DYNAMIC MYOCARDIAL SCINTIGRAPHY TO EVALUATE MYOCARDIAL FUNCTION

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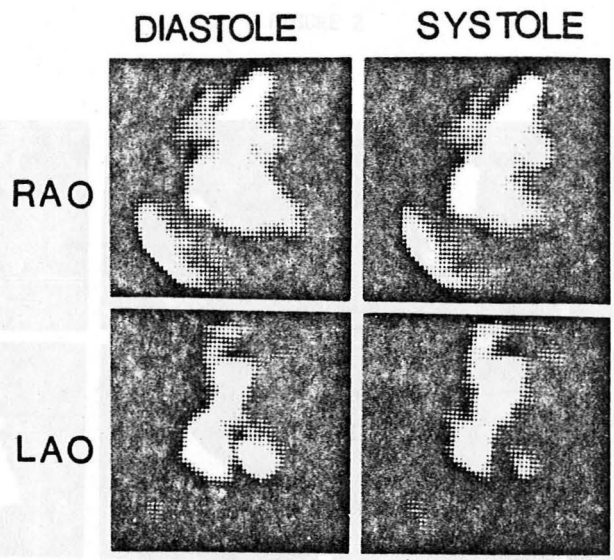
One of the most important problems in the evaluation of patients with cardiac diseases is the assessment of global and regional ventricular function, particularly left ventricular function. The most satisfactory methods for direct assessment of left ventricular function utilize some form of imaging the heart. The traditional method for imaging the ventricles has been contrast angiography and cardiac catheterization. More recently, left ventricular imaging has been performed by echocardiography and myocardial scintigraphy (1,2).

Echocardiography is a useful means to measure ventricular dimensions, to estimate ejection fraction, to analyze wall motion in various portions of the ventricle and to evaluate cardiac valves and the pericardium. However, it is not possible to obtain satisfactory echocardiograms in some patients because they are obese, have important chronic obstructive lung disease, and/or they are not cooperative. Generally speaking, dynamic myocardial scintigrams that provide high quality images of the left and right ventricles may be obtained in virtually every individual studied (Figure 1).

FIGURE 1



Typical end-diastolic and end-systolic gated blood pool images in RAO and LAO views. Right and left ventricles are superimposed in RAO view, but are visualized separately in the LAO view, which looks along the interventricular septum.

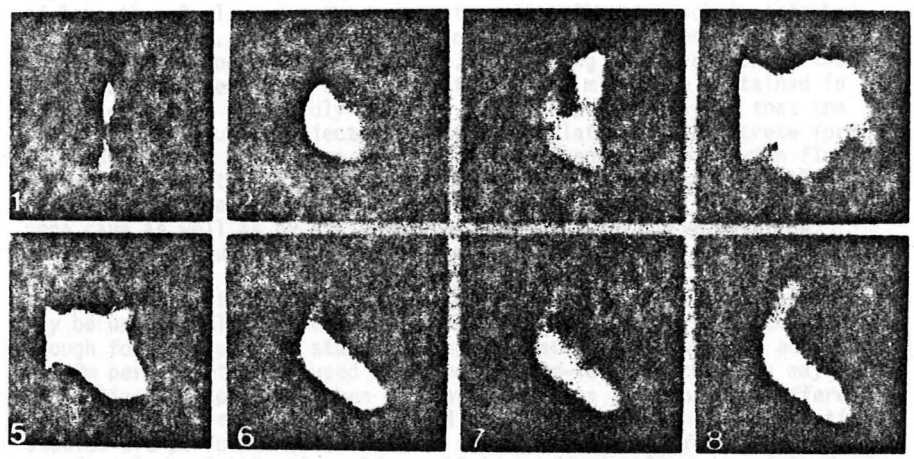
Myocardial scintigraphy as a means to characterize global and regional ventricular function has become increasingly popular because it is convenient, less expensive than angiographic techniques, may be repeated frequently even in sick patients, can be performed close to the patient's bedside, is painless and relatively noninvasive and involves almost no hazard to the patient.

Ventricular images are obtained using two general methods: (1) the "First-Pass" and (2) using "equilibrium" methodology so that one may analyze various portions of the contraction and relaxation pattern of the heart in a continuous manner -- the most popular approaches presently are the "Multigated Image Acquisition" studies or "MUGA Study".

Quantitative analysis of the data from the first pass study is largely dependent upon application of the indicator-dilution principles (3,4). The major assumption utilized in this methodology is that homogenous mixing of the radioactive tracer with blood occurs so that changes in radiographic count rates correspond proportionately to changes in chamber volumes (5). It is important, that a compact radionuclide bolus be injected and complete mixing is facilitated when there is a separate mixing chamber proximal to the ventricle.

Since there is temporal and anatomic separation of radioactivity within each of the cardiac chambers, quantitative evaluation of both right and left heart performance can be made from a single study (Figure 2).

FIGURE 2



Sequential 1-sec images obtained during first-pass of radionuclide bolus through the central circulation. The normal temporal and anatomic separation of radioactivity within the cardiac chambers and great vessels is present. Frame 3 best identifies the right ventricle and pulmonary artery, while frame 8 shows the left ventricle and ascending aorta.

The earliest applications of this technique allowed measurements of chamber-to-chamber transit times and of cardiac output using a scintillation probe (6-8). Initial analysis of the high frequency components of the left ventricular time-activity curve allowed calculation of left ventricular ejection fraction. More recently, this methodology has been used to evaluate indices of systolic left ventricular performance including presence, location and severity of ventricular asynergy and right ventricular ejection fraction (9).

General Approach to Utilizing First-Pass Measurements

First-pass studies may be performed either upright or supine and in any position relative to the detector. This includes the anteroposterior, left and right anterior oblique, and left posterior oblique positions. Temporal separation of radioactivity within individual cardiac chambers makes evaluation of ventricular function possible utilizing the various projections. The anterior projection is the one most often used, because it places the heart close to the detector, thereby maximizing count rate detection (9). It is also the easiest projection to use and standardize during exercise, it provides good separation between the heart and lungs, it is suitable for analysis of segmental wall motion and it allows calculation of both right and left ventricular ejection fractions from a single injection (10-12). Whatever position(s) are chosen for a particular examination, the same positions should also be used for comparative evaluations in future studies.

Injections of the radionuclide material may be made through an antecubital vein, an external jugular vein or directly into the pulmonary artery. A 19 or 20 gauge indwelling catheter is inserted into the vein and an intravenous infusion is established. To facilitate careful bolus injection, the catheter is attached to an extension tube having a volume of less than 3 ml, and a three-way stopcock. The stopcock is attached to the other end. The radioactive bolus contained in less than 1 ml of solution is introduced into the tube. Following the injection of the radionuclide material, a flush injection of 20 ml saline contained in a separate syringe is rapidly injected. This approach assures that the radionuclide bolus is injected into the circulation in a discrete form and that it does not become diluted in the extension tubing with fluid. The adequacy of the injection technique should be assessed visually in each study by analyzing the transit of activity through the superior vena cava as well as by analyzing the time-activity curve over the subclavian and superior vena cava systems (13).

For these studies, any technetium-99m labeled radiopharmaceutical may be used as all of them remain within the intravascular space long enough for a first pass study. Most frequently, high specific activity Tc-99m pertechnetate is used but other Tc-99m-labeled compounds may also be utilized. Especially when sequential studies are planned, different Tc-99m labeled compounds may be used. For example, when two sequential studies are performed (such as rest and exercise), the first injection is often made with Tc-99m sulfur colloid, which is cleared rapidly from

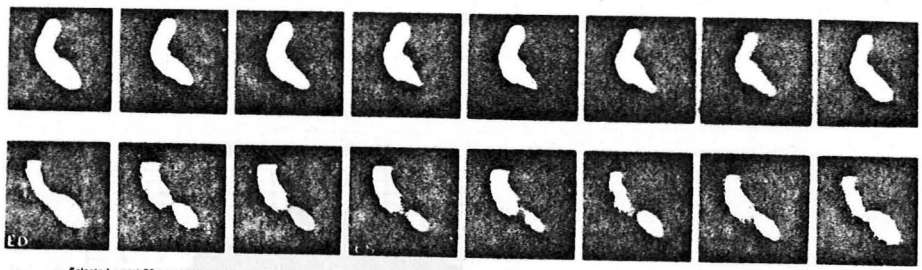
the blood pool by the reticuloendothelial system leaving no residual blood pool activity. The second injection may then be made with technetium 99m-pertechnetate (10,12). An alternative tracer for the first injection in a pair, or when three injections are needed, is Tc-99m-DPTA (diethylenetriaminine pentaacetic acid), which is cleared rapidly by the kidneys. First-pass ventricular performance studies can be combined with acute infarct imaging using Tc-99m stannous pyrophosphate (14-18). First-pass studies also can be performed in combination with subsequent gated cardiac blood pool imaging. In this case, the bolus injection is made with Tc-99m-human serum albumin, *in vitro* labeled red blood cells, or Tc-99m pertechnetate preceded by injection of cold stannous pyrophosphate for subsequent *in vivo* labeling of red blood cells (19-21). Twelve to 25 mCi of the technetium are used for each injection, with a total dose not exceeding 35 mCi for an adult. The whole body and target organ radiation exposures from these radionuclide doses are within accepted limits based upon known dosimetry (9).

Either a scintillation camera or probe may be used for the detection of the radionuclide and for the evaluation of ventricular function. For probe studies, a small radionuclide dose is required. Either a Tc-99m-labeled pharmaceutical or indium 113m chloride is used. The dose generally is 1-2 mCi for each study. The indium 113m binds *in vivo* to transferrin, labeling the intravascular blood pool (9). Because of its high gamma assimilation energies, this tracer is not ideal for use with a scintillation camera. Various probes have been developed to allow evaluation of ventricular function (22-26) including the more recent development of probes that allow gated acquisition data (25,26). One of these gated probes (developed by Wagner) (26) is termed the "nuclear stethoscope". This probe allows the determination of left ventricular ejection fraction from first transit data. Following a bolus injection, approximately 24 seconds of data are collected in 100 msec time frames. Background subtraction is provided and the data are portrayed on a cathode ray tube. An integrated microprocessor calculates theoretical exponential decay of the activity from the user determined peak of left ventricular activity. Patient blood volumes per minute are determined from this relative cardiac output. Cardiac output is calculated by multiplying this value by the patient's actual blood volume. Ejection fraction can be determined from time-activity curves that are generated.

The choice of a scintillation camera for first-pass studies depends on various considerations. The camera chosen must provide adequate temporal and spatial resolution with acceptable counting statistics. The major limiting factor when studies are performed on a conventional single crystal camera is the low count rate of raw data. Because of this factor in data acquisition, first-pass data obtained on a single crystal scintillation camera require application of one of several mathematical techniques to overcome the statistical uncertainty of the low count rate data (9,14).

In contrast, the multicrystal camera allows accumulation of high count rates, up to approximately 450,000 counts per second without dead time losses. This system is composed of a mosaic of 294 individual sodium iodide crystals coupled to 35 photomultiplier tubes. Because radionuclide detection and positioning are independent, the dead time of the system is almost exclusively a function of the speed at which electronics can process the event. With a high sensitivity parallel hole collimator, a 25 mCi dose of Tc-99m results in over 400,000 counts per second in the overall image and a count density of approximately 500 counts per cm^2 in the left ventricle (9). In dynamic studies, edge detection is dependent not only upon intrinsic spatial resolution of the camera and collimator, but also upon count density and target-to-background ratio. Small changes in regional wall motion can be detected at these high count rates (Figure 3) (9).

FIGURE 3



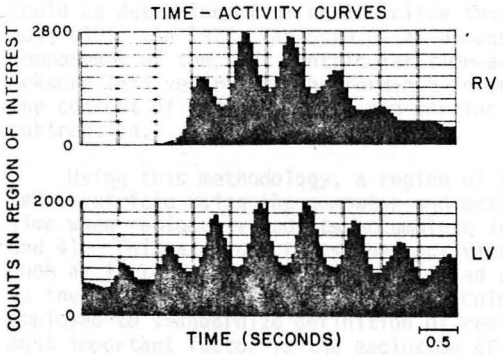
Selected serial 50-msec left ventricular images through the cardiac cycle shown superimposed over the end-diastolic perimeters. The first frame in each series represents end diastole (ED) and the fourth frame end-systole (ES). The upper row of images was obtained at rest and the lower row during maximal bicycle exercise in a patient with coronary artery disease. The two series are displayed at the same heart rate. Regional wall motion is normal at rest. However, inferopical hypokinesis is present during exercise.

Depending upon the scintillation camera and computer used, the image data are often stored in list mode on high speed magnetic disks. In general, studies are obtained at 20-25 frames per second at 40-50 msec intervals to allow accurate analysis of the high frequency components of the regional time-activity curve. The optimal framing interval has been shown to be dependent upon heart rate. At resting heart rates, the framing rates noted above are adequate. However, at elevated heart rates, such as those encountered during exercise and when peak ejection or filling rates are to be determined, higher framing rates of 33-50 frames per second (10-30 msec intervals) are needed. The progressive decrease in the duration of the accumulation interval enhances the accuracy of identification of the end-diastolic and end-systolic counts, but the decrease in the count framing interval also increases the statistical error associated with each data point (9). An appropriate balance between these factors must be used.

Measurement of Global Ventricular Function

Figure 4 demonstrates time-activity curve obtained with the first-pass technique using a computerized multicrystal scintillation camera (9).

FIGURE 4



Right ventricular (RV) and left ventricular (LV) time-activity curves obtained at 20 frames/sec with the computerized multicrystal scintillation camera. Note the extremely high count rates.

Measurement of Right Ventricular Performance

Using first-pass methodology, a high frequency time-activity curve is generated from the right ventricular region of interest (Figure 4). In the anterior postion, there is some overlap between right ventricle and right atrium resulting in a right atrial background contributing to the peak of the right ventricular time-activity curve. Thus, a background region of interest is chosen adjacent to the right ventricle at the interface between the right ventricle and the right atrium. A high frequency time-activity curve is generated from the background region and subtracted temporally from the right ventricular curve. Right ventricular ejection is calculated as the average of several beats at the peak of the background-corrected right ventricular time-activity curve.

Alternatively, studies may be performed utilizing a single crystal camera in the right anterior oblique position (27,28). Background correction is accomplished using standard techniques. The gated first-pass study may be utilized with this approach (28,29). Using this methodology, the cardiac cycle is divided into 16 equal frames based upon the heart rate. First-pass data are acquired in synchrony with the electrocardiogram and stored temporally in the 16 frames per cardiac cycles. Several beats are summed during the right ventricular phase forming a representative cycle. Good correlation has been noted between list mode and gated first-pass right ventricular ejection fraction (29). Background correction appears to be less important for right ventricular ejection fraction than for left ventricular fraction because there is less noncardiac activity during the right heart phase.

Measurement of Left Ventricular Performance

Mullins, Ashburn using a geometric approach similar to that employed with contrast ventriculography demonstrated that ventricular volumes could be determined from radionuclide images of the left ventricle in dogs (30). In 1972, Van Dyke et al demonstrated that the high frequency components of the left ventricular time-activity curve can be used to measure left ventricular performance in man (31). They also introduced the concept of correction for non-cardiac activity, i.e., background subtraction.

Using this methodology, a region of interest is identified over the left ventricle using the computer and activities analyzed only at the time when radioactive counts accumulate in the left ventricle (Figures 2 and 4). This excludes times when activity is in overlapping structures such as in the right ventricle. A fixed region of interest corresponding to the end-diastolic images is used. Color-coded isocount images may be employed to standardize definition of regions of interest (32-34). The most important factor is the exclusion of the proximal aorta from the chosen region.

Three approaches to left ventricular background correction have been employed. Marshall et al used the time-activity curve to aid in determining background (10). A series of frames are chosen immediately prior to the first discernible left ventricular beat on the time-activity curve. This fixed background image represents overlying and scattered radiation from the left atrium and lungs at the time when all the radionuclide activity is in these structures. This provides a regional background correction which enhances precise definition of left ventricular edges. The same number of background frames of left ventricular beats to be analyzed are included.

An alternative approach suggested by Schelbert et al involves placement of a horseshoe-shaped region of interest around the apex of the left ventricle and generation of a low frequency time-activity curve through this region (34,35). After normalization of the area of this region to that of the left ventricle, the background curve is subtracted from the ventricular curve.

Others have suggested either subtracting a constant percentage (such as 35% in the right anterior oblique position) from all studies or eliminating background activity with constant isocount contour subtraction (36).

Correct choice of the background is essential to accurate measurements of left ventricular ejection fractions. Choice of background frames too late in the curve at a time when activity already is in the left ventricle results in a systematic overestimation of ejection fraction. Choice of background too early in the curve results in systematic underestimation (9).

Left ventricular ejection fraction can be determined either as an average of several individual beats or from some cardiac cycle by adding several beats frame by frame (9). Each peak corresponds to maximal activity or end-diastolic volume and each valley to minimal activity or end-systolic volume (Figure 5).

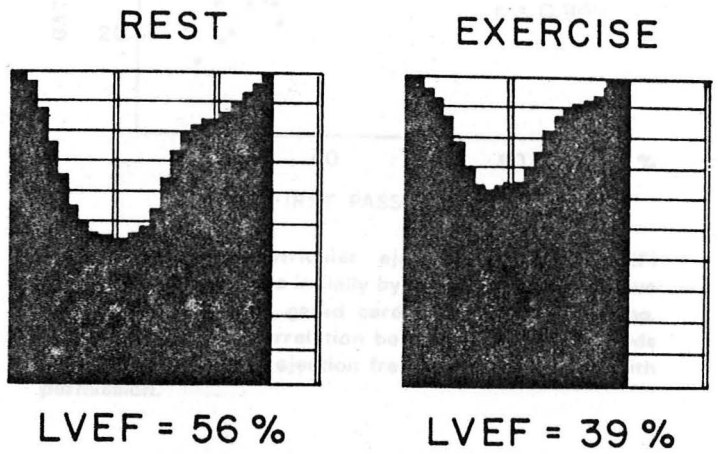
Left ventricular ejection fraction is calculated from background-corrected data as a difference between end-diastolic and end-systolic counts divided by end-diastolic counts. Only beats at the peak of the time-activity curve are used for data analysis. In patients with occasional premature ventricular contractions, premature beats are excluded from the analysis. This does pose potential problems. In addition to left ventricular ejection fraction, other indices of ventricular performance may also be calculated from first-pass data including mean normalized left ventricular ejection rate (9,10), velocity of circumferential fiber shortening (37) and first-third ejection fraction (38).

The overall statistical error of the ejection fraction measurement is composed of the individual errors in the end-diastolic, end-systolic and background counts (9). The error may be decreased by taking the average of several individual beats or by forming a summed representative cycle (Figure 5). Furthermore, weighted digital smoothing and fast

Fourier transformations may be applied to data obtained with a single crystal camera to reduce inherent statistical errors. Other approaches have used left ventricular time-activity curve to define a sine wave and allow calculation of the ejection fraction from a root mean square analysis involving all points in the curve (9).

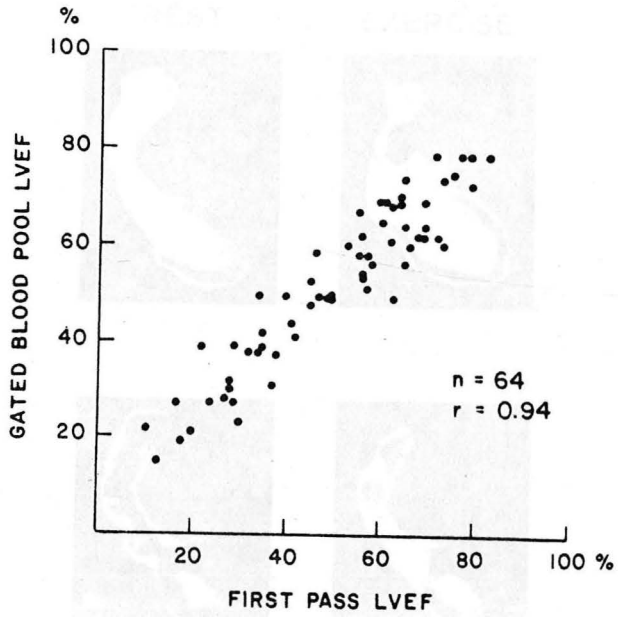
Numerous studies involving both single crystal and multicrystal scintillation cameras demonstrate good agreement between ejection fraction measured by first-pass radionuclide angiocardiography and contrast ventriculography (9,10,30). First-pass data also correlate closely with ejection fractions obtained by multiple gated cardiac blood pool imaging (Figure 6) (9).

FIGURE 5



High frequency representative cardiac cycles obtained at 30 frames/sec in a patient with coronary artery disease. Note the fine detail of the relative ventricular volume curves, especially the period of diastasis. Left ventricular ejection fraction (LVEF) fell with exercise.

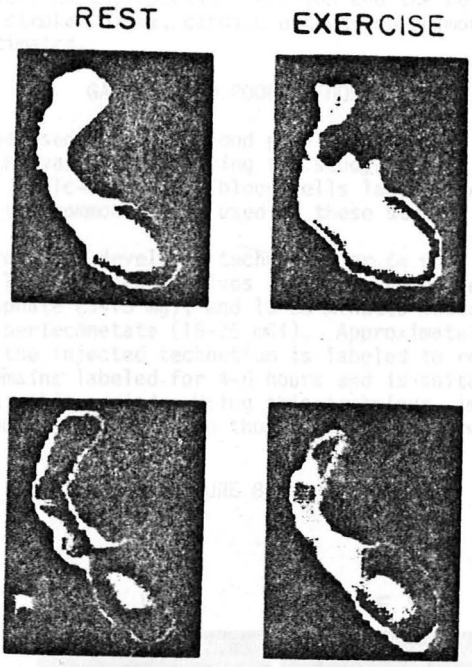
FIGURE 6



Left ventricular ejection fraction (LVEF) obtained in 64 patients initially by the first-pass technique and then by multiple gated cardiac blood pool imaging. Note the excellent correlation between the two methods over a wide range of ejection fractions. Reproduced with permission.

Regional left ventricular performance may also be derived from the first-pass study. Relatively high count density images are available from the summed representative cycle obtained with a multicrystal camera. This curve is analogous to a relative ventricular volume curve and provides a temporal series of images from end-diastole through end-systole. The end-diastolic parameter can be superimposed upon the end-systolic image and regional wall motion evaluated as a difference between these images (Figure 7) (10).

FIGURE 7



Regional wall motion analyses obtained at rest and during maximal upright bicycle exercise in two patients with coronary artery disease. The lower pair of images shows normal wall motion at rest and inferior wall hypokinesis during stress. The left ventricular cavity size appears comparable at rest and exercise. The upper pair of images shows diffuse hypokinesis at rest consistent with a previous myocardial infarction. During exercise, the left ventricular cavity dilates and mitral regurgitation becomes evident. In both cases, the left ventricular ejection fell with exercise.

The entire representative cycle may also be viewed as a continuous endless-loop movie providing a perception of changes in edges and also temporal contraction patterns. Measurements of hemiaxial shortening or digital images that may be processed to form functional images of regional ventricular performance may also be utilized (15,35,36,39-41). The regional ejection fraction image displays the relative contribution of different regions to the total ejection fraction and allows detection of movement of regional wall segments.

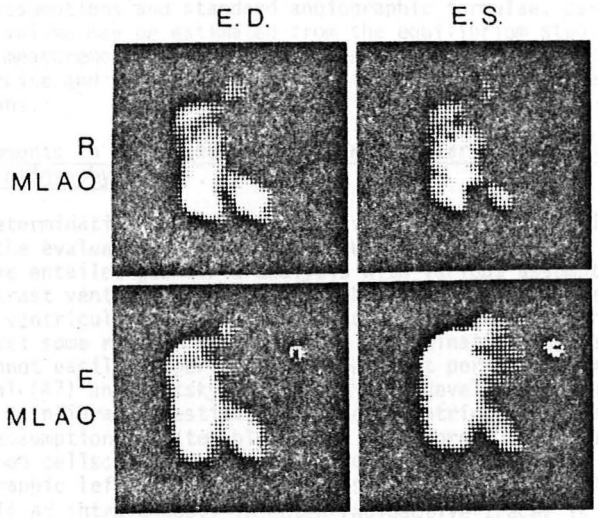
Using conventional area-length geometric approximations, end-diastolic volume has been calculated from the end-diastolic image of the final representative cycle in previous studies (42,43). Using this measurement, as well as the ejection fraction and the heart rate, end-systolic volume, stroke volume, cardiac output and pulmonary blood volume may be estimated.

GATED BLOOD POOL METHODS

Tracers to be used in gated blood pool imaging must remain almost entirely within the vasculature during the study. Human serum albumin labeled with ^{131}I or Tc-99m or red blood cells labeled *in vitro* or *in vivo* (21,44) are the common agents used in these studies.

We use our recently developed technique for *in vivo* labeling of red blood cells with Tc-99m which involves the intravenous injection of stannous pyrophosphate (5-15 mg), and 15-30 minutes later, the injection of Tc-99m sodium pertechnetate (15-25 mCi). Approximately 20 minutes later, 85-90% of the injected technetium is labeled to red blood cells. The blood pool remains labeled for 4-6 hours and is suitable for serial imaging throughout this period. Using this technique, images of the right and left ventricle similar to those shown in Figure 8 may be obtained.

FIGURE 8



Gated scintigrams of a patient with posteroinferior myocardial infarction indicating normal left ventricular wall motion at rest (R) and apical akinesia with submaximal exercise (E).

The term "gating" refers to the fact that the electrocardiogram is interfaced to the computer so that counts may be acquired during diastole and systole or during multiple phases of the cardiac cycle. The most common triggering signal employed to record scan data is the R wave of the electrocardiogram. The signal has several features that makes it desirable: (1) it is easy to obtain in most patients; (2) a signal the size and shape of the R wave only occurs once in the cardiac cycle of most patients; and (3) it bears a fixed relationship to the mechanical event of cardiac contraction in most individuals. In two-frame imaging, one generally acquires counts for a 40-60 msec interval beginning at the peak of the T wave to define systole and a 50-60 msec interval beginning with the R wave to define end-diastole. However, more popular today is the acquisition of multiple gated studies (45,46), in which many (typically 14-28 although up to 36 may be used) composite frames are required corresponding to composite cardiac cycles allowing identification of more subtle wall motion defects that are often unapparent in two frames alone. This is sometimes referred to as "MUGA" imaging. The cine-type playback of these studies on the computer screen gives a more pleasing and easily interpreted display than does alternate viewing of the end-systolic and end-diastolic frames alone.

Clinical Parameters of Left Ventricular Function Measured from Gated Blood Pool Studies

Many of the same parameters of ventricular function measured with first-pass studies are also measured with equilibrium or gated blood pool imaging. Specifically, left ventricular ejection fraction, regional wall motion alterations, previously ventricular volumes estimated utilizing geometric assumptions and standard angiographic formulae, cardiac output and stroke volume may be estimated from the equilibrium studies. Such functional measurements may be made at rest and during stress, i.e., during exercise and with the administration of various pharmacological interventions.

New Developments in the Measurement of Ventricular Volumes Using Equilibrium Dynamic Scintigraphy

The determination of absolute left ventricular volumes is a useful method in the evaluation of left ventricular function (47). Previous methods have entailed geometric analysis with various assumptions being made. Contrast ventriculography, which has been the most common means to measure ventricular volumes in the past, is an invasive procedure that involves some risk in that multiple determinations of left ventricular volumes cannot easily be performed over a short period of time. Recently, Dehmer et al (47) and Slutsky et al (48) have developed methods to allow myocardial scintigraphic estimation of left ventricular volumes without geometric assumptions. Gated blood pool scintigrams are obtained using *in vivo* blood cells. The rationale and methods used for the calculation of scintigraphic left ventricular volumes by Dehmer et al (47) are as follows. If an intravenously injected radioactive tracer is uniformly distributed throughout and confined to the vascular space, the spatial distribution of absolute tracer is identical to that of blood. The

radioactivity per unit volume of tissue should be proportional to the volume of blood contained within that volume of tissue. External monitoring of the changing spatial distribution of radioactivity within the cardiac blood pool is analogous to visualizing the deformations of the blood within the cardiac chambers. Changes in regional radioactivity are proportional to changes in regional blood volume.

Bi-dimensional gamma scintillation camera recordings of radioactivity within the cardiac blood pool produce single plane projections of the central vascular anatomy. The density (or recorded activity) of each picture element (pixel) and the resulting image matrix represents the activity of blood contained within the volume defined by any projection of the pixel area through the patient. If photons originating from any region of this volume are detected with equal sensitivity, the number of detected counts per pixel will be proportional to the total blood volume within the pixel projection. If the detectable radioactivity originating from the left ventricle can be isolated from radioactivity originating from other major vascular structures by a suitable selection of projection angle, total activity of those pixels constituting the left ventricular silhouette should be proportional to left ventricular blood volume. Absolute ventricular volume can then be obtained by normalization of left ventricular activity for the activity of peripheral venous blood.

Calculation of left ventricular volumes requires the determination of background-corrected left ventricular activity normalized for the activity of peripheral venous blood. The equation for calculation of left ventricular volume is simply:

$$\text{Volume (ml)} = \frac{\text{Background-corrected ventricular activity (counts/s)}}{\text{Peripheral blood activity (counts/s/ml)}} \times A$$

where A is an attenuation factor that may be complex. Peripheral blood activity is obtained by counting a known volume of peripheral blood under conditions of similar detector geometry and correcting for isotope decay to reflect the actual blood activity during the image acquisition. Ventricular activity is further defined as follows:

$$\text{Ventricular activity (counts/s)} = \frac{\text{Left ventricular counts at end-systole or end-diastole} - \text{Background counts}}{\text{Total acquisition time (s)/Individual frame}}$$

Total acquisition time per individual frame of the study (T_{frame}) is equal to:

$$T_{frame} = \frac{\text{Percent of cardiac cycle acquired} \times (\text{total study time} - \text{"off time"})}{\text{Number of frames per cardiac cycle,}}$$

where "off time" refers to that segment of the study during which no date are acquired (input halted because of variations in R-R intervals or arrhythmia). In short this can be expressed as:

$$T_{frame} = \frac{\text{Percent of cycle}}{\text{Number of frames}} (T_{total} - T_{off})$$

If the heart rate is perfectly regular and image acquisition continuous, T_{off} equals zero. Because this is the exception rather than the rule, T_{off} must be determined in some fashion. The computer system utilized for this study allows the acquisition of an image for any specified time interval. Should an interruption of image acquisition occur, the computer automatically compensates by lengthening the specified acquisition time interval by a time equal to the "off time". Hence, in the system used for this study, T_{off} always equaled zero, Thus,

$$T_{frame} = \frac{\text{Percent of cycle}}{\text{Number of frames}} \times T_{total}$$

Therefore, in final form the equation for the calculation of scintigraphic volumes is:

Volume (ml) =

$$\frac{\text{Left ventricular counts - Background counts}}{\dfrac{\dfrac{\text{Percent of cycle}}{\text{Number of frames}} \times T_{total}}{\text{Peripheral blood activity} \times e^{-\lambda t}}} \times A,$$

where $e^{-\lambda}$ is the general equation for isotope decay, $\lambda = 0.693/T^{\frac{1}{2}}$, t = time (in minutes) from counting the peripheral blood sample to the midpoint of the gated study, and $T^{\frac{1}{2}}$ for technetium-99m is 360 minutes. It should be emphasized that differences in heart rates between individual subjects are accounted for by these calculations.

Technique of Scintigraphic Left Ventricular Volume Determination

Left ventricular volumes are determined from the isolated end-diastolic and end-systolic frames of the study. The location of these frames in the gated sequence is determined by the generation of a left ventricular time-activity curve for 28 frames of the study. The end-diastolic frame is that frame associated with the peak of the curve, and the end-systolic frame is the one associated with the nadir of the curve. Once isolated, these frames are digitally filtered with a nine point weighted smoothing routine. In order to determine background activity, the end-diastolic frame is utilized to generate horizontal count profiles at three levels through the left ventricular cavity (Figure 9). Each curve typically manifests two peaks, representing the maximal right and left ventricular activity, separated by a valley indicative of diminished activity in the region of the interventricular

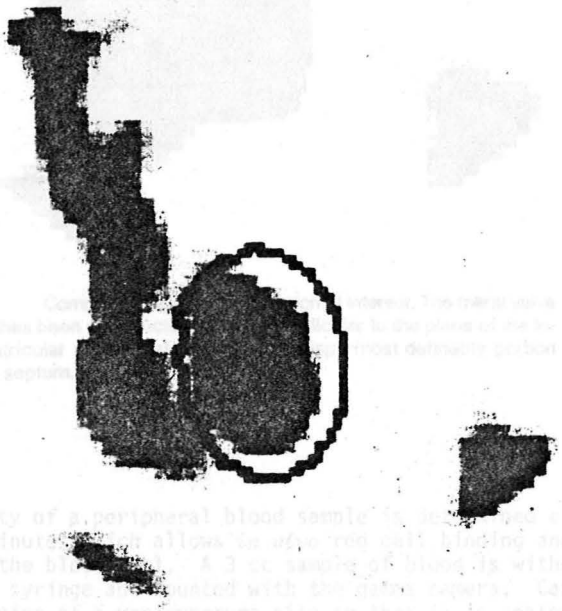
septum. A plateau in the count profile curve is noted in the area immediately adjacent to the left ventricular free wall. These curves can be sampled to determine the number of counts per pixel at any point along the curve. For each of the three curves, the count values at the points where the plateau portions intersect with the adjacent regions reflect diminishing activity at the ventricular borders and they are averaged to obtain the "background activity". In the occasional curve not demonstrating abrupt change in this region, a count value representing the average between the plateau value and a value clearly within the ventricle is used to determine the background activity. Each of the three curves is sampled in order to arrive at an activity value that adequately represents the activity in the area immediately adjacent to the left ventricular free wall. The background activity is subsequently subtracted from the end-diastolic and end-systolic frames.

FIGURE 9

End-diastolic image with horizontal count profile curves. Curves are constructed through the high, mid and low portion of the area of left ventricular activity. These curves can then be sampled to determine the number of counts per pixel at any point along the curve. In general, the count value at the point where the plateau portion intersected with the portion reflecting diminishing activity at the ventricular border was used as the value for the background activity. An **arrow** indicates where background was chosen.

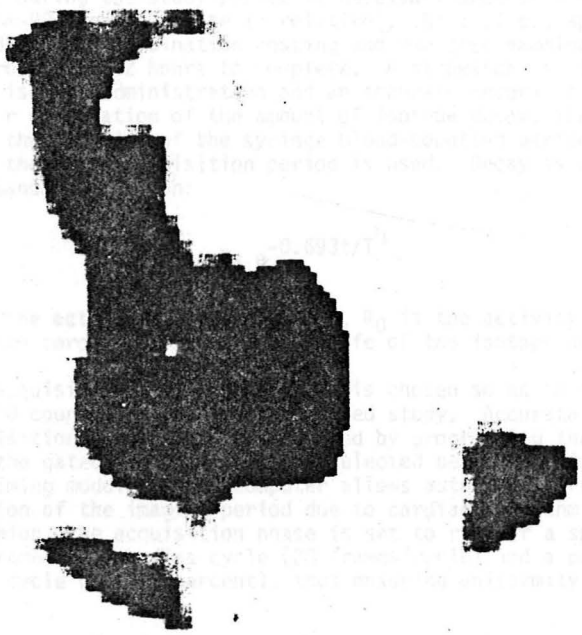
The left ventricular cavity is outlined and a region of interest is constructed over the left ventricle (Figure 10). Careful attention is given to constructing a region of interest so that the left atrial activity is excluded if left ventricular and left atrial activity are clearly separated in the scintigraphic images. If the mitral valve plane is not clearly delineated, the valve plane is assumed to be perpendicular to the plane of the interventricular septum, originating at the uppermost definable portion of the septum. The septal border of the left ventricle is constructed so as to course down the middle of the area of diminished activity representing the interventricular septum. The region of interest is completed so as to include all left ventricular activity (Figure 11). The end-systolic region of interest is constructed in the same fashion and its activity computed.

FIGURE 10



Outline construction for a left ventricular region of interest. The outline bisects the plane of the interventricular septum and is constructed to include all activity along the left ventricular free wall. The background has been subtracted in this representative figure.

FIGURE 11



Completed left ventricular region of interest. The mitral valve plane has been constructed to lie perpendicular to the plane of the interventricular septum originating at the uppermost definable portion of the septum.

The activity of a peripheral blood sample is determined after a minimum of 10 minutes which allows *in vivo* red cell binding and equilibration within the blood pool. A 3 cc sample of blood is withdrawn in a standard Stylex syringe and counted with the gamma camera. Care is taken in the choice of a venipuncture site so that it is anatomically isolated from the site of either pyrophosphate or isotope administration. Venous blood samples are counted in a consistent fashion using a holder designed to insure placement of the syringe at a constant distance of 5.08 cm from the surface of the collimator and in the center of the field of view. The blood in the syringe is counted twice, each period of counting being 2 minutes in length. The activity of the blood sample is determined by the construction of a region of interest over the image

produced by the syringe and by the subsequent determination of the number of counts within the region of interest. The average of these two determinations is used in the equation to calculate left ventricular volumes.

Correction of the left ventricular activity determined for radioactive decay during the study period is necessary because the half-life of technetium-99m pertechnetate is relatively short (i.e., approximately 6 hours) and because combination resting and exercise examinations may require approximately 2 hours to complete. A stopwatch is started at the time of isotope administration and an accurate record of time intervals is kept. For calculation of the amount of isotope decay, the time period from the midpoint of the syringe blood-counting period to the midpoint of the gated acquisition period is used. Decay is calculated using the standard equation:

$$R_t - R_0 \, e^{-0.693t/T^{\frac{1}{2}}}$$

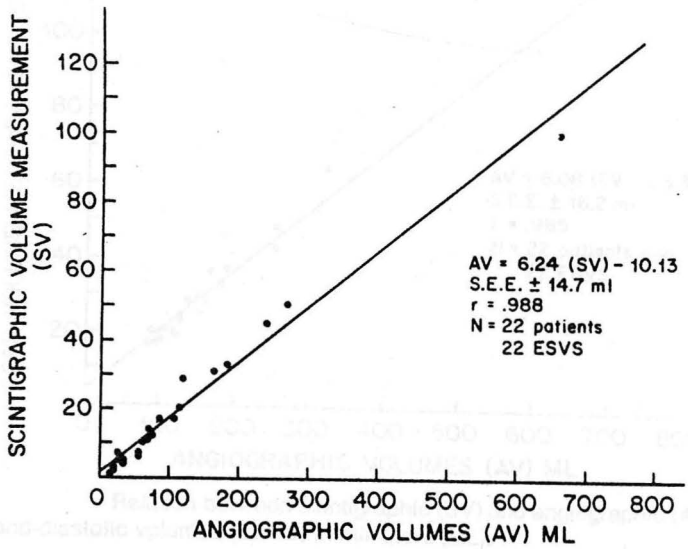
where R_t is the activity at any time (t), R_0 is the activity of the sample at time zero and $T^{\frac{1}{2}}$ is the half-life of the isotope administered.

Total acquisition time of the study is chosen so as to ensure at least 250,000 counts per frame of the gated study. Accurate determination of the acquisition time period is provided by programming the computer to acquire the gated study for that preselected period of time. The intrinsic timing module of the computer allows automatic correction of any disruption of the imaging period due to cardiac arrhythmias. In a similar fashion, the acquisition phase is set to run for a specified number of frames per cardiac cycle (28 frames/cycle) and a percent of the cardiac cycle (90-100 percent), thus ensuring uniformity in these variables.

In the original study performed by Dehmer et al (47), angiographic and scintigraphic volume determinations were made independently in 22 patients. Scintigraphic volume measurements were calculated from individual frames of a modified 35^{0} left anterior oblique projection using methods described above. Angiographic volumes were calculated by the area-length method and the Kennedy regression equation (49). In this study, there was an excellent correlation between scintigraphic and angiographic methods for all volume measurements grouped together as well as for segregated end-diastolic volumes and end-systolic volumes (Figures 12 and 13).

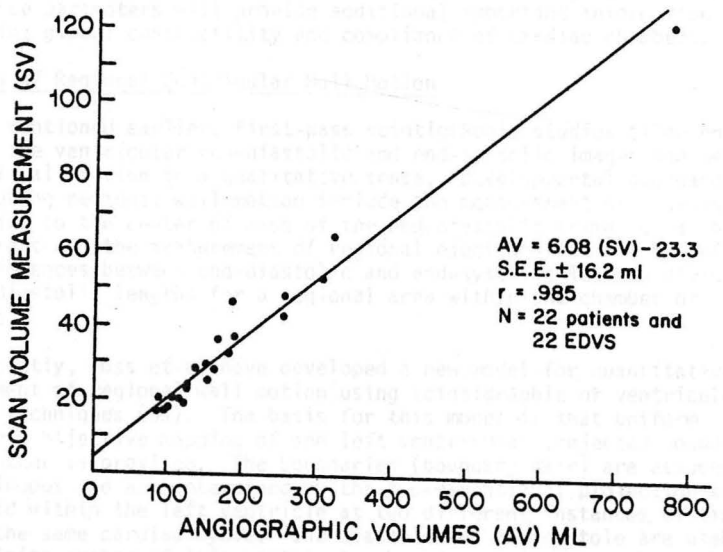
More recent prospective evaluations in an additional 13 patients in whom separate scintigraphic and angiographic measurements of ventricular volumes were obtained also demonstrates excellent agreement between scintigraphic and angiographic measurements (47).

FIGURE 12



Relation between scintigraphic (SV) and angiographic (AV) end-systolic volumes (EDVS) in milliliters (ML).

FIGURE 13



Relation between scintigraphic (SV) and angiographic (AV) end-diastolic volumes (EDVS) in milliliters (ML).

These recent contributions allowing the scintigraphic measurement of ventricular volumes are important in the characterization of global ventricular function since left ventricular end-systolic volumes may be used to estimate global contractility (50-52).

Left ventricular ejection fraction may be calculated using the formula:

$$EF = \frac{EDV - ESV}{EDV}$$

where counts or actual volumes are used for this calculation. Other parameters that might be calculated from the volume curve that is generated in the multiple image acquisition studies include the maximum systolic ejection rate and maximal alterations in rate of filling of respective chamber of interest. With additional clinical research, it seems likely that these parameters will provide additional important information concerning global contractility and compliance of cardiac chambers.

Analysis of Regional Ventricular Wall Motion

As mentioned earlier, first-pass scintigraphic studies allow one to outline the ventricular end-diastolic and end-systolic images and measure regional wall motion in a qualitative sense. Developmental approaches to measuring regional wall motion include the measurement of end-systolic shortening to the center of mass of the end-diastolic frame for a chamber of interest and the measurement of regional ejection fraction by defining the differences between end-diastolic and end-systolic lengths divided by end-diastolic lengths for a regional area within the chamber of interest.

Recently, Doss et al have developed a new model for quantitative measurement of regional wall motion using scintigraphic or ventriculographic techniques (53). The basis for this model is that uniform continuous bijective mapping of one left ventricular projected boundary onto another is provided. The boundaries (boundary pair) are assumed to be continuous and are determined by the two-dimensional projection of the fluid within the left ventricle at two different instances of time during the same cardiac cycle. End-diastole and end-systole are used and a finite number of left ventricular boundary points are chosen by uniformly sampling the end-diastolic and end-systolic boundaries at increments equal to approximately 2% of the total boundary length. Thus, the two boundaries comprising a boundary pair are composed of an equal number of samples. Boundary point sampling is defined by identifying the midpoint of the aortic valve and proceeding either direction around the boundary terminating at the beginning point. Total boundary length is the boundary perimeter including the aortic valve. The term "bijective mapping" means that for each point comprising the end-diastolic boundary, there is exactly one point in the end-systolic boundary such that the end-diastolic point corresponds or maps to its end-systolic position. This model has been tested in chronically instrumented dogs and in patients with various cardiac diseases. The results indicate that this model does allow one to identify the movement of end-diastolic boundary points to their end-systolic locations and that the information obtained from scintigraphic and angiographic studies is comparable in allowing definition of regional wall motion using this technique. In the future, it is anticipated that this model will be applied to allow quantitative

and objective measurements of regional wall motion in patients with various cardiac disease during rest and exercise in order to more sensitively identify alterations in regional ventricular function using equilibrium blood pool imaging techniques.

In my estimation, the most important developments allowing the use of scintigraphic techniques to define global and regional ventricular function are the following: (1) the development of portable gamma scintillation cameras and relatively portable and dedicated computer systems which allow image processing and rapid and objective measurement of various parameters of ventricular function; (2) the development of dependable radionuclide labels for the cardiovascular blood pool and in particular, the development of *in vivo* red blood cell labeling; and (3) the development of interest in sizing and identifying acute myocardial infarcts more precisely utilizing relatively non-invasive methods -- this interest has expanded to include interest in developing non-invasive methodology for the characterization of global and regional ventricular function and of myocardial perfusion not only in those with ischemic heart disease but also in patients with other cardiovascular disorders.

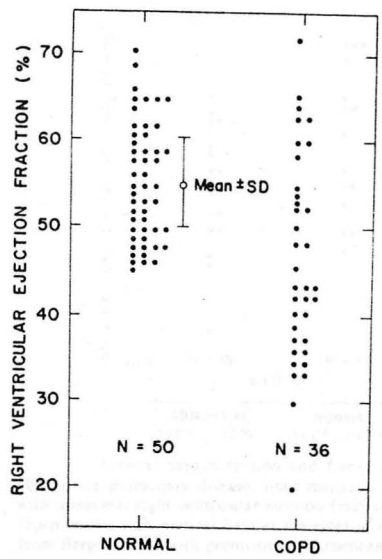
CLINICAL APPLICATIONS

Characterization of Right Ventricular Function

a. Zaret and his associates have evaluated the relationship between right and left ventricular ejection fraction in 36 patients with chronic obstructive lung disease as well as the relationship between ventilatory performance and right ventricular function (54). Right ventricular ejection fractions varied widely in these 36 patients ranging from 19-71% (Figure 14). Right ventricular ejection fraction was abnormal in 19 patients and normal in the remainder. All 10 patients with clinical and electrocardiographic evidence of cor pulmonale had abnormal right ventricular ejection fractions (mean 35 ± 2%) which were significantly lower than in the remaining patients with chronic obstructive pulmonary disease ($p < 0.01$). However, in 9 of 26 patients without evidence of cor pulmonale, but with severe ventilatory impairment, right ventricular ejection fractions were also depressed. Within one year of the original study, 4 of the patients had subsequently developed acute respiratory failure and cor pulmonale. In contrast, none of the patients with normal right ventricular ejection fractions had developed cor pulmonale. This suggests that the radionuclide technique may be sensitive in the early detection of right ventricular dysfunction prior to the development of overt clinical signs of cor pulmonale.

In the entire group, forced expiratory volume average was 1.1 ± 0.1 liters. A distinct relationship between pulmonary function and right ventricular performance was noted. Patients could be divided into those with severe pulmonary impairment ($FEV_1 < 1$ liter) and those with only moderate impairment ($FEV_1 \geq 1$ liter). Of 19 patients with $FEV_1 < 1$ liter, 14 had depressed right ventricular ejection fractions (mean, 42 ± 3%), which were significantly lower than in the remaining 17 patients (52 ± 2%) ($p < 0.01$). An alternate interpretation in Zaret's study was that FEV_1

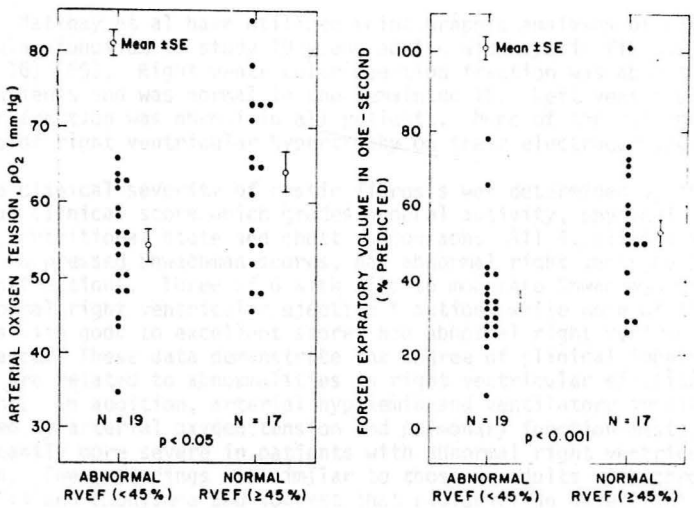
FIGURE 14



Right ventricular ejection fraction in 50 normal adults without cardiopulmonary disease and in 36 patients with chronic obstructive pulmonary disease (COPD). The normal range, defined as the mean ±2 standard deviations (SD), is 45 to 65 percent. Note the wide range of values in the COPD group. (Reproduced from Berger et al. with permission of American College of Cardiology.)

was 37 ± 4% of the predicted value in those patients with abnormal right ventricular ejection fraction compared to 54 ± 4% of the predicted value in the remaining patients. A similar significant difference was found for arterial oxygen tensions (Figure 15).

FIGURE 15



Arterial oxygen tension and forced expiratory volume in one second for 36 patients with chronic obstructive pulmonary disease. Both measures of ventilatory performance were significantly lower in patients with abnormal right ventricular ejection fraction (RVEF) than in those with normal right ventricular function. Open circles with vertical bars at the sides of each panel represent the mean ± standard error. (Reproduced from Berger et al. with permission of American College of Cardiology.)

In contrast, left ventricular ejection fractions did not differ significantly in patients with either normal or abnormal right ventricular performance. Left ventricular ejection fractions ranged from 20-78% and were abnormal in only 9 patients, 6 of whom had documented coronary artery disease or previous myocardial infarctions.

It is obvious that these techniques (in this and other similar patient populations) could be utilized to test the influence of various agents that might reduce pulmonary artery vascular resistance and/or improve right ventricular function and to determine their influence acutely and chronically. This capability represents a potentially important advantage of this methodology which allows such testing to be obtained relatively non-invasively.

b. Matthay et al have utilized scintigraphic analyses of right ventricular function to study 19 young adults with cystic fibrosis (Figure 16) (55). Right ventricular ejection fraction was abnormal in 7 of 19 patients and was normal in the remaining 12. Left ventricular ejection fraction was normal in all patients. None of the patients had evidence of right ventricular hypertrophy on their electrocardiograms.

The clinical severity of cystic fibrosis was determined by the Shwachman clinical score which grades general activity, physical examination, nutritional state and chest radiograph. All 4 patients with severely depressed Shwachman scores, had abnormal right ventricular ejection fractions. Three of 6 with mild to moderate Shwachman scores had abnormal right ventricular ejection fractions while none of the 9 patients with good to excellent scores had abnormal right ventricular performance. These data demonstrate the degree of clinical impairment as they are related to abnormalities in right ventricular ejection fractions. In addition, arterial hypoxemia and ventilatory impairment as judged by arterial oxygen tension and pulmonary function tests, were significantly more severe in patients with abnormal right ventricular function. These findings are similar to those in adults with chronic bronchitis and emphysema and suggest that radionuclide assessment of right ventricular function allows categorization of patients into hemodynamic subsets.

c. Functional impairment of the right ventricle in patients with acute myocardial infarctions does occur, particularly in those with right coronary artery disease and/or inferior myocardial infarcts. Occurrence of right ventricular functional abnormalities are thought to be unusual since pathologic studies have demonstrated isolated right ventricular infarction in less than 5% of autopsies revealing any myocardial damage while concurrent right and left ventricular infarction have been found to be much more common -- approximately 43% of patients in one study (54). A subset of patients with severe hemodynamic abnormalities resulting from right ventricular infarction including cardiogenic shock was first described by Cohn and his colleagues in 1974 (56). These patients had markedly increased right sided filling pressures and presented with hypotension and shock. Recent radionuclide studies with technetium 99m-pyrophosphate infarct imaging have shown that 20-37% of patients with acute inferior wall myocardial infarcts have right ventricular involvement, although most do not present in cardiogenic shock (57,58).

Berger and Zaret, in a study of 31 patients with their first transmural infarcts, found abnormal right ventricular ejection fractions in 9 or 18 patients with inferior infarcts but in only 1 of 13 with anterior infarcts (54). On day 1, right ventricular ejection fractions averaged 48 ± 2% in inferior wall infarcts and 56 ± 2% in anterior wall infarcts. Mean right ventricular ejection fractions in inferior wall infarcts were significantly lower than in anterior infarcts on day 1 and at all times throughout the study ($p < 0.01$). These data suggest that modest functional impairment of the right ventricle is relatively common in acute inferior myocardial infarction but not with anterior infarcts. However, this dysfunction is not invariably associated with the severe clinically evident hemodynamic compromise first reported by Cohn and his associates (56).

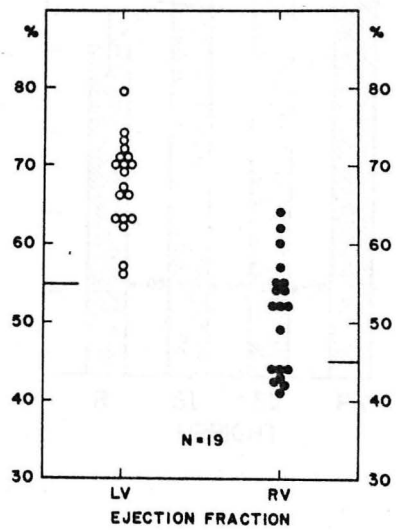
Analysis of Left Ventricular Function

Left Ventricular Performance in Normal Subjects During Upright and Supine Exercise

Scintigraphic techniques described earlier may be utilized to evaluate left ventricular functional responses to multilevel exercise in various positions including the supine and upright ones. Recently, Poliner et al have performed such a study in 7 normal individuals using *in vivo* labeling of red blood cells and multigated image acquisition to measure left ventricular functional responses from rest to exercise (59). In these individuals, mean left ventricular end-diastolic volume (LVEDV) during supine rest was 107 ± 10 (SE) but 85 ± 6 cc ($p < 0.02$) in the upright position; mean resting left ventricular end-systolic volumes (LVESV), upright and supine were not different (Figure 16). LV ejection fraction tended to be slightly higher supine (76 ± 2%) than upright (72 ± 4%) at rest (Figure 17). Resting heart rate was 89 ± 5 beats per minute upright, compared to 71 ± 6 beats per minute supine ($p < 0.05$). Multilevel exercise testing was carried out at a low workload of 300 KPM per minute, an intermediate workload of 600-750 KPM per minute and a peak workload of 1092 ± 56 supine and 946 ± 146 KPM upright ($p < 0.05$). With peak exercise, supine LVEDV increased significantly 27% to 135 ± 13 cc but LVESV did not (Figure 16). LVEF increased from 76 ± 2% to 84 ± 2% in the supine position. With upright exercise, LVEDV also increased significantly 39% above the resting level to 116 ± 8 cc ($p < 0.02$) but remained lower than the corresponding supine volume at intermediate and peak workloads. LVESV significantly decreased 41% to 19 ± 3 cc and was significantly smaller than the corresponding supine volume at intermediate and peak exercise ($p < 0.05$). LVEF increased from 72 ± 4% to 91 ± 2% ($p < 0.05$) which was significantly higher than peak supine LVEF ($p < 0.05$) (Figure 17). Heart rates at rest and during exercise were higher in the upright position ($p < 0.05$), but arterial pressures and double products were not significantly different.

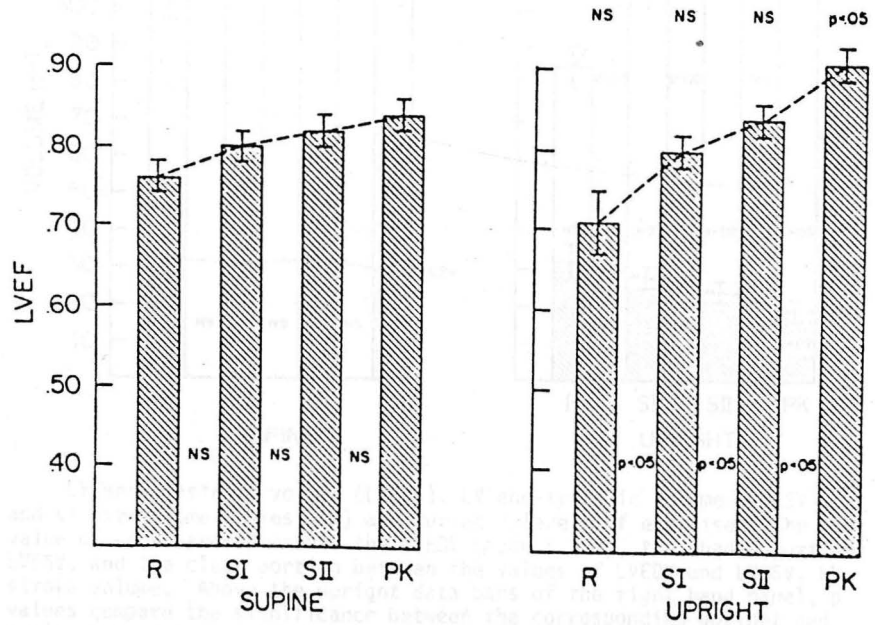
Measurements of LV volumes at rest and during exercise in both the supine and upright positions by dynamic radionuclide scintigraphy suggests that stroke volume and cardiac output during exercise are maintained by a combination of the Frank-Starling mechanism and an enhanced contractile state (Figure 18).

FIGURE 16



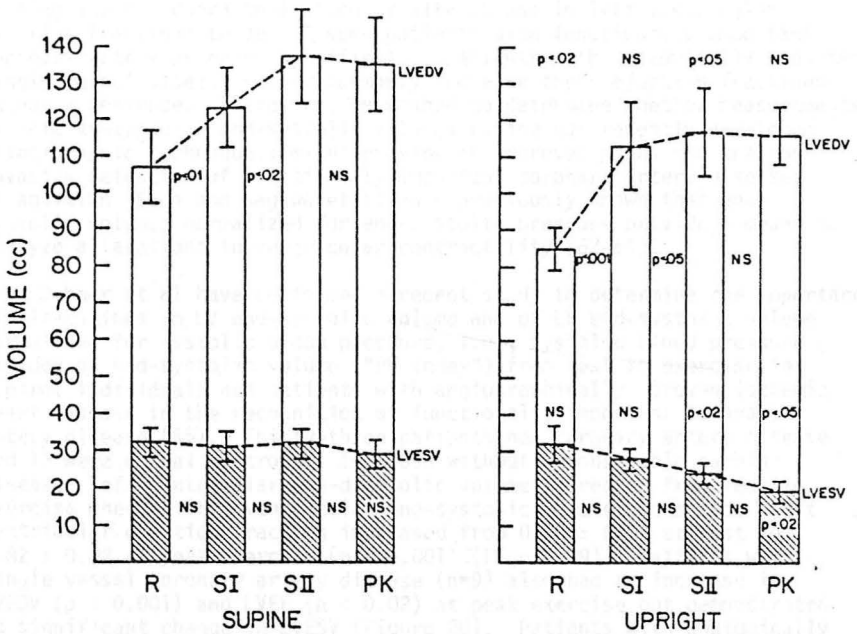
Right ventricular (RV) and left ventricular (LV) ejection fraction in 19 young adults with cystic fibrosis. Note that RV ejection fraction was abnormal (<45%) in 7 patients, while LV ejection fraction was abnormal (<55%) in none.

FIGURE 17



Left ventricular ejection fraction (LVEF) at rest (R) and during 3 levels of exercise. The format and the abbreviations are the same as in Figure 18. The difference between R and peak exercise was significant in both positions ($p < 0.05$ supine, < 0.01 upright). Taken from Reference 59.

FIGURE 18



LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and stroke volume at rest (R) and during 3 levels of exercise. The top value of each bar represents the LVEDV (mean ± SEM), the shaded portion LVESV, and the clear portion between the values of LVEDV and LVESV, LV stroke volume. Above the upright data bars of the right hand panel, p values compare the significance between the corresponding upright and supine measurements of LVEDV at each work load. Likewise, in the upright data panel, the p values above the LVESV data compare the significance of the corresponding supine measurements of LVESV. P values between adjacent bars indicate the significance of the change between progressive work loads. P values enclosed within the small boxes of the peak exercise (PK) bars indicate the significance of change from (R) to peak exercise for LVESV in each position. LVEDV also increased significantly between R and peak exercise in both positions ($p < 0.001$ supine and < 0.02 upright). SI = low level work (300 kpm/min); SII = intermediate level work (600-750 kpm/min). Taken from Reference 59.

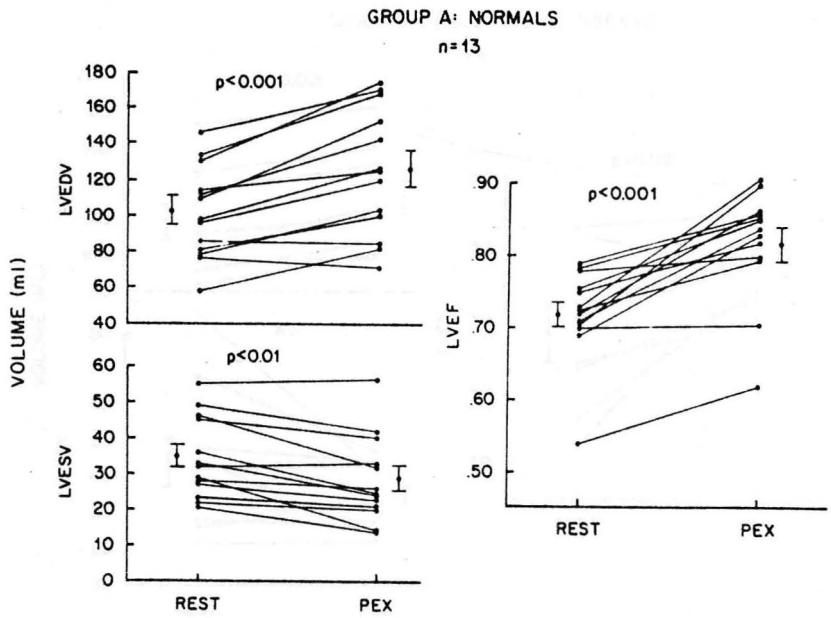
Recognition of Functionally Important Coronary Artery Disease

In contrast to normal individuals, Borer and his associates have demonstrated that patients with extensive coronary artery disease either do not change or decrease their left ventricular ejection fractions at peak exercise (60,61).

However, we have been disappointed with the ability of exercise testing and the characterization of alterations in left ventricular ejection fractions to detect some patients with functionally important coronary artery disease; specifically, patients with anatomically important single vessel disease rather commonly increase their ejection fractions in our experience. Therefore, we wished to determine whether measurements of left ventricular end-systolic volumes (using our recently developed scintigraphic techniques) might provide an improved means for the non-invasive detection of functionally important coronary artery disease. In addition, Suga and Sagawa et al have previously shown that end-systolic volumes normalized for end-systolic pressure provide a means to analyze alterations in ventricular contractility (62-64).

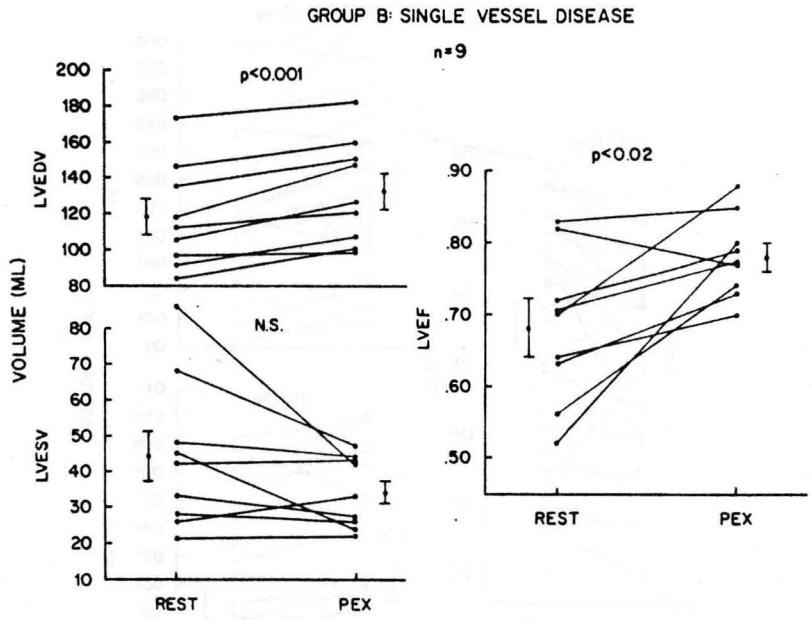
Dehmer et al have performed a recent study to determine the importance of alterations in LV end-systolic volume and of LV end-systolic volume normalized for systolic blood pressure, i.e., systolic blood pressure divided by end-systolic volume ("PV index") from rest to exercise in control individuals and patients with angiographically proven ischemic heart disease in the recognition of functionally important coronary artery disease (65). Thirty-three patients had coronary artery disease and 13 were normal controls. In those without demonstrable cardiac disease, left ventricular end-diastolic volume increased from rest to exercise whereas left ventricular end-systolic volume decreased. Left ventricular ejection fraction increased from 0.72 ± 0.02 at rest to 0.82 ± 0.02 at peak exercise ($p < 0.001$) (Figure 19). Patients with single vessel coronary artery disease (n=9) also had an increase in LVEDV ($p < 0.001$) and LVEF ($p < 0.02$) at peak exercise but demonstrated no significant change in LVESV (Figure 20). Patients with anatomically significant two or three vessel coronary artery disease (n=24) demonstrated an increase in both LVEDV and LVESV at peak exercise and a fall in LVEF (0.56 to 0.52, $p < 0.05$) (Figure 21). The relationship between peak systolic blood pressure (cuff determined) and LVESV index ("PV index") was also utilized to characterize alterations in LV function at rest and during peak exercise. In those without cardiac disease, this index rose substantially during peak exercise (7.6 ± 0.73 at rest to 14.9 ± 1.78 with peak exercise, $p < 0.001$) (Figure 22). This change was less dramatic in those with single vessel disease and absent in patients with two or three vessel disease (4.2 ± 0.60 at rest vs 3.9 ± 0.50 with peak exercise, NS) (Figure 22). The change in LVESV alone was different in each group studied. These data indicate that the assessment of exercise-induced alterations in LVESV and in the "PV index" are useful in the evaluation of left ventricular dysfunction associated with angiographically important coronary artery disease. In this particular study, the sensitivity of alterations in LV ejection fraction for determining the presence of functionally important coronary artery disease in those with single vessel coronary artery alterations was only 0.22. However, the sensitivity of the PV index was 0.55. The sensitivity of the LVEF measurement in the detection of two and three vessel coronary artery disease was 0.88 which was the same sensitivity as the "PV index" in these individuals. Overall sensitivity for detection of functionally important coronary artery disease using these scintigraphic parameters in a combined manner was greater than 90% (65).

FIGURE 19



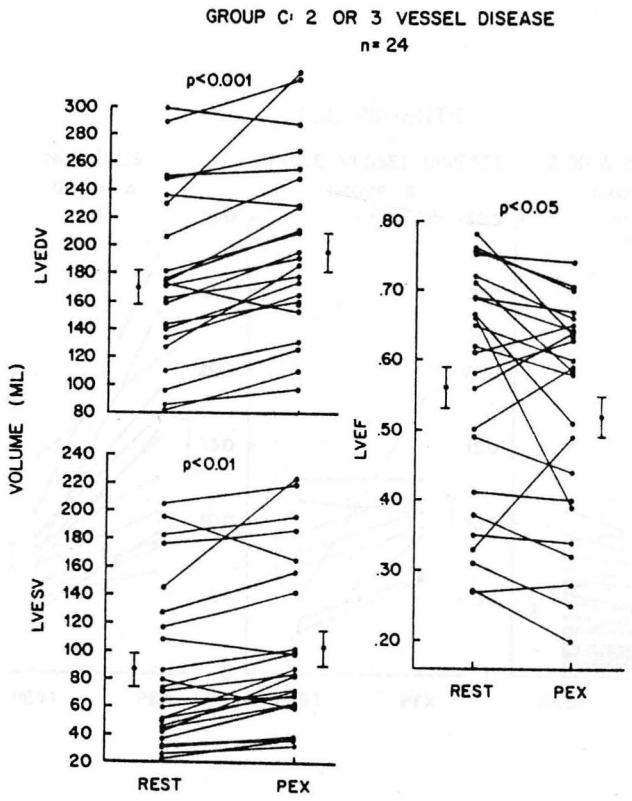
Exercise-induced alterations in left ventricular volumes and ejection fraction in normal individuals (rest vs. peak exercise [PEx]). There was a significant increase in left ventricular ejection fraction (LVEF) while left ventricular end-systolic volume (LVESV) decreased significantly. The error bars represent ± SEM. Taken from Reference 65.

FIGURE 20



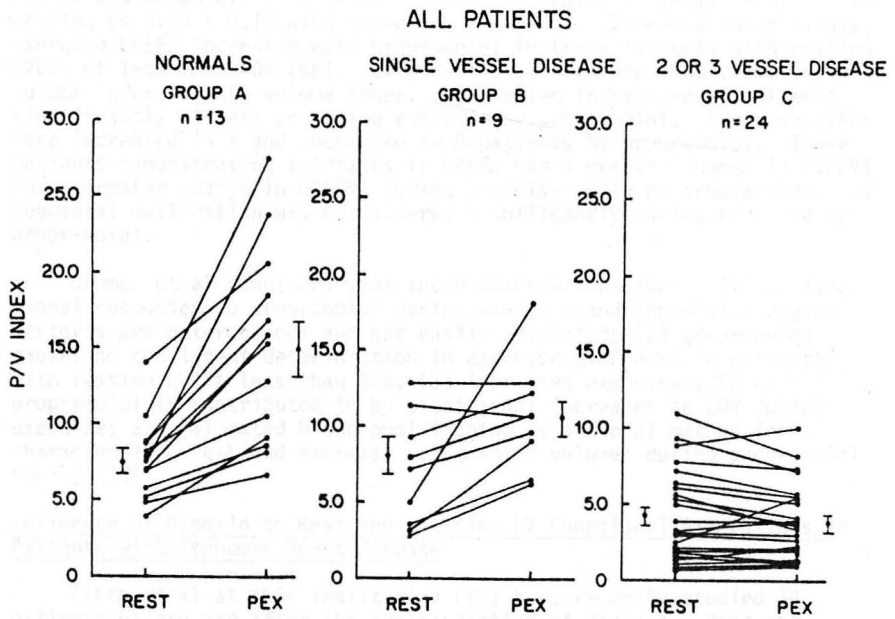
Exercise-induced alterations in left ventricular volumes and ejection fraction in patients with single vessel coronary artery disease (rest vs. PEx). There was a significant increase in LVEDV and LVEF while LVESV did not change. Taken from Reference 65.

FIGURE 21



Exercise-induced alterations in left ventricular volumes and ejection fraction in patients with 2 or 3 vessel coronary artery disease (rest vs. PEx). Both LVEDV and LVESV increased at PEx while the LVEF decreased slightly. Taken from Reference 65.

FIGURE 22



Changes in PV index during exercise in normals and patients with coronary artery disease (all patients). The resting PV index was lower in Group C patients and in addition, the response to exercise was markedly blunted. Taken from Reference 65.

Effect of Oral Propranolol on Rest and Exercise Left Ventricular Ejection Fractions in Patients with Angina Pectoris

Dehmer et al have recently studied the effect of oral propranolol on left ventricular ejection fraction, left ventricular volumes, cardiac output and segmental wall motion using multigated blood pool imaging at rest and during supine exercise in 15 patients with angina pectoris (66). Propranolol had no effect on resting LVEFs (0.60 ± 0.16 before and 0.61 ± 0.18 after propranolol). The mean propranolol dose administered was 160 mg per day. Prior to propranolol, LVEFs did not change during exercise whereas after propranolol LVEFs increased slightly (0.61 ± 0.18 resting vs 0.65 ± 0.18 with exercise, $p < 0.05$). Somewhat surprisingly, exercise LVEFs increased with propranolol in three patients with resting LVEFs of less than 40% (66). LV end-diastolic volume index, end-systolic volume index, stroke volume index, and cardiac index were not altered significantly at rest or during exercise by propranolol. Exercise LVEFs were increased in 5 and unchanged in 8 patients by propranolol. Those patients demonstrating increases in LVEFs had a greater change in LVEDVI and a greater change in LVESVI during exercise while on propranolol. LV segmental wall motion was not altered significantly during exercise by propranolol.

Dehmer et al concluded from these observations that: (1) LV functional responses to propranolol during exercise and those with angina pectoris are heterogenous and not easily predicted; (2) propranolol causes no consistent deterioration in exercise LVEF even in patients with resting LVEFs less than 40%; (3) increased exercise LVEF with propranolol is contributed to by significant increases in EDV during exercise; and (4) gated blood pool imaging is a useful method for characterizing rest and exercise LVEF and LV volumes during propranolol therapy (66).

Influence of Digoxin on Rest and Exercise LV Functional Alterations in Patients with Ischemic Heart Disease

Firth et al at this institution (67) have recently studied 14 patients before and after the administration of digoxin. Rest and supine exercise left ventricular functional alterations were evaluated in these individuals with ischemic heart disease. Previous observations have suggested that digoxin might worsen left ventricular function in those with important ischemic heart disease and extend infarct size in experimental animal models with acute myocardial ischemia. In Firth et al's study (67), chronic digoxin therapy did not cause any significant deleterious effect on left ventricular function but also did not result in any significant improvement in left ventricular function at rest. However, at peak exercise, digoxin resulted in a relative reduction in both LV end-diastolic and end-systolic volume index which was evident in patients with well-preserved resting ejection fractions. The reduction in LV end-systolic volume index implies that digoxin improved ventricular function during exercise in patients with ischemic heart disease who have well-preserved ventricular function. Similar alterations in left ventricular end-systolic volume index were not found in patients with left ventricular ejection fractions below 40%.

Improved Localization of Acute Myocardial Infarcts Using an Overlay of Tc-99m-PYP Scintigrams

Recently, Corbett, Lewis et al at this institution have developed a technique for overlaying technetium 99m-stannous pyrophosphate myocardial scintigrams onto dynamic myocardial scintigrams. The uptake of Tc-99m-PYP is shown in one color and the gated blood pool scintigram in another. This technique has allowed investigators to more precisely localize the site of infarction and to distinguish and differentiate old and new ventricular function alterations. This work is relatively new and as yet has not been published.

Submaximal Exercise Testing After Acute Myocardial Infarction

Pulido et al (68) and Corbett et al (69) have recently demonstrated the value of submaximal exercise testing coupled to myocardial scintigraphy prior to hospital discharge in patients with acute myocardial infarcts. Pulido et al (68) studied the relation between global and regional left ventricular function and electrocardiographic signs of ischemia at rest and during submaximal exercise in 27 patients 2-3 weeks after their acute myocardial infarcts. Gated radionuclide blood pool scintigrams were obtained in a modified left anterior oblique projection. Electrocardiographic monitoring of heart rate and rhythm was provided during the exercise. The submaximal exercise was terminated when the patient's heart rate reached 125 beats per minute or if angina, malignant ventricular ectopy or electrocardiographic evidence of myocardial ischemia developed before this rate was reached.

The data obtained in this study (68) demonstrate that patients with recent anterior myocardial infarcts, in contrast to those with recent inferior or nontransmural infarcts, manifest a significant reduction in left ventricular ejection fraction with submaximal exercise. Additionally, numerous patients developed alterations in either left ventricular ejection fraction or segmental wall motion prior to or without corresponding ECG changes demonstrating the combined value of both electrocardiographic and scintigraphic monitoring in the recognition of ischemic responses that effect either ventricular function or the electrocardiogram. Pulido et al concluded that to identify ischemic responses with submaximal exercise in this patient population, one should ideally use both electrocardiographic monitoring and dynamic myocardial scintigraphy (68).

In a more recent study, Corbett et al (69) have used submaximal exercise testing coupled to dynamic myocardial scintigraphy to evaluate an additional 61 patients with acute myocardial infarcts prior to their hospital discharge. The hypothesis tested in this study was that patients at risk for future cardiac events (cardiac death, new acute myocardial infarct, persistent congestive heart failure, unstable and/or refractory angina) can be identified by this approach. Patients with acute myocardial infarcts were studied 18.6 ± 8.2 (SD) days after their acute myocardial infarcts. Thirty-five of 61 patients developed new cardiac events during the 6 months follow up. The sensitivity and specificity for the occurrence for new cardiac events in these patients is as listed below:

	EKG	LVEF	SWM*	ESV†	PV‡
sensitivity	.46	.97	.80	.94	1.0
specificity	.67	.90	.90	.93	.87

* Segmental wall motion changes at exercise

† Left ventricular end-systolic volume during exercise

‡ Ratio between peak systolic blood pressure and left ventricular end-systolic volume during exercise

In this study, scintigraphic parameters were more sensitive and specific than changes in the electrocardiogram. Furthermore, 85% of the patients without any cardiac event in 6 months had normal responses in their left ventricular ejection fractions, left ventricular end-systolic volumes and their "PV" ratio. Corbett et al concluded from these data that submaximal exercise testing coupled with dynamic myocardial scintigraphy prior to hospital discharge in patients with acute myocardial infarcts identifies those at risk for future cardiac events within the ensuing 6 months.

Value of Radionuclide Ventriculography in the Immediate Charaterization of Patients with Acute Myocardial Infarcts

Sanford et al at this institution (70) have recently tested the hypothesis that admission radionuclide ventriculography provides a different functional characterization of patients with acute myocardial infarcts than physical examinations and chest x-rays. Radionuclide ventriculography was performed in 75 patients with acute myocardial infarcts at Parkland Hospital within 8 ± 3.1 (SD) hours after the onset of pain (70). By clinical criteria, 29 patients were Killip (K) Class I, 38 K II and 8 K III. Mean left ventricular (LV) end-diastolic (ED) and end-systolic (ES) volume indices and ejection fractions (EF) were:

K Class	LVEDVI	LVESVI	LVEF
I	78±32 (ml/M^2)	40±27	.51±.13
II	84±36	49±30	.44±.17
III	99±55	72±44	.29±.08

EF was significantly depressed in K III compared to K I or K II ($p < .05$) due to elevation in ESVI ($p < .05$) rather than significant variation in EDVI. Patients were subdivied into 4 groups based on LVEF: NORM $\geq$ .55, MILD .40-.54, MOD .25-.39, or SEV < .25. In spite of the clinical classification, 6/29 (21%) of K I patients were MOD or SEV and 1/8 (12%) of K III was only MILD. K II patients varied widely (EF .14-.76) with 17/38 (45%) in MOD or SEV. Thus, early evaluation of patients with acute myocardial infarcts by radionuclide ventriculography reveals a significant discrepancy between clinical classification and direct functional evaluation in 32% of patients.

Other Uses for Radionuclide Ventriculography in the Study of Patients with Acute Ischemic Heart Disease

It is obvious that there are many other potential uses for this technique in the evaluation of patients with acute and chronic ischemic heart disease. The technique offers a means to distinguish patients with large ventricular aneurysms from those with global hypokinesis. This is an important distinction in patients admitted with hypotension and/or important heart failure since the ability to recognize a mechanical abnormality that might lend itself to surgical correction can be distinguished from one in which extensive myocardial damage has already occurred and surgical intervention should not be seriously considered. In addition, shunts including ventricular septal defects and atrial septal defects, regurgitant valvular lesions including mitral insufficiency and aortic insufficiency may be detected and their relative severity assessed using these techniques (71-74).

In addition, the influence of various additional physiologic interventions and/or therapeutic attempts may be assessed. Specifically, the influence of exercise training in patients with ischemic heart disease has been evaluated (75) and the functional importance of coronary artery bypass surgery in altering global and regional ventricular function has also been studied (76).

Use of Dynamic Myocardial Scintigraphy to Study Patients with Valvular Aortic Insufficiency

As mentioned above, the presence of regurgitant valvular lesions and an estimate of their relative severity may be obtained using dynamic myocardial scintigraphy (74). However, it is presently uncertain as to the ideal time to recommend valve replacement in patients with hemodynamically important valvular aortic insufficiency. It is clear that if one waits until overt cardiac symptoms develop in these individuals that it may be too late to preserve ventricular function and restore a useful lifestyle. Symptoms develop relatively late in patients with valvular aortic insufficiency and at a point at which aortic valve replacement will do no more than stabilize already present and serious left ventricular dysfunction. Therefore, cardiologists and cardiovascular surgeons have looked for a means to identify the ideal time to replace an aortic valve in patients with important valvular aortic insufficiency allowing preservation of deteriorating ventricular function before such deterioration becomes severe.

Borer et al (77) has suggested that rest and exercise measurements of left ventricular fraction using radionuclide ventriculography may provide such a potential. Patients with important valvular aortic insufficiency typically demonstrate deterioration of the left ventricular ejection fraction at exercise even though it may have been well preserved at rest. Borer and his colleagues have suggested that in those patients that develop important reductions in their left ventricular ejection fractions at exercise, aortic valve replacement should be seriously considered assuming the presence of hemodynamically important aortic

insufficiency. Others have suggested that a certain degree of left ventricular dilatation and/or alteration in left ventricular end-systolic volumes as determined echocardiographically might allow one to decide the ideal time for aortic valve replacement in such individuals (78). Even more recently, Dehmer et al have suggested that radionuclide ventriculography measurements of left ventricular end-systolic volume at rest and during exercise may help one discriminate between various degrees of ventricular dysfunction and better characterize patients with hemodynamically important valvular aortic insufficiency (79).

It is not yet clear which of these parameters (if any of them) will be the best means to noninvasively characterize and serially follow patients with hemodynamically important valvular aortic insufficiency. It will be of interest to follow developments in this regard in the future.

SUMMARY

It is clear that developments in "Nuclear Cardiology" that allow one to visualize the right and left ventricles using radionuclide techniques and to study the influence of various physiological, pharmacological and surgical interventions on global and regional ventricular function provide important diagnostic insight and allow improved therapeutic capabilities. These tests are relatively non-invasive, can be performed serially, may be performed in patients that are seriously ill and they have very limited risks. It seems likely that with the further development of three-dimensional imaging capabilities and continued improvement in techniques for image processing and in the sophistication of the associated computer systems, one may expect additional contributions including a generally increased sensitivity, improved analysis of regional wall motion alterations, studies of diastolic function and of excitation contraction coupling, evaluation of myocardial metabolism and the development of means to estimate intracardiac pressures, to measure myocardial wall thickness, etc.

REFERENCES

1. Strauss HW, Zaret BL, Hurley PJ, et al: A scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterization. Am J Cardiol 28:575, 1971.

2. Kisslo JA, Robertson D, Gilbert BW, et al: A comparison of real-time, two-dimensional echocardiography and cineangiography in detecting left ventricular asynergy. Circulation 55:134, 1977.

3. Meier P, Zierler KL: On the theory of the indicator-dilution method for measurement of blood flow and volume. J Appl Physiol 6:731, 1954.

4. Andreas R, Zierler KL, Anderson HM, et al: Measurement of blood flow and volume in the forearm of man: With notes on the therapy of indicator-dilution and on the production of turbulence, hemolysis and vasodilation by intravascular injection. J Clin Invest 33:482, 1954.

5. Donato L: Basic concepts of radiocardiography. Semin Nucl Med 3:111, 1973.

6. Donato L, Rochester DF, Lewis L, et al: Quantitative radiocardiography. II. Technic and analysis of curves. Circulation 26:183, 1962.

7. Pritchard WH, MacIntyre WJ, Moir TW: The determination of cardiac output by the dilution method without arterial sampling. II. Validation of precordial recording. Circulation 18:1147, 1958.

8. Glick G, Schreiner BF Jr, Luria MN, et al: Determination of cardiac output by means of radioisotope dilution technic. With discussion of "central" blood volume and valvular regurgitation. Prog Cardiovasc Dis 4:586, 1962.

9. Berger HJ, Matthay RA, Pytik LM, et al: Ventricular performance in patients with cardiac and pulmonary disease. In Cardiovascular Medicine. Freeman LM and Blaufox MD, editors. Grune and Stratton, New York, 1980.

10. Marshall RC, Berger HJ, Costin JC, et al: Assessment of cardiac performance with quantitative radionuclide angiocardiography: Sequential left ventricular ejection fraction, normalized left ventricular ejection rate, and regional wall motion. Circulation 56:820, 1977.

11. Berger HJ, Matthay RA, Loke J, et al: Assessment of cardiac performance with quantitative radionuclide angiocardiography. Right ventricular ejection fraction with special reference to findings in chronic obstructive pulmonary disease. Am J Cardiol 41:897, 1978.

12. Berger HJ, Reduto LA, Johnstone DE, et al: Global and regional left ventricular response to bicycle exercise in coronary artery disease. Assessment by quantitative radionuclide angiocardiography. Am J Med 66:13, 1979.

13. Watson DD, Nelson JP, Gottlieb S: Rapid bolus injection of radioisotopes. Radiology 106:347, 1973.

14. Tobinick E, Schelbert HR, Henning H, et al: Right ventricular ejection fraction in patients with acute inferior and anterior myocardial infarction assessed by radionuclide angiocardiography. Circulation 57: 1078, 1978.

15. Folland ED, Hamilton GW, Larson SM, et al: The radionuclide ejection fraction: A comparison of three radionuclide techniques with contrast angiography. J Nucl Med 18:1159, 1977.

16. Bonte FJ, Parkey RW, Graham KD, et al: A new method for radionuclide imaging of acute myocardial infarction. Radiology 110:473, 1974.

17. Parkey RW, Bonte FJ, Meyer SL, et al: A new method for radionuclide imaging of actue myocardial infarction in humans. Circulation 50: 540, 1974.

18. Willerson JT, Parkey RW, Bonte FJ, et al: Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology. Circulation 51:1046, 1975.

19. Wackers FJ, Berger HJ, Johnstone DE, et al: Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: Validation of the technique and assessment of variability. Am J Cardiol 43:1159, 1979.

20. Folland ED, Hamilton GW, Larson SM, et al: The radionuclide ejection fraction: A comparison of three radionuclide techniques with contrast angiography. J Nucl Med 18:1159, 1977.

21. Stokely EM, Parkey RW, Bonte FJ, et al: Gated blood-pool imaging following ^{99m}Tc stannous pyrophosphate scintigraphy. Radiology 120: 433, 1976.

22. Prinzmetal M, Corday E, Bergman HC, et al: Radiocardiography: A new method for studying the blood flow through the chambers of the heart in human beings. Science 108:340, 1948.

23. Flaherty JT, Canent RV, Boineau JP, et al: Use of externally recorded radioisotope-dilution curves for quantitation of left-to-right shunts. Am J Cardiol 20:341, 1967.

24. Hoffmann G, Kleine N: Die methode der radiokardiographischen functions analyse. Nuclearmedizin 7:350, 1968.

25. Wagner HN Jr, Wake R, Nickoloff E, et al: The nuclear stethoscope: A simple device for generation of left ventricular curves. Am J Cardiol 38:747, 1976.

26. Ashburn WL, Schelbert HR, Verba JW: Left ventricular ejection fraction --A review of several radionuclide angiocardiographic approaches using the scintillation camera. Prog Cardiovasc Dis 20:267, 1978.

27. Steele P, Kirch D, LeFree M, et al: Measurement of right and left ventricular ejection fractions by radionuclide angiocardiography in coronary artery disease. Chest 70:56, 1976.

28. McKusick KA, Bingham JB, Pohost GM, et al: The gated first-pass radionuclide angiogram: A method for measurement of right ventricular ejection fraction. Circulation 57/58:II-130, 1978 (abstract).

29. Grove RB, Harolds JA, Powers TA, et al: Gated first-pass radionuclide ventriculography for measurment of right ventricular function. Invest Radiol (in press; abstract).

30. Mullins CB, Mason DT, Ashburn WL, et al: Determination of ventricular volume by radioisotope angiography. Am J Cardiol 240:72, 1969.

31. Van Dyke D, Anger HO, Sullivan RW, et al: Cardiac evaluation from radioisotope dynamics. J Nucl Med 13:585, 1972.

32. Hecht HS, Mirell SG, Rolett EL, et al: Left ventricular ejection fraction and segmental wall motion by peripheral first-pass radionuclide angiocardiography. J Nucl Med 19:17, 1978.

33. Kurtz D, Ahnberg DJ, Freed M, et al: Quantitative radionuclide angiocardiography. Determination of left ventricular ejection fraction in children. Br Heart J 38:966, 1976.

34. Schelbert HR, Verba JW, Johnson AD, et al: Nontraumatic determination of left ventricular ejection fraction by radionuclide angiocardiography. Circulation 51:902, 1975.

35. Henning H, Schelbert H, Crawford MH, et al: Left ventricular performance assessed by radionuclide angiocardiography and echocardiography in patients with previous myocardial infarction. Circulation 52:1069, 1975.

36. Bodenheimer MM, Banka VS, Fooshee CM, et al: Quantitative radionuclide angiography in the right anterior oblique view: Comparison with contrast ventriculography. Am J Cardiol 41:718, 1978.

37. Steele P, LeFree M, Kirch D: Measurement of left ventricular mean circumferential fiber shortening velocity and systolic ejection rate by computerized radionuclide angiocardiography. Am J Cardiol 37:388, 1976.

38. Slutsky R, Battler A, Karliner et al: First third ejection fraction: A new method for assessing patients with coronary artery disease without the use of exercise stress by first-pass radionuclide angiography. Am J Cardiol 43:397, 1979 (abstract).

39. Jengo JA, Mena I, Blaufuss A, et al: Evaluation of left ventricular function (ejection fraction and segmental wall motion) by single pass radioisotope angiography. Circulation 57:326, 1978.

40. Schad N: Nontraumatic assessment of left ventricular wall motion and regional stroke volume after myocardial infarction. J Nucl Med 18:333, 1977.

41. Bodenheimer MM, Banka VS, Fooshee CM, et al: Comparison of wall motion and regional ejection fraction at rest and during isometric exercise: Concise communication. J Nucl Med 20:724, 1979.

42. Rerych SK, Scholz PM, Newman GE, et al: Cardiac function at rest and during exercise in normals and in patients with coronary heart disease. Ann Surg 187:449, 1978.

43. Jones RH, Rerych SK, Newman GE, et al: Noninvasive radionuclide procedures for diagnosis and management of myocardial ischemia. World J Surg 2:811, 1978.

44. Alderson PO, Bernier DR, Ludbrook PA, et al: Serial radionuclide determinations of the ejection fraction with ^{99m}Tc-labeled red blood cells. Radiology 119:729, 1976.

45. Green MV, Ostrow HG, Douglas MA, et al: High temporal resolution ECG-gated scintigraphic angiocardiography. J Nucl Med 16:95, 1975.

46. Burow RD, Strauss HW, Singleton R, et al: Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging. Comparison to contrast angiography. Circulation 56:1024, 1977.

47. Dehmer G, Lewis S, Hillis LD, et al: Nongeometric determination of left ventricular volumes from equilibrium blood pool scans. Am J Cardiol 45:293, 1980.

48. Slutsky R, Karliner J, Ricci D, et al: A new method for estimation of left ventricular volumes from equilibrium radionuclide angiography independent of geometry. Circulation 48:II-157, 1978 (abstract).

49. Kennedy JW, Trenholme SE, Kasser IS: Left ventricular volume and mass from single plane cineangiocardiogram. A comparison of antero-posterior and right anterior oblique methods. Am Heart J 80:343, 1970.

50. Grossman W, Braunwald E, Mann T, et al: Contractile state of the left ventricle in man as evaluated from end systolic pressure volume relations. Circulation 56:845, 1977.

51. Suga H, Sagawa K: Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 35:117, 1974.

52. Mitchell JH, Wildenthal K: Analysis of left ventricular function. Proc Roy Soc Med 65:542, 1972.

53. Doss JK, Hillis LD, Curry G, et al: A new model for the scintigraphic assessment of regional ventricular wall motion. Submitted, 1980.

54. Berger HJ, Zaret BL: Noninvasive radionuclide assessment of right ventricular performance in man. In Nuclear Cardiology. Willerson JT, editor. F.A. Davis Company, Philadelphia, p 91, 1980.

55. Matthay R, Ellis J, Steele P: Effects of dextran loading on left ventricular performance in cystic fibrosis: Assessment by noninvasive radionuclide angiocardiography. Chest 72:407, 1977.

56. Cohn J, Guiha N, Broder M, et al: Right ventricular infarction: clinical and hemodynamic features. Am J Cardiol 33:209, 1974.

57. Tobinick E, Schelbert H, Henning H, et al: Right ventricular ejection fraction in acute myocardial infarction assessed by radionuclide angiography. Circulation 56:II-140, 1977.

58. Sharpe N, Notvinick E, Shames D, et al: Noninvasive diagnosis of right ventricular infarction: A common clinical entity. Circulation 54:II-76, 1976.

59. Poliner LR, Dehmer GJ, Lewis SE, et al: Comparison of supine and upright left ventricular performance during rest and exercise in normal subjects. Circulation, in press, 1980.

60. Borer JS, Kent KM, Bacharach SL, et al: Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease. Circulation 60:572, 1979.

61. Borer JS, Bacharach SL, Green MV, et al: Real-time radionuclide cineangiography in the non-invasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 296:839, 1977.

62. Suga H, Sagawa K, Shoukas AA: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 32:314, 1973.

63. Sagawa K, Suga H, Shoukas AA, et al: End-systolic pressure/volume ratio: A new index of ventricular contractility. Am J Cardiol 40:748, 1977.

64. Nivatpurmin T, Katz S, Scheuer J: Peak left ventricular systolic pressure/end systolic volume ratio: A sensitive detector of left ventricular disease. Am J Cardiol 43:969, 1979.

65. Dehmer GJ, Lewis SE, Hillis LD, et al: Exercise induced alterations in left ventricular volumes and the pressure/volume relationship: A sensitive indicator of left ventricular dysfunction in patients with coronary artery disease. Submitted, 1980.

66. Dehmer GJ, Falkoff M, Lewis SE, et al: Effect of oral propranolol on rest and exercise left ventricular ejection fraction, volumes and segmental wall motion in patients with angina pectoris: Assessment with equilibrium gated blood pool imaging. Submitted, 1980.

67. Firth BG, Dehmer GJ, Corbett JR, et al: The effect of chronic oral digoxin therapy on ventricular function at rest and peak exercise in patients with ischemic heart disease: Assessment with equilibrium gated blood pool imaging. Am J Cardiol, in press, 1980.

68. Pulido J, Doss J, Twieg D, et al: Submaximal exercise testing in patients following acute myocardial infarction: Myocardial scintigraphic and electrocardiographic observations. Am J Cardiol 42:19, 1978.

69. Corbett J, Dehmer GJ, Lewis SE, et al: The prognostic value of submaximal exercise testing with radionuclide ventriculography following acute myocardial infarction. Submitted, 1980.

70. Sanford CF, Corbett J, Curry GC, et al: Value of radionuclide ventriculography in the immediate characterization of patients with acute myocardial infarcts. Submitted, 1980.

71. Anderson PA, Jones RH, Sabiston DC: Quantitation of left-to-right cardiac shunts with radionuclide angiography. Circulation 49:512, 1974.

72. Boucher CA, Ahluwalia B, Block PC, et al: Inhalation imaging with oxygen-15 labeled carbon dioxide for detection and quantitation of left-to-right shunts. Circulation 54:632, 1977.

73. Rigo P, Murray M, Strauss HW, et al: Left ventricular function in acute myocardial infarction evaluated by gated scintiphotography. Circulation 50:678, 1974.

74. Rigo P, Alderson PO, Robertson RM, et al: Measurement of aortic and mitral regurgitation by gated blood-pool scan. Circulation (in press).

75. Wallace AG, Williams RS, Rerych SK, et al: Effects of physical conditioning on patients wtih angina pectoris: Assessment by radionuclide angiocardiography. Submitted, 1980.

76. Kent KM, Borer JS, Green MV, et al: Effects of coronary revascularization on left ventricular function during exercise. N Engl J Med 298:1434, 1978.

77. Borer JS, Bacharach SL, Green MV, et al: Exercise-induced left ventricular dysfunction in symptomatic and asymptomatic patients with aortic regurgitation: Assessment with radionuclide cineangiography. Am J Cardiol 42:351, 1978.

78. Henry WL, Bonow RO, Rosing DR, et al: Observations on the optimum time for operative intervention for aortic regurgitation. II. Serial echocardiographic evaluation of asymptomatic patients. Circulation 61:484, 1980.

79. Dehmer GJ, Corbett J, Hillis LD, et al: Value of rest and exercise changes in left ventricular volumes in the scintigraphic characterization of patients with aortic regurgitation. Submitted, 1980.