Evaluation of Ventricular Function in Patients with Coronary Artery Disease

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The recent expansion of interventional cardiovascular technologies has stimulated a concomitant expansion of noninvasive cardiac studies, both to assist in diagnosis and to evaluate treatment outcomes. Radionuclide ventricular function studies provide a reliable, reproducible means to quantify global left ventricular systolic performance, a critical determinant of prognosis in patients with cardiovascular disease. In addition, the ability to evaluate regional left ventricular wall motion and to assess ventricular performance during exercise have secured a fundamental role for such studies in the screening and treatment of patients with coronary artery disease. Radionuclide techniques have been extended to the evaluation of left ventricular relaxation/filling events, left ventricular systolic/diastolic function in the ambulatory setting, and with appropriate technical modifications, to the assessment of right ventricular performance at rest and with exercise. As a complement to radionuclide perfusion studies, cardiac blood-pool imaging allows for thorough noninvasive description of cardiac physiology and function in both normal subjects and in patients with a broad range of cardiovascular diseases.

Recent developments in interventional cardiac catheterization technology have shifted the emphasis in the invasive laboratory from pure diagnosis to diagnosis and treatment. This transition has stimulated a concomitant expansion in the role of noninvasive cardiac evaluation, both to assist in diagnosis (and thereby streamline the catheterization procedure) and to evaluate the outcome of interventional procedures, such as angioplasty/valvuloplasty or bypass surgery. This article will review the data that can be obtained from radionuclide ventriculography for the evaluation of systolic and diastolic function in patients with coronary artery disease (CAD). The technical aspects of data acquisition and the physiology of cardiac contraction are considered first, followed by a section on clinical applications of radionuclide cardiac studies to measure systolic function. A separate section detailing the technical, physiologic, and clinical application of diastolic measurements follows, reflecting the growing recognition of abnormal left ventricular (LV) relaxation and filling in a variety of clinical cardiac syndromes.

SYSTOLE

Biology and Mechanism of Cardiac Contraction

Anatomy. The heart consists of two syncytiae of striated muscle, atrial and ventricular, attached to a framework of fibrous tissue that contains the valves and their supporting structures. The prominent organelles in each myocyte are the contractile apparatus (thin strands of actin and thick strands of myosin), and many mitochondria (Fig. 1); each cell is supplied by a single capillary. The sarcolemma, or muscle cell membrane, forms tight junctions (intercalated disks) at the boundaries of individual cells. These junctions have extremely low electrical resistance, that facilitates rapid passage of the action potential between cells. The functional result of this arrangement is that excitation of a single cell causes depolarization of the entire syncytium, allowing coordinated mechanical contraction.

Biology of Contraction

As an action potential sweeps over the sarcolemma it also spreads to the interior of the cell, causing release of calcium ions from the sarcoplasmic reticulum into the sarcoplasm. Intracellular Ca^{++} levels rise from 10^{-7} to 10^{-5} mEq/l: this increased calcium level catalyzes the interaction of actin and myosin by inhibiting the repressor effects of troponin I and contraction ensues.
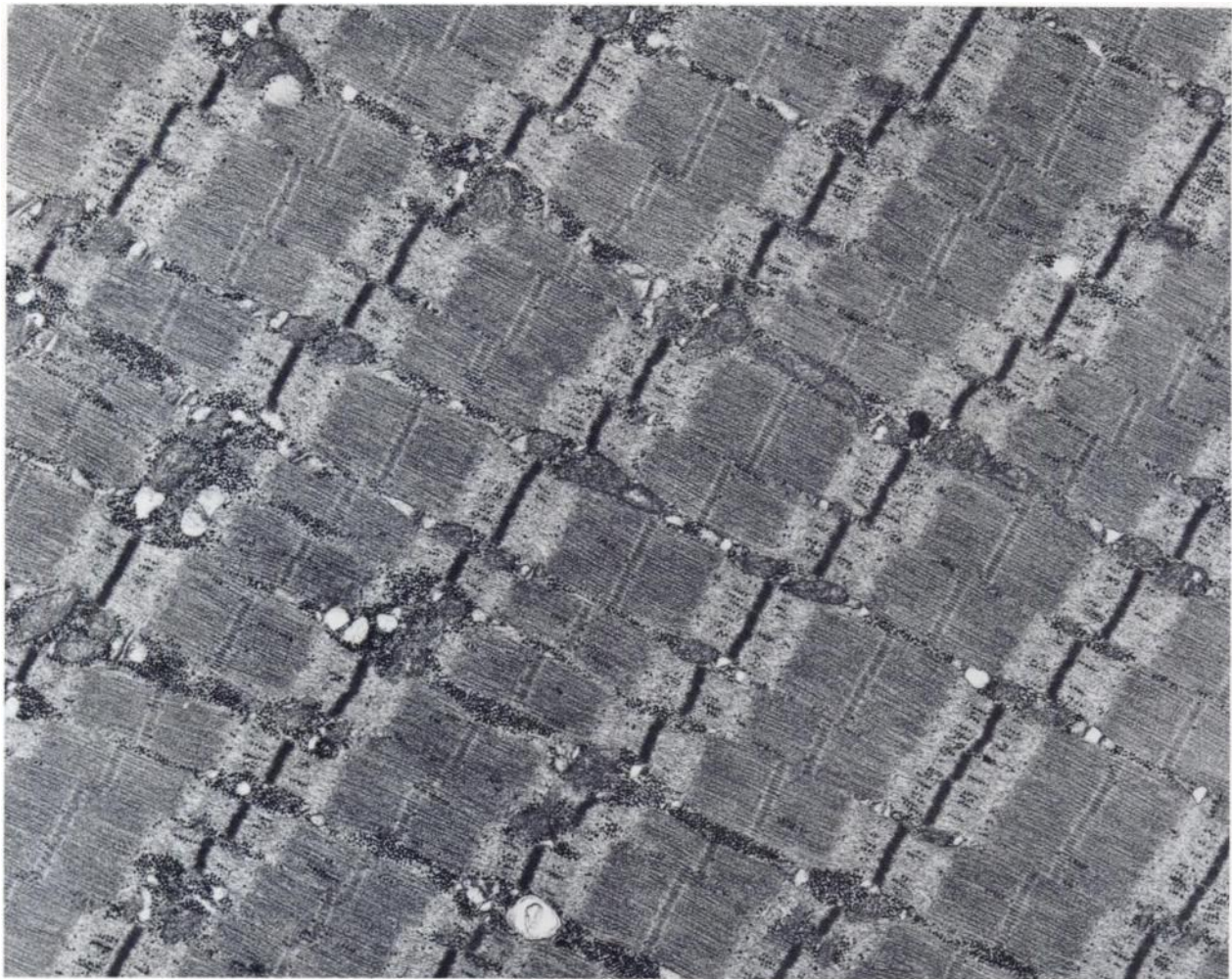
FIGURE 1
Electron micrograph (20,000 ×) of a human skeletal muscle biopsy specimen showing characteristic banding. Alternating dark broad bands (A bands) and light broad bands (I bands) are seen. The I bands contain a dark line, the Z band, whereas the central dark and light bands of the A bands are called the M and H bands, respectively. The area between Z bands is known as a sarcomere. In addition, glycogen granules, mitochondria, and sarcotubular elements are easily recognized.

Relaxation (i.e., the deactivation of the actin-myosin complex) occurs when the protein phospholamban catalyzes the transport of Ca^{++} back to the sarcoplasmic reticulum (*1*). Both the release and uptake of calcium at the sarcoplasmic reticulum are ATP (energy) dependent. Thus, both contraction and relaxation are active, energy requiring processes, and may be affected by disease processes which impair the delivery or utilization of energy substrates.

Hemodynamics of Cardiac Contraction

The relationship of electrical events to left ventricular pressure and volume is shown in Figure 2. Following the QRS complex, the ventricular syncytium is depolarized and contraction begins. The onset of shortening causes increased intraventricular pressure, which results in closure of the AV valves; as myocyte shortening continues, intraventricular pressure increases without a change in volume (isovolumic systole). During this isovolumetric phase, the left ventricle becomes more spherical as a consequence of longitudinal fiber shortening and wall thickening. Ultimately, ventricular pressure exceeds diastolic pressure in the aorta or pulmonary artery and ventricular ejection ensues. The maximal rate of rise of intraventricular pressure (dp/dt) occurs just prior to the inward motion of the ventricular wall. Potential energy (developed as pressure during isovolumic systole) is now converted to kinetic energy as blood is ejected into the great arteries.

Ventricular ejection consists of two phases: (a) the early active phase, during which myocyte shortening continues and (b) a later passive phase, when no additional shortening occurs. Under normal circumstances the majority of ventricular emptying occurs during the
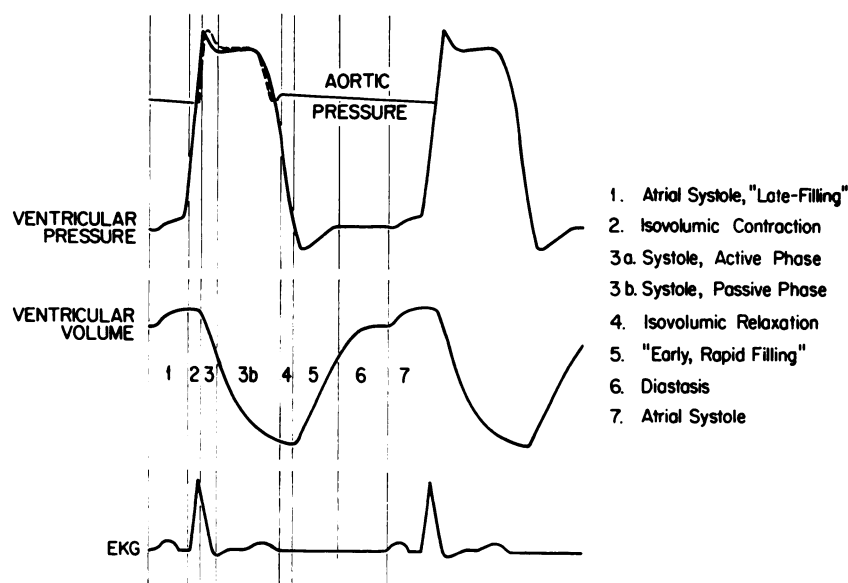
1. Atrial Systole,"Late-Filling"
2. Isovolumic Contraction
3a. Systole, Active Phase
3b. Systole, Passive Phase
4. Isovolumic Relaxation
5. "Early, Rapid Filling"
6. Diastasis
7. Atrial Systole

FIGURE 2
Temporal relationship of relative left ventricular pressure and volume to the surface EKG (schematic) for a single cardiac cycle.

active phase, which concludes when the ejection velocity of blood reaches a maximum. The momentum imparted to blood during the active phase of systole permits continued emptying of the ventricle despite the fact that ascending aortic pressure exceeds ventricular pressure during the late passive phase of ejection. The duration of this passive phase of systole varies with the state of peripheral resistance. For example, with vasodilation, systole is prolonged, and the passive phase contributes a relatively greater percentage to overall stroke volume. Closure of the semilunar valves marks the end of the passive phase and ventricular relaxation begins (2). The pressure and volume events characterizing ventricular relaxation and filling are detailed in the section on diastole.

The major parameter of interest during systole is the ejection fraction. While many other indices of systolic function can be calculated, such as systolic ejection rate, they offer limited clinically relevant information.

Measurement of Systolic Function

Evaluation of ventricular function is useful for diagnosing myocardial ischemia (3–6), identifying patients at high risk for future cardiac events (7–17), and selecting appropriate management strategy. Serial measurements can be recorded to evaluate the effect of mechanical (bypass surgery or angioplasty) or medical therapy on ventricular function (18–24).

Radionuclide angiography (RNA) may be performed by first-pass or equilibrium techniques. While the techniques of data recording and the radiopharmaceuticals differ, (Table 1) the quantitation of global ventricular function (ejection fraction and end diastolic volume) produce similar results with both techniques. The selection of the data recording technique best suited to the clinical question to be addressed will be described below.

Radiopharmaceuticals

Radiopharmaceutical requirements for first-pass studies are a high photon flux (all left ventricular function data must be collected in <10 sec) at a low delivered radiation dose. Clinically, ^{99m}Tc-labeled pharmaceuticals are used most often for this purpose. Since the agents transverse the lungs, they permit measurements of both right and left ventricular function. The relatively short residence times of ^{99m}Tc-labeled sulfur colloid and diethylenetriaminepentaacetic acid (DTPA) in the vasculature allow two or three observations to be recorded in a short interval of time (e.g., rest and stress), each with a low blood background. These agents have the advantage of an extremely low radiation burden to the patients.

The radiopharmaceuticals for equilibrium measurements can also be employed for first pass studies, but are typically used if only a single measurement is desired. These radiopharmaceuticals should have an unchanging concentration in the blood pool during the interval of measurement. Two ^{99m}Tc-labeled agents, red cells and albumin, meet this criteria. The two agents differ in their target to background activity ratio (better with red cells) and their ease of use (better with albumin, which is available as a multi-dose kit, while each dose of red cells must be individually prepared). Image contrast is usually better with red blood cells, making this the preferred radiopharmaceutical for most applications. In some severely ill patients, however, it is diffi-

TABLE 1
Radiopharmaceuticals for Blood-Pool Imaging

First pass	Equilibrium
[^{99m}Tc]SC	[^{99m}Tc]albumin
[^{99m}Tc]DTPA	^{99m}Tc RBCs
[^{99m}Tc]pertechnetate	

cult to get good labeling of red cells. In these patients, it may be preferable to use albumin.

First Pass

Following rapid injection of 10–20 mCi through an intravenous catheter placed in the median antecubital vein, sequential images of the distribution of radioactivity are recorded as the bolus passes through the heart and great vessels. The tracer is administered in a small volume by a modification of the Oldendorf technique (25). Data can be recorded with the patient in the supine or upright position. The 30° right anterior oblique projection is usually used to optimize separation of the ventricles and atria, and to view the ventricles parallel to their long axes. While the RAO view maximizes overlap of the right and left ventricles, this is not a problem in most patients, since the timing of tracer appearance reliably identifies each chamber sequentially.

The radionuclide data may be recorded as a sequence of images (ungated) or in synchrony with the patient's electrocardiogram (gated). If the data collection is ungated, a minimum framing rate of 25 frames/sec (40 msec/frame) is recommended to permit an accurate determination of end systole; this follows from the fact that the duration of end systole is 80 msec at rest; as required from sampling theory, accurate quantitation would require a twofold greater sampling frequency, i.e. 40 msec. If the data collection is gated, two separate data sets are recorded: (a) the right heart phase (from bolus injection to lung visualization) and (b) the left heart phase (from left atrium to aortic visualization). Usually six to seven cardiac cycles are summed in each phase of the study.

Advantages of the first pass technique are the high target-to-background ratio, rapidity of imaging, and the temporal separation of the right and left ventricles. While repeated assessment of cardiac function under rapidly varying conditions is possible with repeated injections, the technique is impractical for more than three determinations at one time. If many measurements are desired, as may occur during a pharmacologic intervention, short (i.e., 2 min) equilibrium collections should be used.

Equilibrium

Five to 10 minutes after injection of an equilibrium radiopharmaceutical (usually 20–25 mCi), data are recorded in a computer system synchronized with the R-wave of the patient's electrocardiogram. While few counts are recorded during a single portion of any one cardiac cycle, the summation of information from ~800–1,000 cycles in phase produces an average cardiac cycle with high resolution. Images are usually acquired in three standard projections: anterior, left anterior oblique, and left posterior oblique (or left lateral) for a

preset count of at least 500k/frame (count density of about 300 cts/cm^2 over the LV). The combination of high count density and multiple views enhances the sensitivity of equilibrium images for the detection of wall motion abnormalities.

Gating Requirements and Number of Frames

The triggering signal for the computer should be a rapidly changing signal that occurs once/cardiac cycle. The R wave of the patients EKG usually fulfills this requirement. However, in patients with low voltage on their EKG, tall peaked T waves, or in patients with pacemakers, the gating signal may be ambiguous, leading to two or more gating signals/beat. If data are recorded under this circumstance, ventricular function will appear to be substantially reduced, leading to an erroneous interpretation. To avoid this problem the electrodes should be moved until a single triggering signal for each cardiac cycle is provided to the computer.

Division of the R-R interval into at least 16 frames per cycle (<50 msec/frame) provides adequate temporal resolution for clinical evaluation of regional wall motion and ejection fraction at rest (heart rate of 80); for exercise studies data should be recorded for shorter intervals (<25 msec/frame). To assess regional ejection fraction and/or diastolic filling parameters, a minimum of 32 frames per cycle is necessary, even at resting heart rates. Wide changes in heart rate during gated data acquisition, due to multiple premature contractions, will underestimate global systolic function. Although arrhythmia filtering can be used to reject beats outside of a specified R-R interval, this approach significantly prolongs acquisition time and may not improve the quality of the resultant data. Since contractile function on any given beat is dependent on the preceding beat, it is better to control the arrhythmia prior to recording the data, if at all possible, rather than filter the arrhythmic beats. In general, a gated scan is not materially degraded by aberrant beats of <10% incidence.

To optimize the detection of circumscribed wall motion abnormalities, pixel size in the computer should be <5 mm (some state-of-the art computers have sufficient image memory to permit recording 32 frames/cardiac cycle at a spatial resolution of 2 mm/pixel).

Imaging Instrumentation

The extremely high count rates that are characteristic of first pass studies require either a multi-crystal camera or an Anger camera modified to handle over 200,000 events/sec in the energy window. A standard or large field-of-view gamma camera equipped with a general all-purpose collimator provides an acceptable trade-off between sensitivity and resolution to record rest equilibrium blood-pool images. The limited time for data collection in exercise studies usually requires a change

from the all purpose to a high-sensitivity collimator (sensitivity improvement by a factor of 2).

Radionuclide Ventriculography: Image Interpretation

The data are analyzed in two parts: qualitative inspection of the data as an endless cinematic loop of the cardiac cycle, and quantification of volumes and function.

From inspection of the cinematic display, the size of the chambers and great vessels are determined, regional wall motion is assessed, thickness of the muscular wall is estimated, and evidence is sought for pericardial effusion, and/or para-cardiac spaces/masses. Normal subjects of average body build empty at least half the end-diastolic volume of their right and left ventricles each beat (normal LVEF ranges from 50–65%); shorten the long axis of their left ventricle by >25% and the short axis >45%; and have left ventricular end-diastolic volumes of <200 ml (114 ml/m^2) (26). Inspection permits the subjective grading of regional wall motion into normal (regional shortening of a radius of at least 25%), hypokinetic (regional shortening of a radius of 10–25%), akinetic (regional shortening of 0–5%) and dyskinetic (systolic expansion), based on a comparison of end diastolic to end systolic outlines. Quantitative approaches to regional shortening measurements have been described, but their precision is limited by the relatively poor (>5 mm) spatial resolution of existing systems.

Ejection Fraction

The ejection fraction, usually calculated by dividing the stroke counts by the background corrected end-diastolic counts, is the most important and widely applied indicator of global ventricular function. It is highly reproducible and provides prognostic information in patients with CAD (7–17). The values for ejection fraction obtained by either first-pass or equilibrium techniques method are comparable.

The ejection fraction is best calculated using a count-based technique; this method is independent of geometric considerations and permits the use of automatic edge detection programs to compute the ejection fraction from the left anterior oblique images on equilibrium studies, with high accuracy and reproducibility (27). In the count based method the ejection fraction is derived from the ventricular time-activity curves, which closely parallels the angiographic time-volume curve (28).

Prior to calculation of the ejection fraction, the total counts in each frame of the data collection should be normalized, and a spatial and temporal smoothing of the data performed. A region of interest is then assigned over the left ventricle using either a manual, threshold, second derivative or phase analysis (see below) algo-

rithm, to define the edges of the ventricle in each frame. Since ~50% of the total counts measured in the left ventricular region of interest arise from outside the ventricle, a representative periventricular zone of background must be selected to differentiate "true" LV counts from background. The background subtracted counts in the left ventricle in each frame are then used to generate the time-activity curve. From the time-activity curve, ejection fraction and rates of ejection and filling can be obtained.

An alternative approach for generating time-activity curves from gated equilibrium scans uses a single region of interest, based on the end-diastolic frame. The advantage of using a single region of interest is that it provides smoother time-activity curves, especially useful for calculating rates of ejection and filling. The calculated ejection fraction by this method is usually about 5% lower than that obtained by the variable region of interest technique.

For the first pass technique, ejection fraction is calculated by assigning a region of interest over the ventricle and generating a time-activity curve with a temporal resolution of at least 25 frames per second. The six to seven cardiac cycles that have maximal activity are then summed in phase to create a composite curve from which ejection fraction is calculated.

Ventricular Volume

Left ventricular volumes can be calculated by either a geometric (area length) method (29) or by a count-based method (30). The geometric method requires calibration of the gamma-camera to determine the relative size of the left ventricle in each of two views. The volume of the chamber is then calculated using either an area/length formula or the Simpson rule approach (to calculate the volume of irregularly shaped objects). A minimum interobserver variation of ~35 ml (~20%) can be expected with the geometric approach, due to variation defining the borders of the chamber. The count based method requires a blood sample as a counting standard and correction for attenuation of blood-pool activity by overlying chest wall. The count based method has better precision than the geometric approach (minimum error of ~10%), but may have substantial inaccuracy due to the difficulty computing attenutation.

Regional Wall Motion

Regional wall motion is evaluated qualitatively by viewing the cardiac cycle in a closed-loop cine display in multiple projections, with myocardial segments described subjectively as either normal, hypokinetic, akinetic, or dyskinetic, as previously outlined. Alternatively, quantitation of regional function can be achieved either by measuring regional radial shortening (as done

in contrast ventriculography) (*31*), or by assessing regional ejection fraction by sector analysis (*32–35*). These two approaches differ fundamentally: contrast studies measure changes in edges, while regional ejection fraction measures changes in volumes. Quantitation of regional function has been reported to increase the specificity of detecting coronary artery disease despite the problem of spatial resolution noted earlier.

In addition to the standard methods of analyzing blood-pool data, functional images, such as ejection fraction images (*36*), paradox images (*37*), and amplitude and phase images (*38,39*) can be readily calculated. These images have been useful in characterizing regional asynergy and asynchrony.

Phase Analysis

Functional images can reduce complex information into a single image representing both anatomy and physiology. The stroke volume image and the paradox image provide useful data but do not take full advantage of the cyclic nature of the gated blood-pool scan. A more general method of data evaluation is provided by the technique of Fourier analysis. Briefly, any periodic function can be represented mathematically by a sum of sinusoidal and cosinusoidal curves of various amplitude and frequency. To generate functional images of the heart, Fourier analysis is employed to approximate the volume curve with the first Fourier harmonic, a pure sine or cosine function with a period equal to the period of the cardiac cycle.

Analysis of a time-activity curve by Fourier transformation yields the best fit values for amplitude and phase. When this analysis is performed for each pixel in an image, amplitude and phase images are obtained. The amplitude image is qualitatively similar to the stroke volume image, but has two important differences: (a) The stroke volume image is calculated from only two points in time in the cardiac cycle, while the amplitude image is computed from the entire time-activity curve of each pixel; (b) The atria are detectable in the amplitude image (unlike the stroke volume image where negative changes in activity are ignored, amplitude image values are always positive since, by convention, the positive square root is always taken).

The phase image reflects the timing of regional ejection and is not determined solely by any particular cardiac event, but depends on function in general. Since the amplitude and phase images are computed from entire local time-activity curves, they possess smaller uncertainties than simpler images such as the stroke volume image.

Fourier analysis of gated blood-pool data will never replace the subjective evaluation of the cinematically displayed data by an experienced observer, but the additional quantification provided by this technique has important clinical applications. The analysis of wall motion is dependent on changes in edges, while phase and amplitude data primarily reflect changes in regional volume. These two phenomena are often similar, but are not necessarily identical. As a result it is not useful to consider phase and amplitude analysis as a quantitative means of assessing regional wall motion. Phase analysis may be useful to follow subtle changes in ventricular function after medical and/or surgical intervention and has been particularly useful for evaluating premature ventricular contraction and accessory conduction pathways.

CORONARY ARTERY DISEASE: STRATEGIES FOR DETECTION

Two major factors determine the prognosis of patients with coronary heart disease: (a) the degree of *irreversible* myocardial damage (the consequence of prior infarction) and (b) the extent of *jeopardized*, but viable, myocardium (the severity of underlying disease). The impact of irreversible myocardial damage is primarily defined by abnormalities in regional and global systolic function at rest, while the effect of provocable ischemia is defined by transient impairment of systolic performance during exercise. Most patients with CAD and no prior infarction have normal ventricular function at rest; a subgroup of these patients may have reversible left ventricular dysfunction at rest. This dissociation between function and viability has been referred to as "stunned" or "hibernating" myocardium (*35,40–42*) depending on the acuity of the ischemic insult (acute vs. subacute/chronic, respectively). Augmentation of blood flow to the ischemic but viable muscle results in improved global and regional function (*35,40–42*).

Since regional wall motion abnormalities may appear before symptoms of angina or ischemic ECG abnormalities (*43,44*), exercise radionuclide angiography has been proposed as a potentially sensitive technique for detecting ischemia. Data are recorded in the modified best septal left anterior oblique view, to isolate the left ventricle (*45*). In this view, the septum represents left anterior descending artery territory (Fig. 3) and the posterolateral segment represents left circumflex artery territory; the right coronary artery may contribute to posterolateral perfusion depending on the dominance of the circulation.

In 1977, Borer observed that normal subjects generally increase their ejection fraction by at least 5% from rest to exercise, while patients with coronary artery disease demonstrate either a fall or no change in ejection fraction compared to their resting values. This initial study reported 95% sensitivity and 100% specificity for detection of coronary artery disease (*45*), which represents a substantial improvement when compared to routine ECG-treadmill testing (sensitivity = 64%, specificity = 89% [*46*]). However, when a relatively unse-
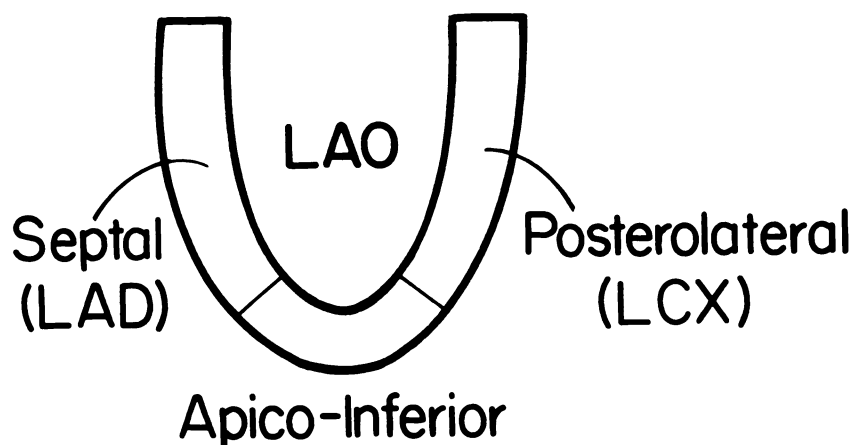
FIGURE 3
Standard myocardial segmentation scheme, "best septal" left anterior oblique projection. The postero-lateral segment is most commonly supplied by the left circumflex; however, the right coronary artery can contribute to posterolateral perfusion (depending upon the dominance of the circulation). The apicoinferior segment may receive supply from all three-coronary arteries.

lected series of patients were subsequently studied, the overall sensitivity remained high at 90%, but the specificity fell to 58% (47). The lower specificity in the unselected population most probably reflects the presence of abnormal left ventricular reserve in noncoronary heart disease such as cardiomyopathy, valvular heart disease, and hypertension (48). When evaluating the sensitivity for detecting significant coronary stenosis in individual vascular territories, the sensitivity is 80% to 96% for left anterior descending artery and substantially lower (58% to 61%) for the left circumflex artery (45,49). The sensitivity for detecting three-vessel coronary disease is excellent (95%) in contrast to 73% for single or two-vessel disease (50).

A second major problem using exercise RNA for the detection of coronary disease follows from the fact that extent of myocardium at jeopardy must be sufficient to impair regional contractile function before it can be appreciated on the exercise scan. This problem is most apparent for the detection of isolated right coronary disease, particularly when the vessel does not make a major contribution to posterolateral perfusion (i.e., co-dominant or left dominant circulation). Maddahi and co-workers reported that right ventricular ejection fraction response to exercise may be useful in this circumstance (51). However, others have cautioned that this response is more complicated, and dependent upon RV afterload as well as right coronary blood flow. Thus, detection of isolated right coronary artery disease remains problematic; sensitivity improves as the dominance of this vessel increases.

When compared to exercise radionuclide angiography, stress and redistribution thallium scintigraphy provides comparable sensitivity for CAD detection. The specificity of exercise thallium testing has been reported to be greater than that of exercise RNA (presumably reflecting the occurrence of ventricular dysfunction despite normal coronary perfusion in patients with non-coronary heart disease as noted above). Since blood-pool imaging provides insight into the functional significance of CAD not available (except by inference)

from a myocardial perfusion study, this test should, perhaps, not be viewed primarily as a means to detect CAD, but for its unique capacity to define the impact of ischemia on ventricular function. Thus it is useful to view cardiac function and perfusion studies as complementary rather than competitive in the evaluation of patients with CAD.

Chronic Stable Angina: Risk Stratification

The overall mortality rate for patients with chronic stable angina is 4% per year (52). However, this risk is not uniform: Identification of patients at high risk is imperative if one is to impact on the natural history of the disease. Humphries and associates have reported that prognosis in patients with chronic stable angina varies greatly depending on the location and extent of coronary artery disease. One-year mortality for patients with significant left main stenosis was 15–25%, compared to 10–12% for patients with three-vessel and only 1–4% for patients with single vessel coronary disease (53). Furthermore, independent of coronary anatomy, severity of left ventricular dysfunction at rest has been associated with higher annual mortality (11): in patients with chronic stable angina, those with resting left ventricular ejection fraction of less than 30% had mortality of 20–25% over an 18 to 24-mo period, compared to only 2% mortality in patients with left ventricular ejection fraction of 30% or greater (54). In the latter group, when left ventricular ejection fraction dropped by greater than 10% with exercise, the annual mortality increased to >6%. When medically treated patients from the Coronary Artery Surgery Study (CASS) registry were stratified according to resting ejection fraction, the mortality increased progressively with decreasing ejection fraction: Four-year mortality was 8% in patients with normal ejection fraction, 17% in patients with ejection fractions 35% to 49% and 43% in patients with ejection fractions of <35% (11).

In 1983, Jones and coworkers described the prognostic implications of left ventricular function during exercise (12). In their series, patients with abnormal ejec-

tion fraction response to exercise had 20% higher 3-year mortality compared to patients with a normal increase in exercise ejection fraction. Of note, resting ejection fractions were comparable between the two groups with different exercise responses. As such, differences in survival could not be explained by differences in resting ejection fraction alone.

In 1984, Pryor and associates analyzed the prognostic implications of coronary arteriographic data relative to resting ejection fraction as well as ejection fraction response to exercise (13). They confirmed prior reports that coronary anatomy is associated with clinical outcome (p < 0.001), when considered alone or after adjustment for resting ejection fraction. However, after adjustment for the exercise ejection fraction, the prognostic importance of coronary anatomy declined (p < 0.05), but remained significant. The National Heart, Lung and Blood Institute (NHLBI) reported similar results in a group of three-vessel CAD patients and preserved left ventricular function at rest, where the high risk subgroup was characterized by a decrease in ejection fraction during exercise, positive ST-segment response on ECG, and poor exercise capacity with 4-yr mortality of 29% versus 0% in all other patients with three-vessel disease (14). Thus, patients without objective evidence for ischemia have an excellent prognosis, even with three-vessel coronary artery disease and mild to moderate impairment of resting systolic function. Additional data available from the European Coronary Surgery Study, Coronary Artery Surgery Study (CASS) registry as well as Gohlke and associates, support the above findings: a high risk subgroup of patients can be identified on the basis of inducible ischemia during exercise radionuclide angiography (15-17). These studies support the concept that noninvasive assessment of exercise-induced ischemia provides additional prognostic information to the coronary anatomy in patients with CAD.

Myocardial Infarction

Myocardial infarction is the proximate cause of an estimated 550,000 deaths per year, with 55% of patients dying before reaching a hospital (55). Of the initial survivors who are subsequently admitted to a coronary care unit, nearly 10% die during their hospitalization, and an additional 10% die within 6–12 mo after hospital discharge (56). However, 1 year after an acute infarction, the mortality rate is reduced to 5% per year (52) (Figs. 4–6).

Prognosis in myocardial infarction is related to infarct size, which is reflected in the ejection fraction and extent of akinesis (57). Abnormalities in ventricular function following myocardial infarction range from extensive wall motion abnormalities with associated depressed left ventricular ejection fraction, to regional wall motion abnormalities with preserved systolic function, to absence of either wall motion abnormality or

systolic dysfunction (58,59). The location of the infarct relates to the extent of left ventricular systolic dysfunction: patients evolving anterior myocardial infarction generally have lower ejection fractions than those evolving inferior myocardial infarction.

Ejection fraction and regional wall motion abnormalities frequently change dramatically in the first 3–5 days postinfarct, tend to stabilize by Day 10, and remain relatively unchanged beyond 3 mo. The improvement may be because of either spontaneous or pharmacologic reperfusion preserving the infarct zone, or reversal of myocardial stunning (31,60–64). Thus, clinical decisions regarding interventional therapy should not be based solely upon single measures of systolic performance. This caveat reflects the vexing problem of clinical determination of myocardial viability.

In the acute peri-infarction period, Shah and coworkers reported that the outcome of patients with ejection fraction <30% was poor: all patients dying within 14 days of infarction had mean ejection fraction of 27% compared to 46% in all others who survived (65). Several reports have also indicated the importance of resting left ventricular ejection fraction after acute myocardial infarction for long-term prognosis (66–68). In 1983, the Multicenter Post-Infarction Research Group reported that 1-year mortality in patients surviving myocardial infarction increased exponentially as the resting ejection fraction decreased below 40% (67). Their data revealed a one-year mortality of 2–4% in patients with either normal or mildly reduced ejection fractions, 12% in patients with ejection fraction 20 to 39% and 47% in patients with ejection fractions <20%. In addition to the prognostic importance of resting left ventricular ejection fraction, Morris and associates reported that ejection fraction assessed during exercise to be the most potent predictor of mortality after acute myocardial infarction. In their study, the 2-yr mortality increased dramatically as exercise-induced ejection fraction fell below 45% as follows: when exercise ejection fraction was >50% the mortality was <11%, when exercise ejection fraction fell to 30% the mortality was 29%, and when ejection fraction dropped to 15% the associated mortality was 56% (68).

DIASTOLE

Physiology

Diastole is not a passive period, dependent solely on venous inflow and transvalvular pressure gradients to refill the ventricle. Recent studies suggest that relaxation of the myofibril is an energy requiring process, that may be altered in myocardial hypertrophy due to hypertension, hypertrophic cardiomyopathy, infiltrative/restrictive myopathies (69–76) and ischemic heart disease secondary to epicardial coronary obstruction (77–
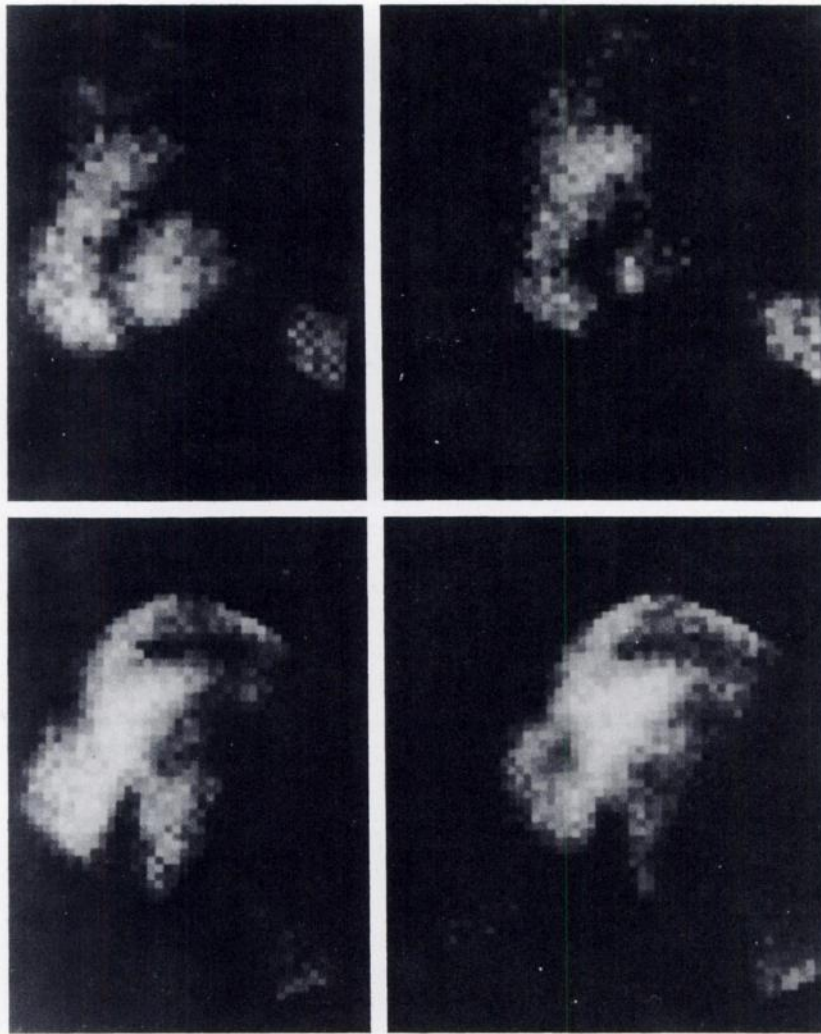
FIGURE 4
LAD distribution myocardial infarction, LAO projection. Upper panels reveal normal regional contraction (left = end-diastole, right = end-systole). Lower panels demonstrate distal septal/apical wall motion abnormalities (left = end-diastole, right = end-systole).

79). Since changes in diastolic function may antedate depression of systolic function, measurement of diastolic parameters might enhance the early detection of left ventricular dysfunction.

Classically, diastole has been viewed as a series of temporally distinct phases (*80*). The first phase, isovolumic relaxation, comprises the period from end-ejection to mitral valve opening. During this interval, left ventricular volume is unchanged, and left ventricular pressure declines at an exponential rate. As left ventricular pressure falls below atrial pressure during the latter portion of isovolumetric diastole, the blood volume stored in the atrial reservoir during systole and isovolumetric relaxation now fills the ventricle: This constitutes the early rapid filling phase of diastole. The third phase of diastole, diastasis, consists of the period following the abolition of the transmitral pressure gradient and concludes with the onset of atrial systole. It should
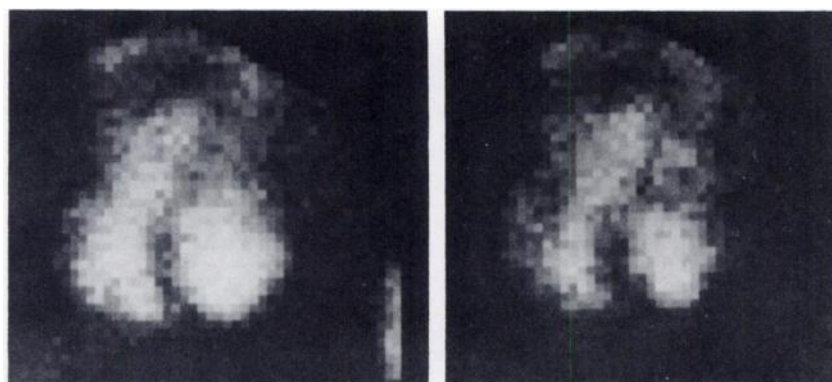

FIGURE 5
RCA distribution myocardial infarction, LAO projection: The wall motion abnormality involves the apicoinferior segment. Figures 4 and 5 illustrate the difficulty of assigning apical wall motion abnormalities to a specific coronary vascular territory. (left = end-diastole, right = end-systole).
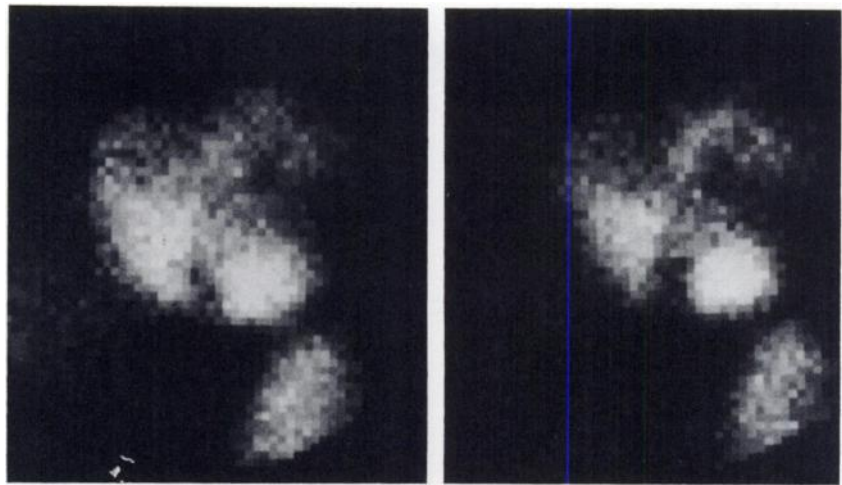
FIGURE 6
Left circumflex distribution myocardial infarction, LAO projection (left = end-diastole, right = end-systole). The wall motion abnormality involves the posterolateral segment.

be noted that although the rate of transmitral flow is reduced during diastasis, left ventricular volume increases significantly during this interval (*81*). The atrial contribution to left ventricular filling, which follows electromechanical atrial systole, concludes diastole.

Left ventricular pressure continues to decline during the early relaxation period, beyond the point at which rapid filling begins (*82*). This observation underlies the concept of diastolic suction as a contributor to early filling. As such, it cannot be assumed that the time of onset of filling as determined from the radionuclide time-activity curve corresponds to the minimum LV end-diastolic pressure.

Parameters

Left ventricular relaxation and filling can be evaluated by analysis of ventricular time-activity curves generated from high temporal resolution radionuclide angiography. There are four parameters which have been derived from the radionuclide data and applied to characterize diastolic ventricular function (Fig. 7):

1. The peak filling rate (PFR), calculated by differential analysis of the early rapid filling phase, is the most widely applied parameter of diastolic function, and is often viewed as an index of LV compliance.

2. The time to peak filling rate (TPFR), is the time from end-systole (minimum LV counts) to the time of PFR. This parameter is viewed as an index of left ventricular relaxation.

3. The average filling rate (AFR), which integrates the filling events that occur during the early, rapid filling phase.

4. The atrial contribution to LV filling, which quantifies the late increment in ventricular count activity attendant to atrial systole.

The peak filling rate (PFR) is seen as an index of "early" left ventricular filling (i.e., pre-diastasis). However, it is widely appreciated that PFR is dependent upon relaxation (loading conditions, inactivation/disengagement of the contractile elements) (*83–84*), ejection fraction and heart rate (*85*). As a result, this value is subject to major changes as a result of factors other than primary changes in the rate of left ventricular filling. An alternative descriptor of early filling is the average filling rate (AFR), which integrates filling characteristics throughout the rapid filling phase (i.e., from end-systole as defined by minimum LV counts through the end of the rapid filling period). However, this parameter is also dependent upon LV relaxation, cardiac cycle length and integrity of systolic function.
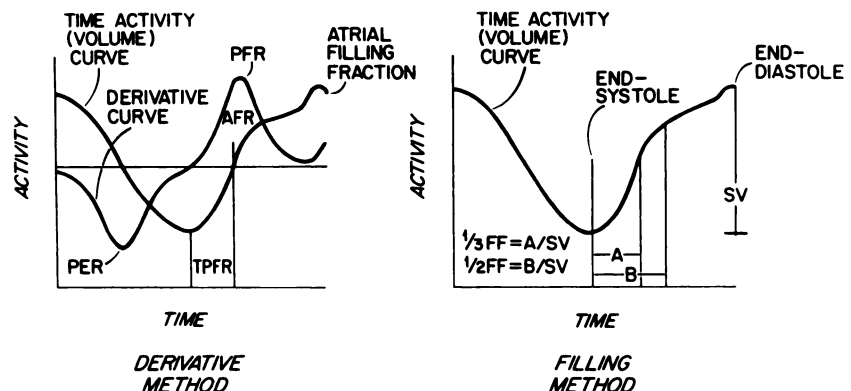

FIGURE 7
Left ventricular diastolic filling parameters, derivative versus filling fraction method. PER = peak ejection rate; PFR = peak filling rate; AFR = average filling rate; TPFR = time to PFR; FF = filling fraction; SV = stroke volume. (modified from Bashore TM, Shaffer P. Diastolic function. In: Gerson MC. *Cardiac nuclear medicine*. New York: McGraw-Hill, 1987.)

As an alternative to absolute filling rates, the temporal pattern and extent of filling has been proposed to describe diastolic events. Rather than derive the rate of change of LV activity, these approaches essentially quantify the change in left ventricular counts which occur during specified time intervals as a percentage of stroke counts. For example, Wickemeyer and colleagues (86) advocated the first third filling fraction as an index of early filling. Similarly, atrial filling fraction has been described as an index of late diastolic filling by Bonow et al. (87) and essentially serves as a negative correlate of early left ventricular filling events. An additional extension of "temporal" analysis of LV filling is reflected by the measurement of the time to PFR (TPFR), defined as the time from end-systole (minimum LV counts) to the time of occurrence of the PFR; the measurement has typically been advocated as an index of the rate of left ventricular relaxation, analogous to the isovolumic relaxation time. This TPFR analysis is difficult to implement given the difficulty determining the precise end of systole, as well as the obvious influence of early filling upon this parameter. These problems have been reflected in the poor correlation between TPFR and invasively defined hemodynamic descriptors of diastole, as contrasted with the good correlation between PFR and maximum negative dP/dt and the time constant of LV relaxation (88, 89).

Diastolic Dysfunction in Coronary Artery Disease

Abnormalities of left ventricular relaxation and filling have been observed at cardiac catheterization in patients with coronary artery disease, both in the presence and absence of active myocardial ischemia (77–79, 89, 90). Similar observations were made by Bonow and colleagues utilizing blood-pool images recorded with a high temporal resolution list-mode technique.

These investigators reported subnormal left ventricular filling (PFR <2.5 EDV/sec, TPFR >180 msec) in 91% of a series of 231 CAD patients (91). This finding was prevalent in patients without prior Q-wave infarction (85%) and in patients with normal resting LV systolic function (82%). The abnormalities in filling improved following medical (92) and mechanical (93) CAD treatment (Fig. 8). These latter findings have important implications regarding the mechanism underlying impaired diastolic filling in such subjects, with "reversibility" implying a dynamic etiology. Yamagishi and co-workers have reported that global diastolic "dysfunction" may reflect asynchronous regional filling (94); Bonow has reported that such "asynchronous" filling in patients with single vessel CAD is reversible following successful PTCA (95).

Reduto and colleagues (96) studied PFR and first-third filling fraction in 68 CAD patients. At rest, PFR and "1/3 F.F." were reduced in CAD subjects when compared to controls, with a greater reduction in patients with abnormal LV ejection fraction at rest. With exercise, the expected increment in left ventricular filling rates was blunted in the CAD group, most pronounced in the group with subnormal LVEF. Comparison of the change in ⅓ FF from rest to exercise identified a fall in the CAD cohort with normal systolic function, while it remained normal in the control subjects. Poliner et al. (97) extended the application of diastolic parameters by examining the utility of filling rates for the diagnosis of coronary artery disease. These investigators demonstrated that the ratio of exercise to rest PFR was a powerful discriminant between normals and CAD patients (sensitivity = 98%; specificity = 94%).

It should be emphasized that the blunted heart rate and exercise ejection fraction in the CAD cohort may
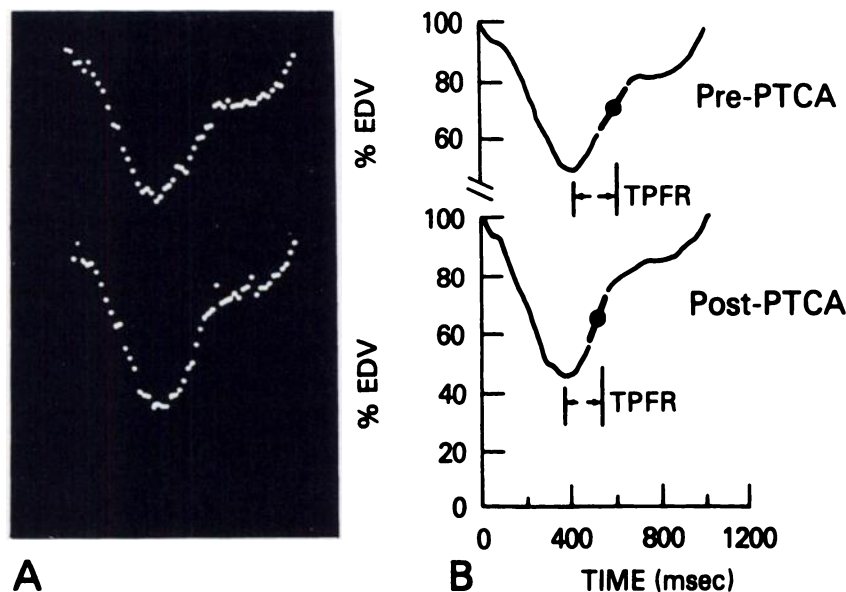

A

B TIME (msec)

FIGURE 8
Left ventricular time-activity curves (with schematic diagrams) in a patient before and after PTCA. Note the increase in LV peak filling rate after PTCA [Reproduced with permission from Bonow et al., Ref (93)]

contribute to the differential PFR response. This finding in CAD patients is consistent with data previously reported by Okada and colleagues which demonstrated an increment in pulmonary blood volume (and by inference, decreased left ventricular filling) during supine exercise in patients with coronary disease involving the left coronary artery (98). Subsequent work by this group established that exercise related changes in pulmonary blood volume correlated with directional changes in left ventricular filling pressures, thus suggesting that abnormalities of left ventricular filling during exercise do reflect hemodynamically significant events in CAD patients (99).

Thus, abnormalities of left ventricular relaxation/filling are demonstrable in CAD patients. Further, these abnormalities occur in the absence of active ischemia, prior infarction or left ventricular systolic dysfunction and do not correlate with the severity or extent of the underlying coronary disease. Given the well-recognized effect of ischemia upon intracellular calcium flux and de-activation of the contractile apparatus, it is likely that the abnormalities described above may reflect the primacy of relaxation abnormalities in CAD patients.

Additional factors to consider when examining LV filling rates in patients with CAD include: (a) normal age related decline in PFR (presumed to reflect decreased myocardial compliance with age); (b) impact of intercurrent disease processes upon PFR, particularly systemic arterial hypertension (74,75); (c) the effects of anti-ischemic therapy upon PFR and its inotropic, chronotropic and load determinants; (d) approaches to "normalization" of filling rates. Since PFR is typically normalized to end-diastolic counts, normalization is of particular importance when left ventricular volumes differ among subjects or change to a significant degree during the course of serial determinations (100).

As noted, "diastolic dysfunction" has been reported in a variety of noncoronary disease states (69–76, 101–112). The common pathologic substrate in each of these conditions is left ventricular hypertrophy. A number of investigators have suggested that "coronary insufficiency" (relative to LV mass) is the proximate cause of abnormal left ventricular relaxation and filling in such cases, thereby providing a unifying mechanism for the occurence of such dysfunction.

FUTURE DIRECTIONS

Blood-Pool Tomography

Tomographic gated blood-pool imaging is a natural extension of planar gated blood-pool scanning and rotating Anger camera SPECT technology. When these tomograms are recorded with a large field-of-view gamma camera, a sufficient volume is sampled to permit reconstruction of the data in multiple planes. The true three-dimensional nature of this process allows the evaluation of regional wall motion of all the cardiac chambers, unencumbered by overlapping structures. Recording data from gated blood-pool scans with SPECT offers an opportunity to reconstruct the data in orientations that cannot be recorded with conventional planar images: (a) an apical four chamber view can be obtained to provide simultaneous information about atrial and ventricular wall motion; (b) a true LV long axis view can be reconstructed to provide information about LV wall motion without overlying RV activity; (c) the short axis of the ventricle can be sampled at multiple points, to permit independent assessment of motion at the base and apex of the left ventricle. Thus, precise evaluation of cardiac function is possible in patients with coronary artery and noncoronary heart disease. In addition to evaluation of regional wall motion, precise determination of ventricular volumes and ejection fractions are possible. Early clinical experience has demonstrated the superiority of tomographic gated blood-pool imaging over planar blood-pool imaging (and conventional contrast ventriculography) for precise definition of subtle functional abnormalities (113, 114). Gated SPECT can be particularly useful in patients with apical aneurysms and left ventricular failure, to determine if retained function at the base is sufficient to warrant surgery (113–116). Unfortunately, the enormous amount of data generated by this procedure taxes the capacity of most nuclear medicine computer systems, requiring up to 3 hr for reconstruction of a single study. However, the availability of 32-bit processors and large amounts of image memory in new machines should ultimately reduce this processing time to clinically suitable duration.

In addition to single photon imaging, gated blood-pool tomography can also be performed with positron emitting tracers and data can be recorded with gated positron tomographs (117). Previously, [11]CO has been employed for this purpose (118). The use of positron techniques has several advantages over single photon methods: (a) improved image resolution, (b) absolute quantitation of cardiac and pulmonary volumes, (c) facility for sequential imaging pre- and postintervention, and (d) lower radiation burden to the patient.

Nonimaging Nuclear Probe

The dynamic range of changes in ventricular function as patients perform activities of daily living can be measured continuously with an ambulatory ventricular function monitor. This information can be used to assess the impact of altered ventricular function on an individual's life style, and may be useful to optimize medical therapy. The instrument consists of two small radionuclide detectors, an ECG recorder and associated electronics placed in a garment which is worn like a vest (hence, the name of the device VEST). The VEST records beat-to-beat left ventricular time activity curves over several hours. Preliminary studies have demonstrated changes in left ventricular ejection fraction dur-

Situation	Rationale	Comments
Detection of CAD	Functional impact of ischemia	Thallium preferred Need sufficient ischemia to impair function
Stable angina	Risk stratification Functional impact of CAD	Rest/ex. RVG Selection of Rx
Dyspnea	Differentiate cardiac and pulmonary etiology	Rest/ex. RVG
Acute infarction	Evaluate for beta blockade assess viability	Rest RVG
Left heart failure	Differentiate diastolic from systolic dysfunction	Rest RVG

ing nonstressful daily activities (*119*) and rapid sequential changes in ejection fraction during treadmill exercise in normal subjects (*120*). When ventricular function was monitored in patients with coronary artery disease, transient decreases in ejection fraction with or without ECG changes were frequently observed normal during daily activity (*121*). The VEST may also supply prognostic information. Kayden et al. (*122*) monitored patients within 10 days of thrombolytic therapy. They observed 11 patients with a transient decrease in ejection fraction during a 3-hr interval of monitoring. During a 42-wk follow-up, six of these patients had coronary events, while only 1/16 patients without a decrease in EF had an event.

CONCLUSION

Catheter based procedures designed to treat patients with coronary artery disese have stimulated the development of a wide variety of technologies to characterize ventricular performance. Radionuclide evaluation of LV systolic function can be used to detect CAD by demonstrating the impact of exercise induced ischemia upon global and/or regional ventricular function. In addition radionuclide ventriculography can provide important prognostic information in CAD patients by defining the extent/severity of underlying disease and by quantifying the degree of functional impairment in patients with prior infarction.

For routine clinical purposes, the rest radionuclide study should be acquired in multiple projections with qualitative assessment of regional wall motion; minimum of 16 frames per cardiac cycle with an information density of 300,000 cts/frame should be acquired. Standardized programs can be applied quantify left ventricular volumes and ejection fraction. Quantitation of regional function mandates greater spatial and temporal (32 frames per cycle) resolution; this latter requirement also applies to data acquired during exercise, and is fundamental to the accurate quantitation of left ventricular filling rates for the characterization of diastolic function. Although such filling rates have provided

important mechanistic insight into the pathophysiology of a variety of disease states, their utility as a diagnostic tool is not as yet defined. Similarly, since most clinical decisions regarding ventricular function in CAD patients are based upon assessment of wall motion, other volume derived measurements (e.g., regional EF and phase analysis) are presently most applicable in clinical research settings.

Given these technical difficulties and the limitations inherent in "single projection" data acquisition to define regional ventricular function, it is our contention that stress/redistribution thallium-201 scintigraphy is the study of choice for CAD detection. Alternatively, exercise radionuclide ventriculography is preferred for the definition of the functional impact of, and prognosis associated with, coronary disease (Table 2). Further, the combined application of myocardial perfusion and function studies represents a broadly available means for evaluation of myocardial viability, a major issue in the thrombolytic/interventional era. The recent description of blood-pool tomography and the development of ambulatory ventricular function monitors continues to expand the repertoire of radionuclide techniques suitable for the characterization of left ventricular function.

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