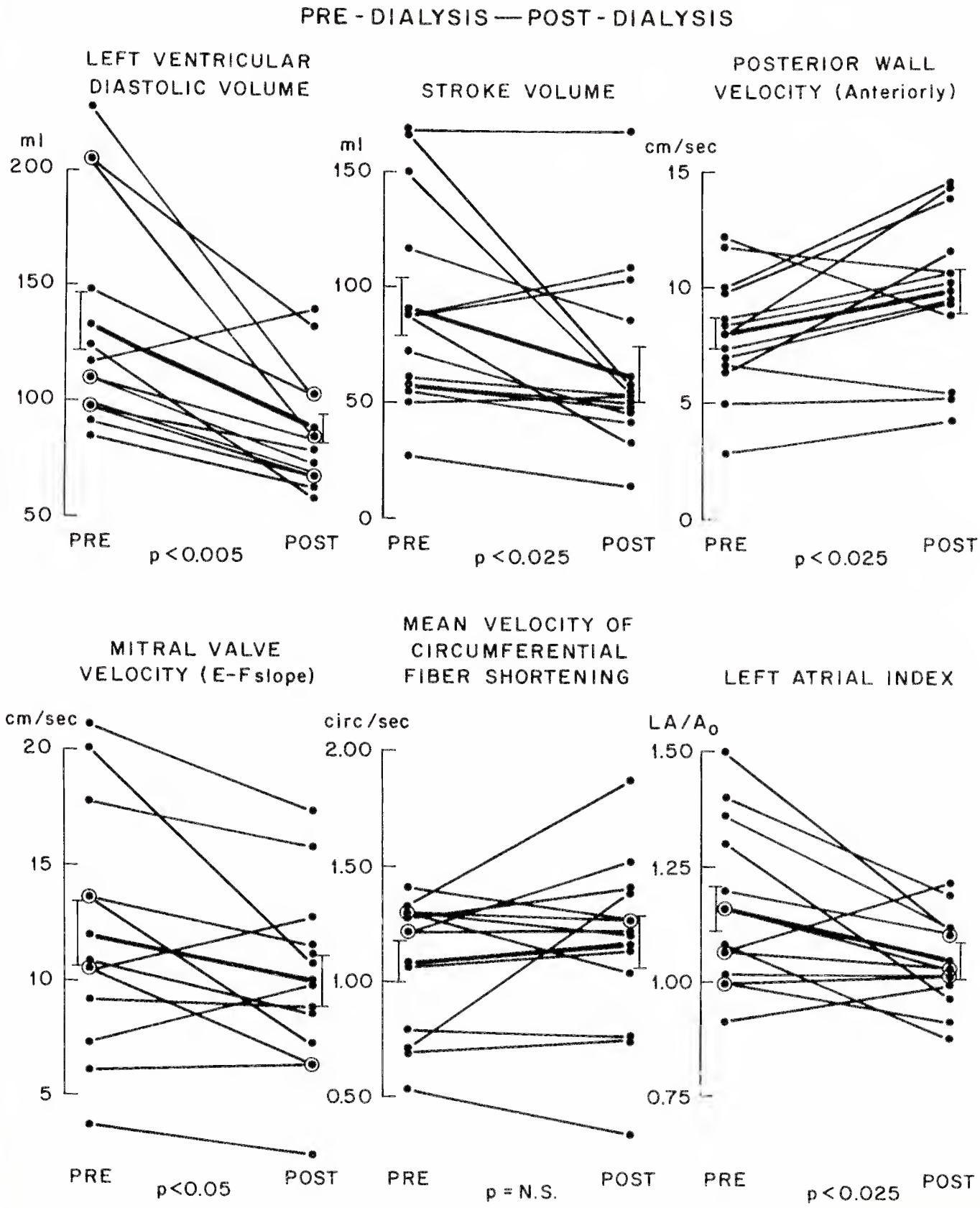

PRE - DIALYSIS — POST - DIALYSIS
LEFT VENTRICULAR DIASTOLIC VOLUME
ml
200
150
100
50
PRE
POST
p < 0.005
STROKE VOLUME
ml
150
100
50
0
PRE
POST
p < 0.025
POSTERIOR WALL VELOCITY (Anteriorly)
cm/sec
15
10
5
0
PRE
POST
p < 0.025
MITRAL VALVE VELOCITY (E-F slope)
cm/sec
20
15
10
5
PRE
POST
p < 0.05
MEAN VELOCITY OF CIRCUMFERENTIAL FIBER SHORTENING
circ/sec
2.00
1.50
1.00
0.50
PRE
POST
p = N.S.
LEFT ATRIAL INDEX
LA/Ao
1.50
1.25
1.00
0.75
PRE
POST
p < 0.025

Figure 3

Figure 4

Representative Echocardiograms: Changes with Dialysis

(A) Pre-Dialysis

(B) Post-Dialysis

Legend

$LVID_d$	-	Left Ventricular Internal Diameter, diastolic
$LVID_s$	-	Left Ventricular Internal Diameter, systolic
PWV_{ant}	-	Posterior Wall Velocity, anteriorly
CW	-	Chest Wall
RV	-	Right Ventricle
IVS	-	Interventricular Septum
AMV	-	Anterior Mitral Valve Leaflet
PMV	-	Posterior Mitral Valve Leaflet
En	-	Endocardium
Ep	-	Epicardium

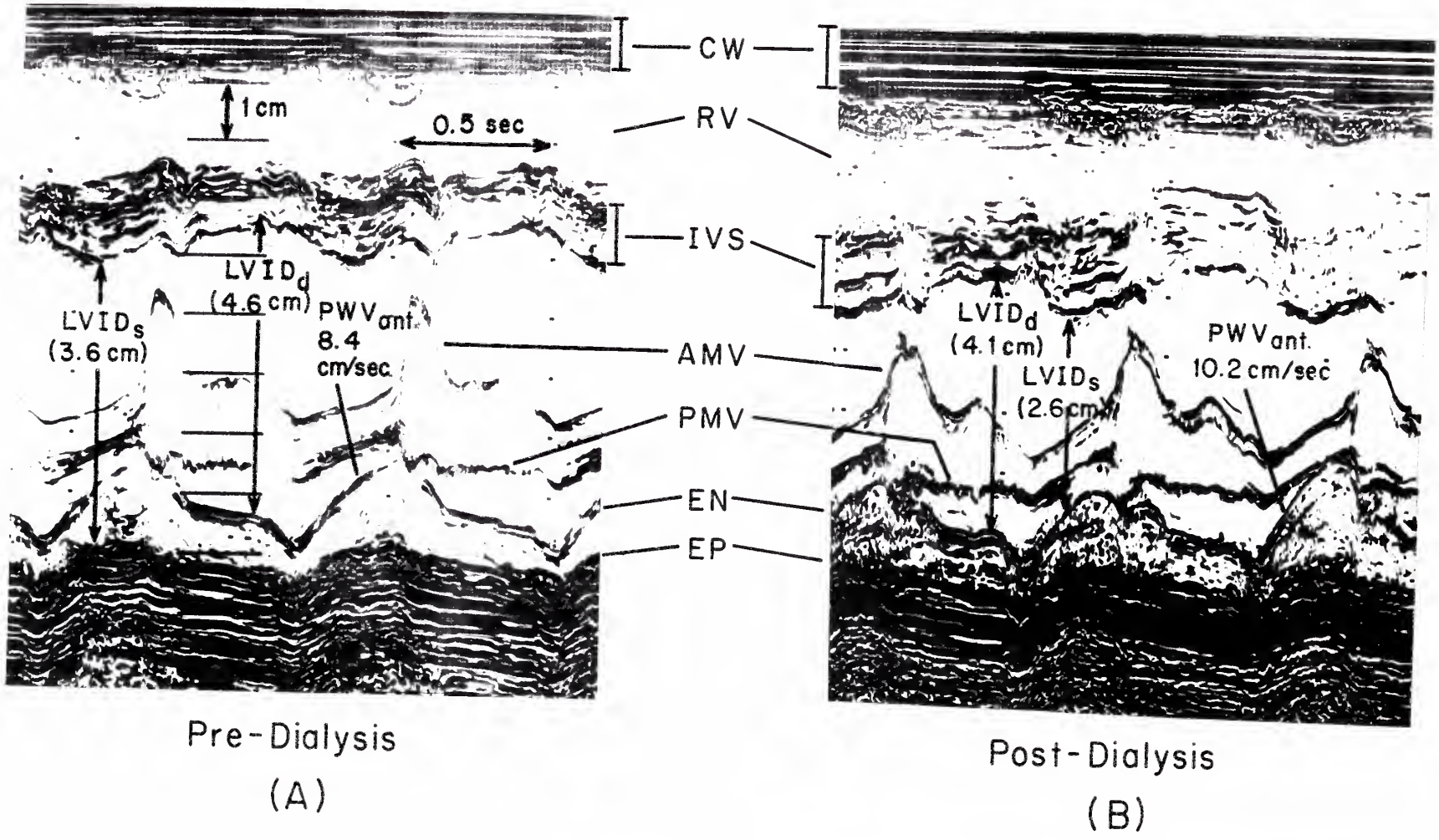

CW
RV
IVS
AMV
PMV
EN
EP
1 cm
0.5 sec
LVIDd
(4.6 cm)
LVIDs
(3.6 cm)
PWVant.
8.4
cm/sec
LVIDd
(4.1 cm)
LVIDs
(2.6 cm)
PWVant.
10.2 cm/sec
Pre-Dialysis
(A)
Post-Dialysis
(B)

Figure 4

Figure 5

Echocardiographic Changes: Post-Dialysis (A) - Post-Dialysis Plus Infusion (B)

Legend

Heavy Black Line	-	Mean Change
Brackets	-	$\pm$ Standard Deviation
N.S.	-	Not significant

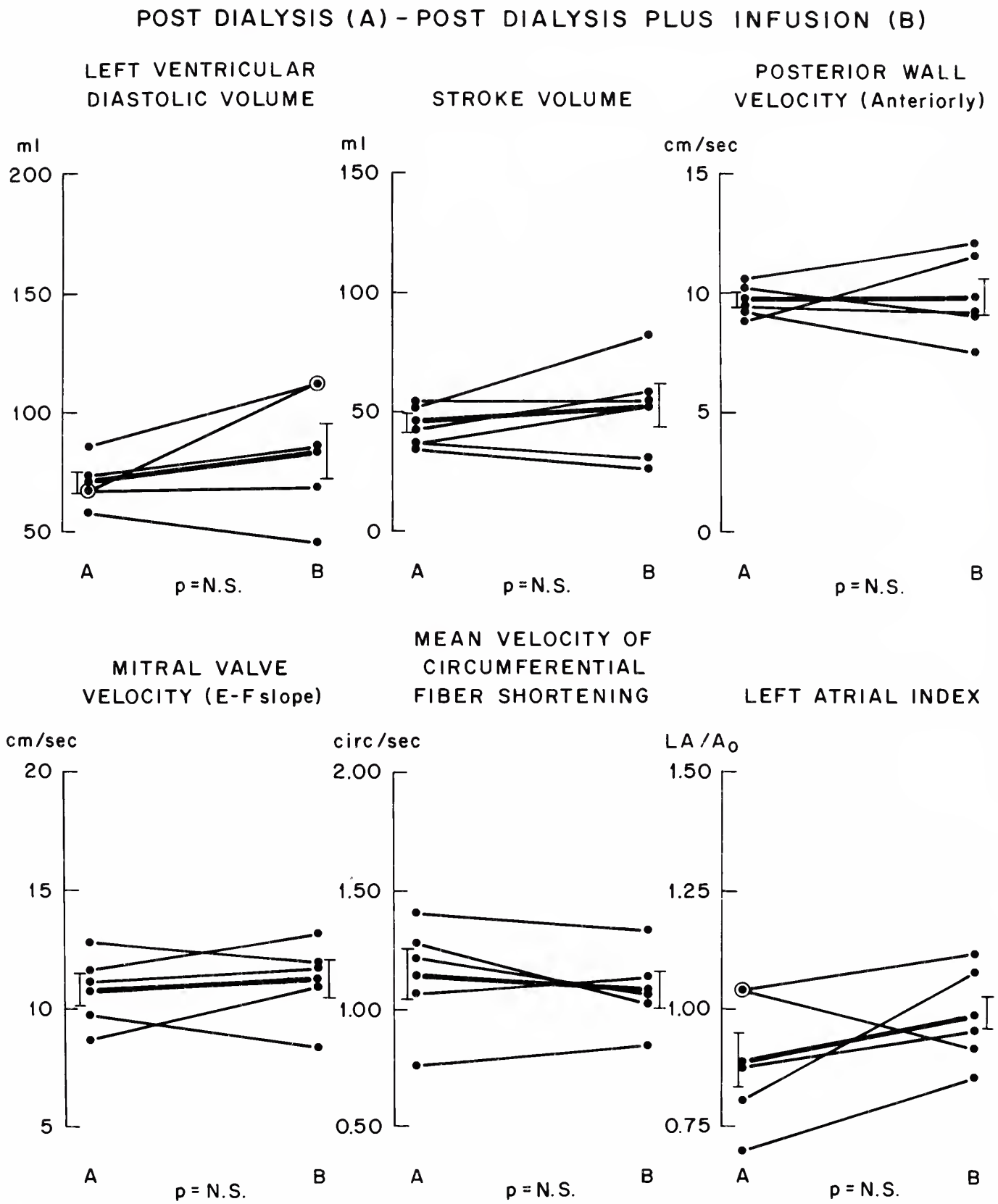

POST DIALYSIS (A) - POST DIALYSIS PLUS INFUSION (B)
LEFT VENTRICULAR DIASTOLIC VOLUME
ml
200
150
100
50
A
B
p = N.S.
STROKE VOLUME
ml
150
100
50
0
A
B
p = N.S.
POSTERIOR WALL VELOCITY (Anteriorly)
cm/sec
15
10
5
0
A
B
p = N.S.
MITRAL VALVE VELOCITY (E-F slope)
cm/sec
20
15
10
5
A
B
p = N.S.
MEAN VELOCITY OF CIRCUMFERENTIAL FIBER SHORTENING
circ/sec
2.00
1.50
1.00
0.50
A
B
p = N.S.
LEFT ATRIAL INDEX
LA/Ao
1.50
1.25
1.00
0.75
A
B
p = N.S.

Figure 5

Figure 6

Echocardiographic Changes: Post-Dialysis (A) - Pre-Next Dialysis (B)

Legend

Heavy Black Line	-	Mean Change
Brackets	-	$\pm$ Standard Deviation
N.S.	-	Not Significant

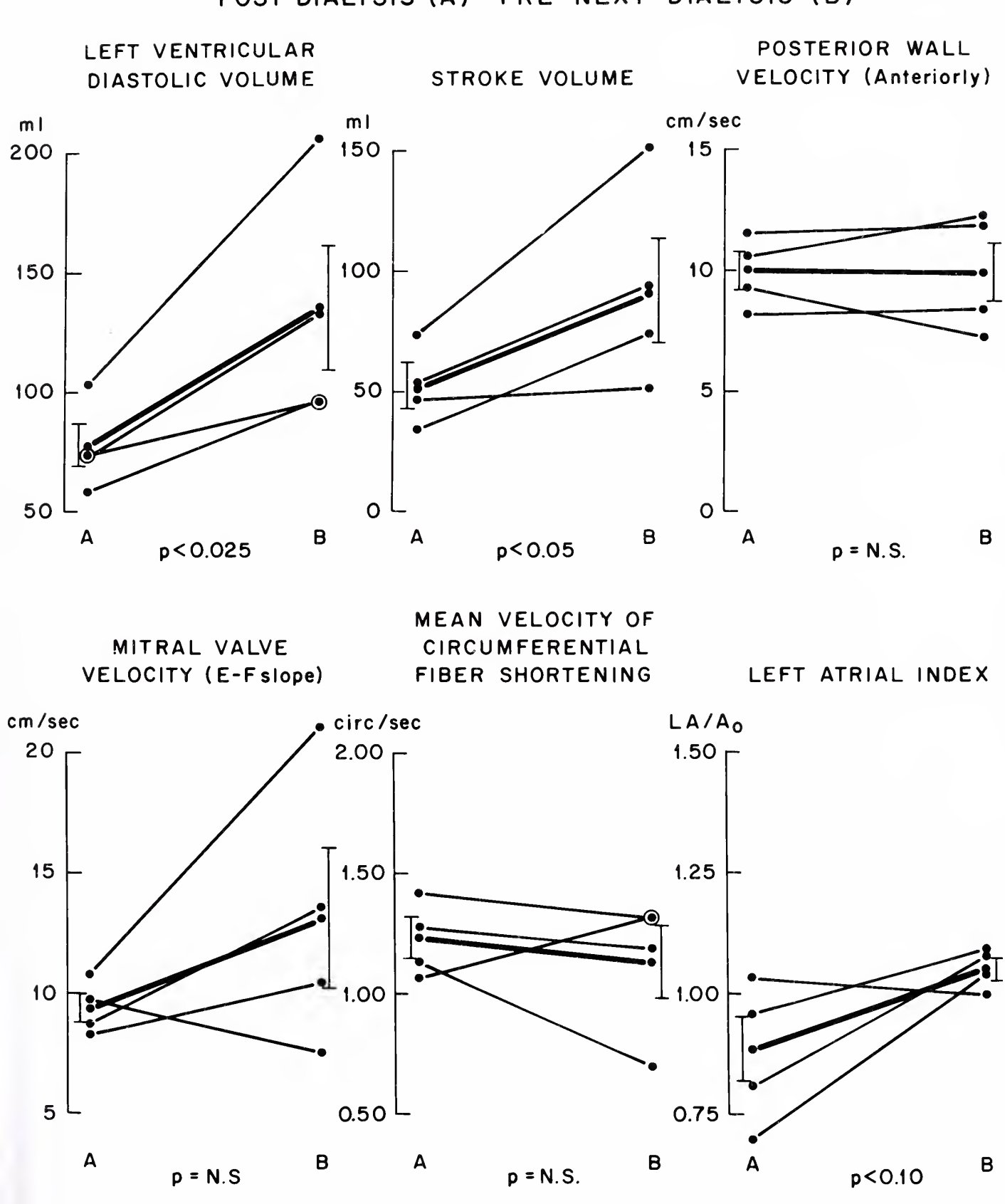

POST DIALYSIS (A) - PRE NEXT DIALYSIS (B)
LEFT VENTRICULAR DIASTOLIC VOLUME
ml
200
150
100
50
A
B
p<0.025
STROKE VOLUME
ml
150
100
50
0
A
B
p<0.05
POSTERIOR WALL VELOCITY (Anteriorly)
cm/sec
15
10
5
0
A
B
p = N.S.
MITRAL VALVE VELOCITY (E-F slope)
cm/sec
20
15
10
5
A
B
p = N.S
MEAN VELOCITY OF CIRCUMFERENTIAL FIBER SHORTENING
circ/sec
2.00
1.50
1.00
0.50
A
B
p = N.S.
LEFT ATRIAL INDEX
LA/Ao
1.50
1.25
1.00
0.75
A
B
p<0.10

Figure 6

Figure 7

Echocardiographic Changes: Leg Raising - Normals

Legend

Heavy Black Line	-	Mean Change
Brackets	-	$\pm$ Standard Deviation
N.S.	-	Not Significant

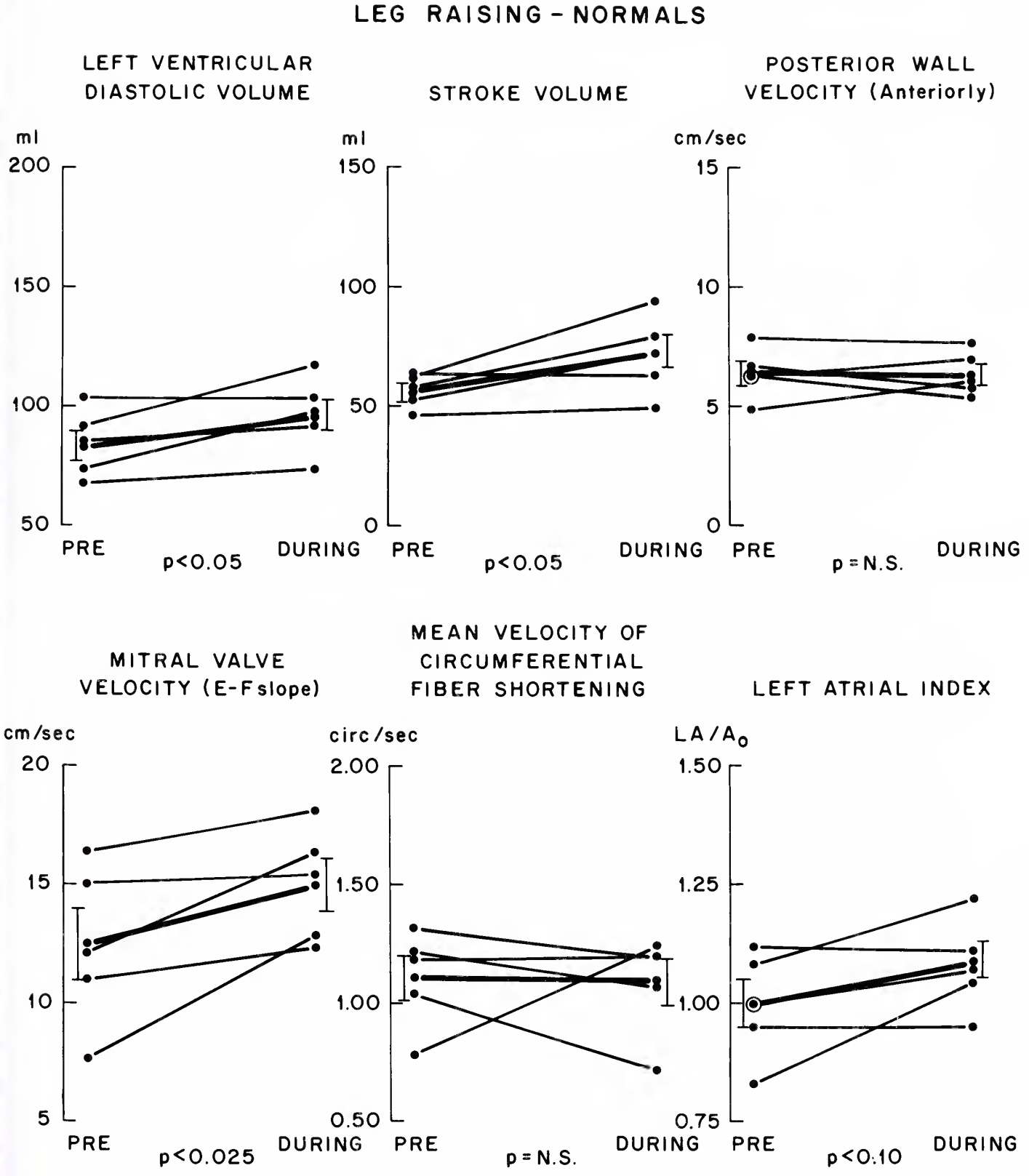

LEG RAISING - NORMALS
LEFT VENTRICULAR DIASTOLIC VOLUME
STROKE VOLUME
POSTERIOR WALL VELOCITY (Anteriorly)
ml
200
150
100
50
ml
150
100
50
0
cm/sec
15
10
5
0
PRE
p<0.05
DURING
PRE
p<0.05
DURING
PRE
p=N.S.
DURING
MITRAL VALVE VELOCITY (E-F slope)
MEAN VELOCITY OF CIRCUMFERENTIAL FIBER SHORTENING
LEFT ATRIAL INDEX
cm/sec
20
15
10
5
circ/sec
2.00
1.50
1.00
0.50
LA/A0
1.50
1.25
1.00
0.75
PRE
p<0.025
DURING
PRE
p=N.S.
DURING
PRE
p<0.10
DURING

Figure 7

Figure 8

Echocardiographic Changes: Leg Raising - Coronary Artery Disease Patients

Legends

Heavy Black Line	-	Mean Change
Brackets	-	$\pm$ Standard Deviation
N.S.	-	Not Significant

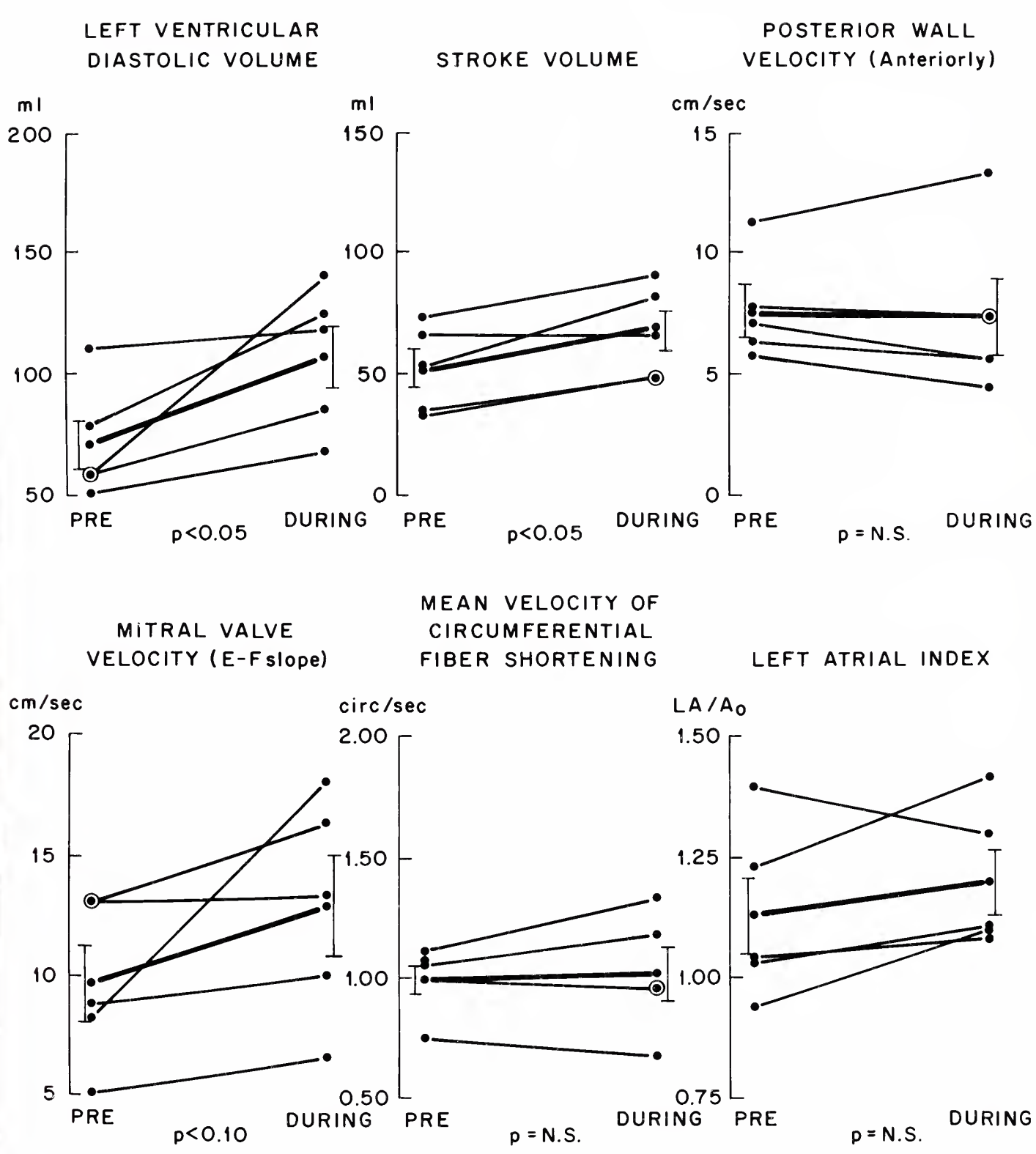

LEG RAISING - CORONARY ARTERY DISEASE PATIENTS
LEFT VENTRICULAR DIASTOLIC VOLUME
STROKE VOLUME
POSTERIOR WALL VELOCITY (Anteriorly)
ml
200
150
100
50
ml
150
100
50
0
cm/sec
15
10
5
0
PRE
p<0.05
DURING
PRE
p<0.05
DURING
PRE
p = N.S.
DURING
MITRAL VALVE VELOCITY (E-F slope)
MEAN VELOCITY OF CIRCUMFERENTIAL FIBER SHORTENING
LEFT ATRIAL INDEX
cm/sec
20
15
10
5
circ/sec
2.00
1.50
1.00
0.50
LA/Ao
1.50
1.25
1.00
0.75
PRE
p<0.10
DURING
PRE
p = N.S.
DURING
PRE
p = N.S.
DURING

Figure 8

Figure 9

Serial Echocardiographic and Clinical Changes

with Congestive Heart Failure (patient #1)

Legend

SV	-	Stroke Volume
LV_{vol-d}	-	Left Ventricular Volume, diastolic
$V_{\overline{CF}}$	-	Mean Velocity of Circumferential Fiber Shortening
LAI	-	Left Atrial Index
LA	-	Left Atrial Diameter
Ao	-	Aortic Root Diameter
C/T (CXR)	-	Cardio-Thoracic Ratio, from the chest X-ray
SOB	-	Shortness of Breath

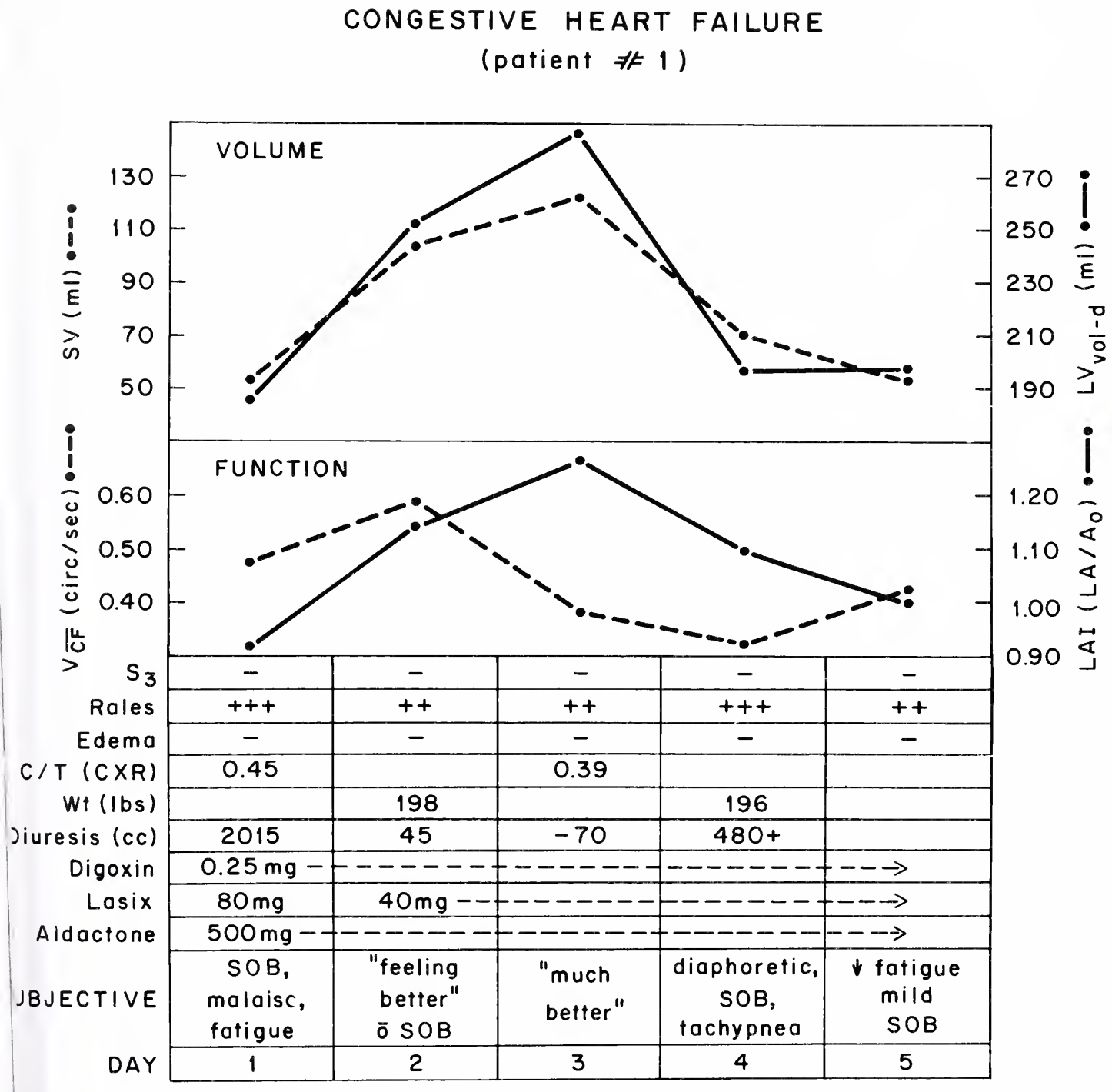

CONGESTIVE HEART FAILURE
(patient #1)
VOLUME
FUNCTION
SV (ml)
LV vol-d (ml)
VCF (circ/sec)
LAI (LA/Ao)
130
110
90
70
50
270
250
230
210
190
0.60
0.50
0.40
1.20
1.10
1.00
0.90
S3 – – – – –
Rales +++ ++ ++ +++ ++
Edema – – – – –
C/T (CXR) 0.45 0.39
Wt (lbs) 198 196
Diuresis (cc) 2015 45 −70 480+
Digoxin 0.25 mg →
Lasix 80mg 40mg →
Aldactone 500mg →
SUBJECTIVE SOB, malaisc, fatigue "feeling better" ō SOB "much better" diaphoretic, SOB, tachypnea ↓ fatigue mild SOB
DAY 1 2 3 4 5

Figure 9

Figure 10

Representative Echocardiograms: Changes with Congestive Heart Failure

(Patient #1)

(A) Day 1

(B) Day 2

(C) Day 3

Legend

$LVID_d$	-	Left Ventricular Internal Diameter, diastolic
$LVID_s$	-	Left Ventricular Internal Diameter, systolic
CW	-	Chest Wall
RV	-	Right Ventricle
IVS	-	Interventricular Septum
AMV	-	Anterior Mitral Valve Leaflet
PMV	-	Posterior Mitral Valve Leaflet
ECG	-	Electrocardiogram
En	-	Endocardium
Ep	-	Epicardium
P	-	Pericardium

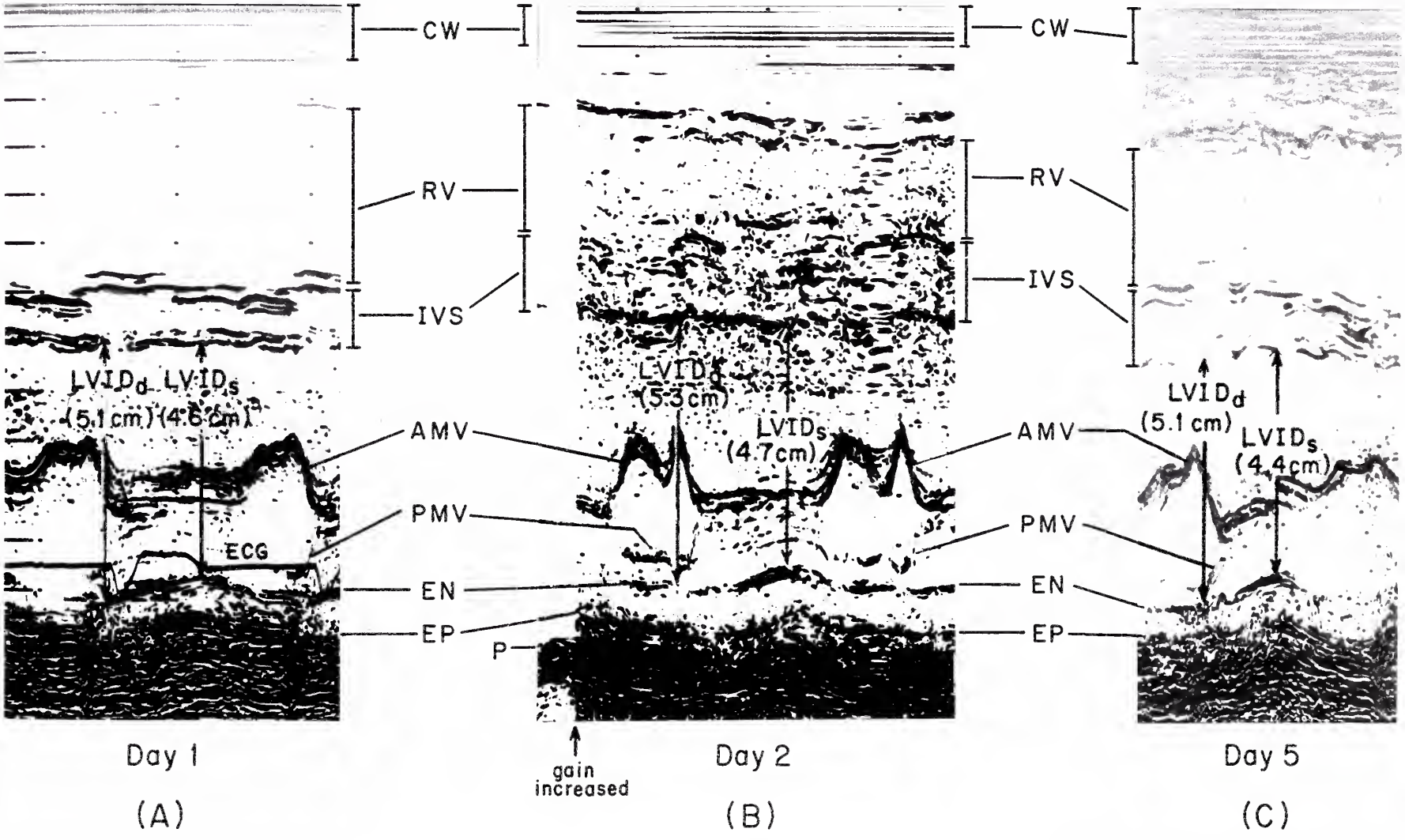

CW
RV
IVS
LVIDd
(5.1 cm)
LVIDs
(4.6 cm)
AMV
PMV
ECG
EN
EP
Day 1
(A)
LVIDd
(5.3 cm)
LVIDs
(4.7 cm)
P
gain
increased
Day 2
(B)
CW
RV
IVS
LVIDd
(5.1 cm)
LVIDs
(4.4 cm)
AMV
PMV
EN
EP
Day 5
(C)

Figure 10

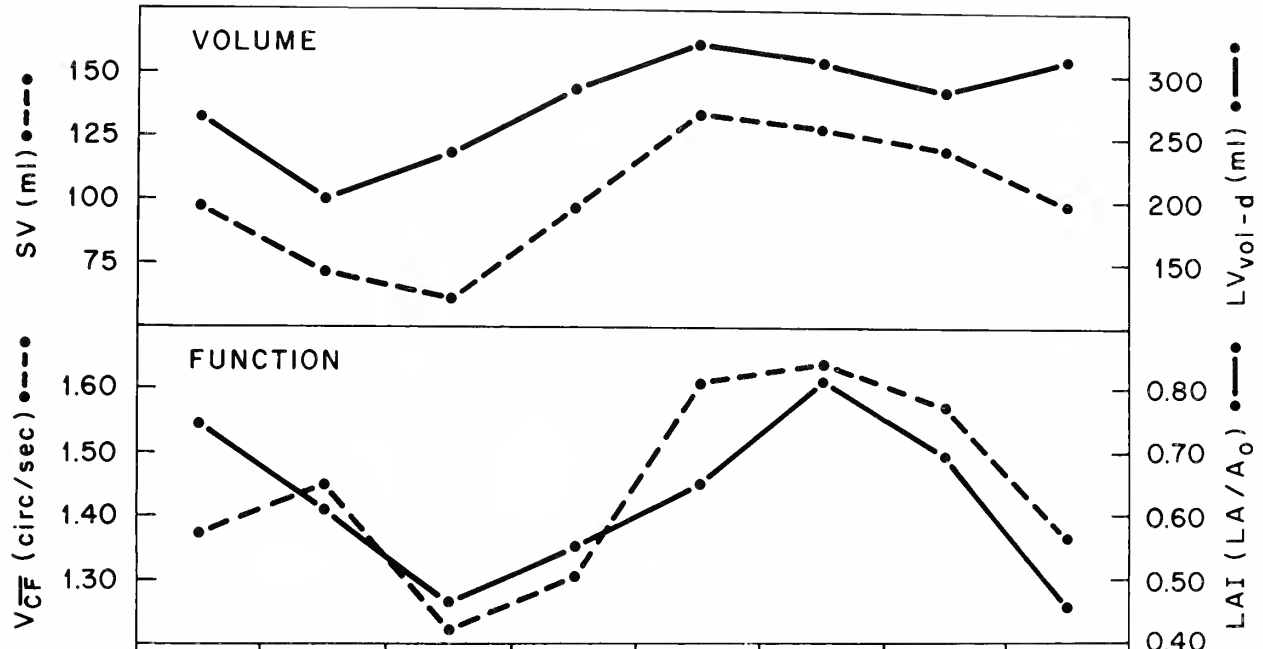
Figure 11

Serial Echocardiographic and Clinical Changes with Congestive Heart Failure (Patient #2)

Legend

SV	-	Stroke Volume
LV_{vol-d}	-	Left Ventricular Volume, diastolic
$V_{\overline{CF}}$	-	Mean Velocity of Circumferential Fiber Shortening
LAI	-	Left Atrial Index
LA	-	Left Atrial Diameter
Ao	-	Aortic Root Diameter
C/T (CXR)	-	Cardio-Thoracic Ratio, from the chest X-ray
SOB	-	Shortness of Breath

CONGESTIVE HEART FAILURE
(patient #2)



S_3	+	+	+	+	+	–	–	–
Rales	+++	++	++	+	+	–	+	+
Edema	+	+	+	+	–	–	–	–
C/T (CXR)	0.71				0.63			
Wt (lbs)	185					178		
Diuresis (cc)	810		300+	900	650			
Digoxin	0.75 mg	-----	-----	-----	-----	-----	-----	-----
Lasix	160 mg	80 mg	-----	-----	-----	-----	-----	-----
Aldactone	100 mg	-----	-----	-----	-----	-----	-----	-----
SUBJECTIVE	SOB, fatigue 2000 cc	↓SOB Diuresis	↓SOB "feeling better"	↓ SOB	ō SOB	ō SOB	ō SOB poor night's sleep	↑ SOB fatigue
DAY	1	2	3	4	5	6	7	8

Figure 11

Figure 12

Representative Echocardiograms: Changes with Congestive Heart Failure (Patient #2)

(A) Day 1

(B) Day 5

Legend

$LVID_d$	-	Left Ventricular Internal Diameter, diastolic
$LVID_s$	-	Left Ventricular Internal Diameter, systolic
CW	-	Chest Wall
ECG	-	Electrocardiogram
RV	-	Right Ventricle
IVS	-	Interventricular Septum
AMV	-	Anterior Mitral Valve Leaflet
PMV	-	Posterior Mitral Valve Leaflet
En	-	Endocardium
Ep	-	Epicardium

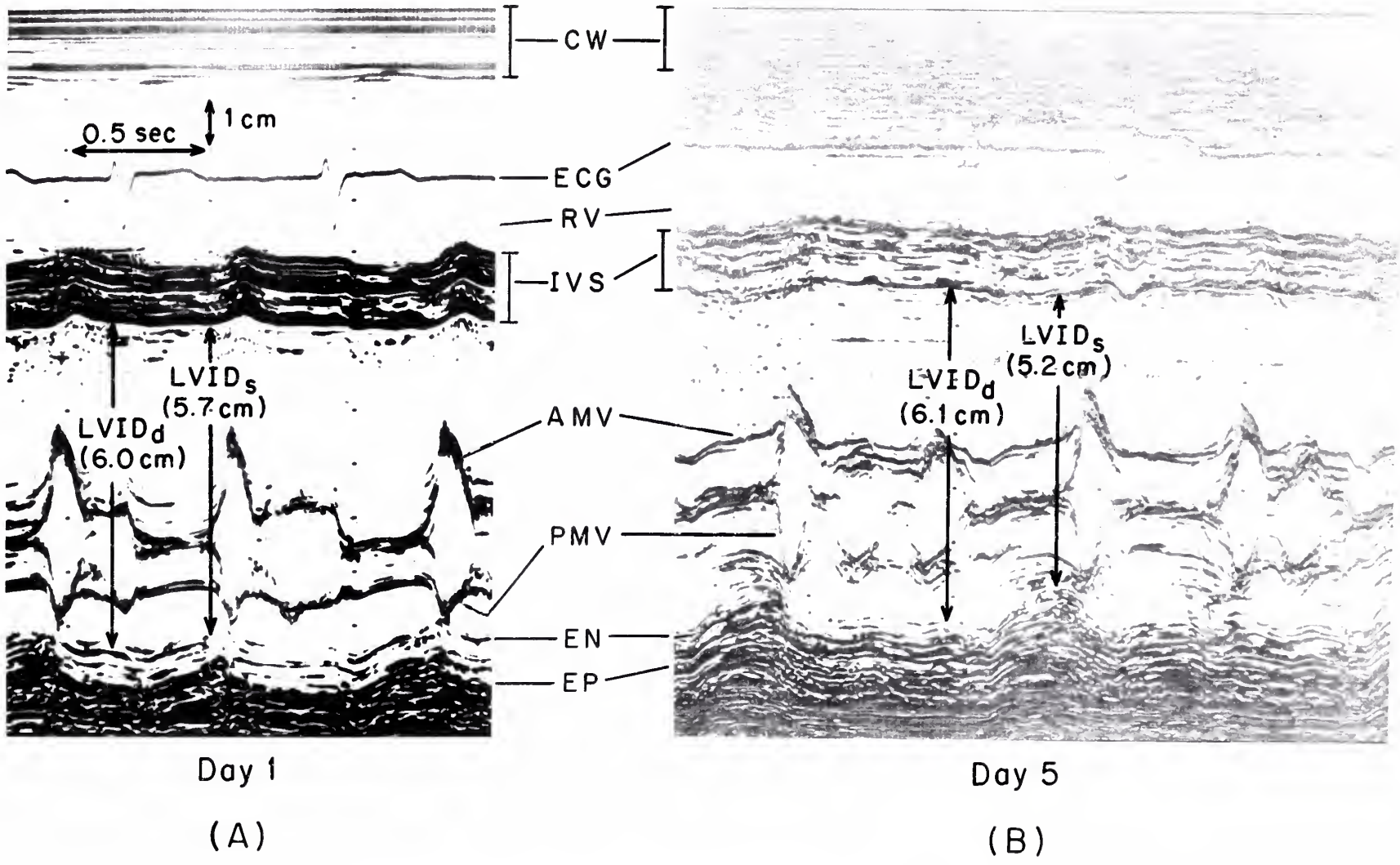

CW
0.5 sec
1 cm
ECG
RV
IVS
LVIDs
(5.7 cm)
LVIDd
(6.0 cm)
AMV
PMV
EN
EP
LVIDd
(6.1 cm)
LVIDs
(5.2 cm)
Day 1
(A)
Day 5
(B)

Figure 12

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