Twelfth Bethesda Conference

Sponsored by the American College of Cardiology
June 5 and 6, 1981, Heart House, Bethesda, Maryland

Noninvasive Technology in the Assessment of Ventricular Function*

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Introduction

HAROLD T. DODGE, MD, FACC, Chairman • J. WARD KENNEDY, MD, FACC, Co-Chairman

Over the past 35 years invasive techniques of cardiac catheterization and angiography have been highly developed for establishing diagnoses, evaluating the severity of abnormalities and assessing the effects of therapeutic interventions, including surgery. Based on information provided through applications of these invasive techniques, more recently there has been a remarkable development of noninvasive technology for providing diagnostic information in cardiology.

The Twelfth Bethesda Conference on Noninvasive Technology in the Assessment of Left Ventricular Function was held at Heart House, the headquarters of the American College of Cardiology, in Bethesda, Maryland on June 5 and 6, 1981. The idea for the Conference developed from Dr. Borys Surawicz, American College of Cardiology President, whose article, “How to Cope with the New Technology? The Knowledge and the Prudence,” had been published on the President’s Page of this Journal.1 In that thoughtful discussion, Dr. Surawicz pointed out the need for better understanding and thoughtful integration of the new technology into the general practice of cardiology. He proposed that several state of the art conferences be held in an effort to meet this need. The proceedings of the first of these conferences are the subject of this report.

In developing a plan for the conference, the Chairman, Co-Chairman and some members of the Bethesda Conference Committee decided to limit the scope of the conference to new technology. With this definition, it was agreed to include diagnostic ultrasonic (techniques of M mode, two dimensional) and pulsed Doppler echocardiography and various nuclear cardiology techniques. In addition, it was decided to include discussions of cardiac computed X-ray tomography and intravenous angiography utilizing digital video subtraction techniques as two methods, currently in the developmental stage, that may soon have clinical application. Older noninvasive methods, including exercise stress testing, systolic time intervals, carotid pulse tracings and phonocardiography, were not considered within the scope of this mini-Bethesda Conference. With the expertise available at the Conference, it seemed appropriate to devote some time to consideration of future developments in echocardiography and nuclear medicine.

It was the overall aim of the Conference to develop a diagnostic strategy that would take full advantage of the new technology and at the same time carefully consider the cost effectiveness of the diagnostic approach to various clinical problems. It was appreciated by all that considerable overlap exists in the information on left ventricular function provided by the various diagnostic methods. It was also understood that, while the Conference was directed toward the evaluation of left ventricular function, in a specific clinical situation the additional anatomic information provided by one method might make the use of that method preferable to another.

New methods are developed or adopted, or both, at different rates in individual institutions and therefore new technology may be unevenly applied from one institution to another. This problem was discussed in the planning of this Conference and it was agreed that expertise in the use of the new technology would be assumed in all of the discussions of the Conference.

It is the purpose of the Bethesda Conference to reach a consensus, when possible, on the problems under discussion. In this Conference we have utilized the evaluation of specific clinical problems in order to focus the discussion and attempt to develop a conclusion. The goal of reaching a consensus was often but not always achieved. It is the hope of the participants at this Twelfth Bethesda Conference that these position papers and case discussions will be helpful to the physician who must integrate the new technology into the practice of cardiology.

Reference


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Introduction: Echocardiographic Evaluation of Ventricular Function: An Overview

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Analysis of ventricular function is fundamental in assessing the significance of certain kinds of heart disease. For example, the degree of left ventricular dysfunction in patients with coronary artery disease is an important determinant of the "natural history" of patients who do not undergo surgery, and it plays a central role in determining operative risk. The presence of left ventricular dysfunction may influence the timing of valve replacement in patients with certain lesions such as aortic or mitral regurgitation. Classically, variables of ventricular function have been measured using invasive hemodynamic and angiocardiographic methods. Because it is impractical to subject asymptomatic or minimally symptomatic patients to the risk of these procedures, or to perform invasive measurements repeatedly in a given patient, newer noninvasive techniques have been developed and used to assess ventricular function. One of the major noninvasive techniques currently used to evaluate ventricular function is echocardiography. In a generic sense, echocardiography uses ultrasonic signals reflected from cardiac structures to provide data on cardiac anatomy and dynamics. Several specific adaptations have been developed, including M mode echocardiography, two dimensional echocardiography and Doppler echocardiography. These related techniques have not all developed simultaneously, and they should not be considered equally important in the assessment of ventricular function.

Both M mode and two dimensional echocardiography use pulsed ultrasound to demonstrate the distance between the transducer and ultrasonic targets such as myocardial-blood interfaces. The intensity of echoes reflected from these interfaces is also demonstrated. These techniques can be used to measure ventricular cavity size, shape and wall thickness. M mode and two dimensional echocardiography can be considered proved, clinically accepted methods for assessing ventricular function.

Doppler echocardiography uses the frequency shift of ultrasound reflected (or "backscattered") from moving targets within blood, such as red cells, to evaluate the nature, direction and velocity of blood flow. At present, this should probably be considered an exciting technique that is currently undergoing intensive evaluation but is not yet a clinically proved independent method for assessing ventricular function.

Newer echocardiographic techniques for evaluating ultrasonic energy backscattered from ventricular myocardium have been used to characterize normal, ischemic and myocardial myocardium. These techniques hold great promise but need substantial further evaluation.

Clinical Applications

In the clinical setting, the echocardiographic techniques should be viewed as interdependent and used in this fashion. Although more complete discussions of the uses and limitations of each individual technique follow, an initial brief overview seems appropriate.

Amoung the various echocardiographic techniques, two dimensional echocardiography provides the greatest spatial sampling, and it is thus best used to provide an anatomic "overview" to determine the symmetry or asymmetry of ventricular contraction and to define spatial relations. When regional disorders are present, such as segmental contraction abnormalities or ventricular aneurysm, they are best identified by two dimensional echocardiography. Global ventricular function and the extent of regional dysfunction can be estimated readily, but quantitation is somewhat tedious to perform at present.

M mode echocardiography has passed the test of widespread clinical usage over several years. This technique is well understood, and conventions for recording and measuring data have been accepted. M mode echocardiography offers extremely high temporal resolution and is thus useful for the study of rapidly moving structures such as valve leaflets. Easily quantitated, M mode records provide an excellent appreciation of global cardiac performance when function is uniform. However, when regional abnormalities are present (as demonstrated on a two dimensional echocardiographic study, for example), the extrapolation of M mode data to global ventricular function is hazardous.

Doppler echocardiography allows evaluation of blood flow, and hence offers a method for assessing ventricular performance that is independent of ventricular geometry. This technique also provides addi-
tional data on the integrity of valve function, which may be important in a patient in whom ventricular impairment is suspected. Doppler evaluation of flow is best used in conjunction with M mode or two dimensional echocardiographic evaluation of anatomy.

Choice of technique: Obviously, the various non-invasive (echocardiographic and other) techniques may not all be necessary or even helpful in a particular clinical application. The clinical vignettes that follow the discussion of the various techniques are meant to provide a perspective on when to use these tests. In many instances, the same index of ventricular performance can be measured using several different approaches. For example, M mode and two dimensional echocardiography, first pass and equilibrium gated radionuclide angiography and contrast ventriculography can all measure left ventricular ejection fraction, and the results of one approach generally correlate rather well with those of the other approaches. In order to define which approach is most accurate, these tests would need to be compared with an independent and absolute "reference standard"; unfortunately, in the case of ejection fraction (and most other indexes of function), this cannot be done. Thus, the choice of which test to use often depends on the availability of the tests, the quality of the local laboratory and the ancillary data sought. For example, it might be most sensible to measure left ventricular ejection fraction by contrast angiography in a man with disabling angina who needs coronary arteriography anyway, by radionuclide angiography in a patient with a suspected intracardiac shunt (which could be defined and quantitated at the same time), and by echocardiography in a pregnant woman with dyspnea and a heart murmur (because chamber and valve function could be assessed without risk to the fetus).

In the final analysis, the physician caring for an individual patient may be able to choose among several "reasonable" approaches to evaluating ventricular function. A more complete understanding of the strengths and limitations of the various techniques available should be helpful in making this choice, and the discussions that follow are directed toward this end.

References


M Mode Echocardiographic Assessment of Left Ventricular Function

RICHARD L. POPP, MD, FACC

Echocardiography in modern usage includes both M mode and two dimensional ultrasonic investigation of the heart. This discussion is confined to M mode echocardiography. The physical principles and techniques of M mode echocardiography can be reviewed in more extensive works on the method 1 2 so these aspects will not be covered in detail here.

From the outset it should be mentioned that M mode echocardiography is most often best performed in conjunction with the two dimensional study. However, this discussion will be focused on M mode applications only, assuming that in many circumstances M mode echocardiography is the only method available. This may provide a basis to view the incremental contribution of two dimensional methods discussed in other papers of this conference and elsewhere. 1

A specific assumption is that the methods described are performed very well. Obviously application of a technique such as echocardiography may be qualitatively different from laboratory to laboratory, but we will not discuss suboptimal use of the method. We simply add a caution that the people performing these tests must be known for good quality work by the local physician referring his patients to the laboratory.
TABLE 1

Echocardiographic Variables of Left Ventricular Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symbol/Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular dimension</td>
<td>D</td>
</tr>
<tr>
<td>Change in dimension</td>
<td>ΔD = D_{diastole} - D_{systole}</td>
</tr>
<tr>
<td>Ventricular volume</td>
<td>V = ΔD × K</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>SV = EDV - LSv</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>EF = SV/EDV</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>%FS = (ΔD/ΔD_{max}) × 100</td>
</tr>
<tr>
<td>Percent ΔD</td>
<td>%ΔD = (ΔD/ΔD_{max}) × 100</td>
</tr>
<tr>
<td>Circumference</td>
<td>C = ΔD</td>
</tr>
<tr>
<td>Velocity of circumferential shortening change (mean)</td>
<td>Vcf = ΔD/Δt</td>
</tr>
<tr>
<td>Normalized Vcf</td>
<td>Vcf = ΔD/ΔD_{max}</td>
</tr>
<tr>
<td>Ventricular mass</td>
<td>M = [(D + septal thickness + posterior wall thickness)² - V \ diastole] × 1.05, M = regression equation</td>
</tr>
</tbody>
</table>

ΔD = diastolic dimension; ΔDV = end-diastolic volume; LSv = end-systolic volume; Δt = ejection time; K = constant.

Available Variables and Measurements

The echocardiogram can be used to assess the left ventricle by looking at variables of myocardial function, ventricular function and notation of signs or indexes that have been developed to point toward left heart disease. The signs include left atrial enlargement and subtelitis of mitral valve motion, for example. We will not discuss measurements of right ventricular, right atrial and valve disease as specific entities or their assessment as secondary complications of left heart disease because we are mainly interested in discussing left ventricular function.

Directly measured values: Echocardiographic measurements of the left ventricle can be segregated into three categories: (1) directly measured values, (2) calculated or derived values, and (3) indirect indicators of ventricular function (Table 1). Direct measurements include (a) the thickness of the interventricular septum, (b) the thickness of the left ventricular posterior wall (at points corresponding to end-diastole or end-systole, or both), and (c) the distance between the endocardial surfaces of the septum and posterior wall that represents the left ventricular internal dimension. In fact, these few values along with time are the raw data from which most other indexes of function are calculated. Left atrial dimension also is measured directly. A great deal of time and experience has gone into determining methods of standardizing measurement of left ventricular internal dimension and wall thickness.6-7 Most people agree where the recordings should be made within the left ventricle. There is one set of recommendations for standardized points of measurement within the cardiac cycle developed by the American Society of Echocardiography that may gain wide acceptance and that seems useful.7

Calculated or derived values: The extent of left ventricular myocardial contraction and reduction in cavity size during ejection are often expressed by dividing the change in thickness or cavity dimension by the diastolic value. When this is done for the left ventricular internal dimension, the value is usually multiplied times 100 in order to get a "percent change in diameter" (%ΔD) or "fractional shortening" (%FS). These terms express the same measurement and calculation. It is this type of simple calculation that crosses the border from direct measurements to derived measurements. Other such variables include the change in dimension per unit time (ΔD/Δt) expressed either as a mean or a maximal value. Values of this type during ejection and relaxation have been calculated. One may express the relation of myocardial thickness to cavity size by making a ratio of ventricular wall thickness (h/r) to radius.

Other values commonly derived include extrapolation of the measured ventricular dimension to a left ventricular volume.8-11 This extrapolation may be made at end-diastole, end-systole or any other point within the cardiac cycle. The calculation assumes that all hearts have a constant shape so there is a fixed relationship between the measured dimension and the dimensions of the heart in the directions not measured. In the past, most investigators have assumed a circular cross section for the ventricle, and the measured dimension is assumed to be a diameter of this circle. Also, a roughly ellipsoidal ventricular shape is assumed, with the long axis of this ellipsoid ventricle being twice the measured dimension. If these assumptions are made, then the geometry permits us to simply cube the measured dimension to approximate ventricular volume. The difference between the end-diastolic and end-systolic volumes is the stroke volume, and stroke volume divided by end-diastolic volume is the ejection fraction. If the measured dimension represents the diameter of a circular cross section of the ventricle, then the circumference of this ventricle is π times the diameter, and a change in circumference (πD) divided by ejection time (Δt) gives the velocity of circumferential shortening (Vcf) which may be normalized for the end-diastolic circumference (ΔD/Δt = Vcf). These derived variables have been used by various investigators and normal values for each of them have been determined (Table II).10,11 The reader should note that the rate of volume change represents flow and so the mean ejection rate can be determined from these values. Similarly, rate of left ventricular filling may be measured.10-11 Some investigators choose to observe the time from the onset of systole to peak left ventricular emptying, time to peak left ventricular rate of emptying, or time to peak left ventricular filling in diastole. Here we should mention that each of these variables may be observed serially during interventions with pharmacologic or physiologic maneuvers. Many people object to extrapolation from measured dimensions to volumes, so they prefer to express fractional shortening (%FS) or dimensions alone. It is common to observe the %FS with drug studies or after exercise.

Attempts at derivation of pressure within the left ventricle have been made from measurement of left ventricular wall thickness. This method is based on the assumption that there is a constant and normal value for systolic wall stress in a compensated myocardium.
Left ventricular wall thickness increases as a result of pressure overload of the ventricle in order to normalize wall stress across the myocardial wall. If one knows wall thickness and assumes stress at a constant value, then left ventricular pressure can be determined. Obviously one can measure brachial arterial pressure by cuff manometer in most people. In patients with aortic stenosis, the calculated left ventricular pressure should be higher than the measured brachial arterial pressure by a factor that represents the aortic valve gradient.

**TABLE II**

**Normal Measurement Values**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular dimension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>33.5–88</td>
<td>3</td>
</tr>
<tr>
<td>Systolic</td>
<td>28.41% decrease from diastolic</td>
<td>3</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>28–41%</td>
<td>3</td>
</tr>
<tr>
<td>Interventricular septal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thickness (mm)</td>
<td>6.12</td>
<td>3</td>
</tr>
<tr>
<td>Systolic</td>
<td>6.11</td>
<td>3</td>
</tr>
<tr>
<td>Posterior left ventricular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wall thickness (mm)</td>
<td>6.12</td>
<td>3</td>
</tr>
<tr>
<td>Systolic</td>
<td>6.11</td>
<td>3</td>
</tr>
<tr>
<td>Normalized mean Vcf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(circumferences/m²)</td>
<td>1.02±1.50</td>
<td>17</td>
</tr>
</tbody>
</table>

Equations for predicting normal echocardiographic measurements from body weight and age:

- **LV end-diastolic dimension**
  \[22.4 \text{ (wt)}^{1.023} - 0.03 (age) - 7.2 \pm 12\%

- **LV end-systolic dimension**
  \[14.2 \text{ (wt)}^{1.03} - 0.03 (age) - 41 \pm 18\%

- **Systolic thickness**
  \[1.86 (wt)^{0.48} + 0.03 (age) + 1.5 \pm 18\%

- **LV free wall thickness**
  \[1.92 (wt)^{0.38} + 0.03 (age) + 1.1 \pm 16\%

Observation of the electrocardiogram and the echocardiographic motion of the aortic valve allows us to measure the pre-ejection period from the onset of the QRS complex to the opening of the aortic valve, as well as left ventricular ejection time from the duration of aortic valve opening. The isovolumic contraction time and isovolumic relaxation time can be observed if the aortic and mitral echoes are observed carefully. The indirect carotid pulse tracing may be used to measure ejection time also, of course.

**Indirect indicators of left ventricular function:**

The indirect indicators include the observations that the mitral valve early diastolic slope may reflect the rate of left ventricular filling and that in patients with reduced global left ventricular function, the mitral valve maximum opening, or E point, is displaced from the interventricular septum. This latter sign seems due to a combination of dilation of the ventricle in some patients and possible reduction in transmural flow in others. Very subtle variations in the waveform of the mitral valve during diastole have been correlated with abnormalities of left ventricular function. A very low E point with an accentuated A wave has been associated with elevation of the early diastolic pressure in the left ventricle. A shoulder or hesitation on the closure of the mitral valve at end-diastole ("H notch") led to the realization that prolongation of the P-R minus A-C interval was correlated with a large A wave elevated left ventricular end-diastolic pressure. Systolic signs of left ventricular function include the area of the aortic valve opening and apparent early closure of the valve during ejection. The configuration of the ventricle can be appreciated to some degree. Progressive dilation of the submural left ventricular dimensions indicates a dilated left ventricle. Multiple combinations of these signs and ratios have been used to accentuate differences between normal and abnormal patients.

In general, the measured raw data are always reported because this is very useful in assessing wall thickness or left ventricular hypertrophy as well as the size and dynamics of the ventricle. Simply calculated variables also are expressed by most laboratories. Timing data may be useful in many situations, but the measurement of rates of change of dimensions often involves obtaining multiple discrete data points during individual cardiac cycles. This is usually done with some sort of "digitizing" tablet and a microprocessor or computer to acquire, process and express these data. All assumptions made for the derived calculations may be less valid as disease states affect the shape and dynamics of the ventricle. In coronary artery disease, the characteristic segmental nature of myocardial involvement in the process may make any assumption of uniformity of contraction invalid. This will be discussed in more detail later. This last point and technical difficulty in recording the ventricular walls have prompted use of the indirect indicators of left ventricular function. These signs have been used most in known abnormal states.
Assessment of Echocardiographic Variables

Many variables have been described, but are they valuable? We still need to ask the questions: How accurate are these measurements, how reproducible are they and how should they be used clinically? These questions are properly put in the context of clinical care, because patients should have had at least a history, physical examination and an electrocardiogram before the echocardiogram is considered. The physical examination, electrocardiogram, chest roentgenogram, echocardiogram, angiogram, flow-directed catheter thermodilution techniques and radionuclide studies may be used to assess left ventricular function.

Correlation with physical and electrocardiographic findings: By palpation of the cardiac apical impulse, Conk and Cole showed that 81 percent of patients (29 of 36) with the left ventricular impulse limited to one intercostal space had normal left ventricular volumes, whereas 79 percent of those (11 of 14) with the left ventricular impulse palpated in two or more intercostal spaces had cardiac enlargement. In these patients a holosystolic left ventricular impulse correctly indicated increased left ventricular mass in 88 percent of patients. Normal left ventricular mass was present in 78 percent of those patients whose apical impulse was confined to early systole. These values for left ventricular hypertrophy and increase in myocardial mass may not be matched by the most well accepted electrocardiographic criteria or even by chest roentgenograms measured in conventional fashion.

Correlation with angiographic findings: If one compares echocardiographic measurements of left ventricular size or mass, or both, with angiographically derived values, the reported correlations are good. However, there are problems inherent in each of these measurement procedures and the correlation between two such procedures is never perfect. In studies accumulated over several years, the coefficient of correlation between echocardiographic left ventricular volume and angiographic volume has varied from 0.97 to 0.52. A general value of approximately 0.85 is commonly found. For any one patient the error of the estimate (versus expected angiographic estimate) may be more than 30 ml. This may represent a significant uncertainty in the large normal ventricle (175 ml) or mildly diseased ventricle (200 to 250 ml). For this reason the method is considered inaccurate or unacceptable for volume measurement by some physicians. Most use the method while understanding its limitations. The difficulty with comparison of echographic and angiographic work stems from the method of performance of the studies, the type of patients included, the specifics of record measurement, and the facility of the laboratories with echocardiographic versus angiographic techniques. It is interesting to contrast these data with values for left ventricular stroke volume determined by angiography, thermodilution methods and echocardiography. One excellent study examining the problem found internal consistency (reproducibility) was best with thermodilution techniques, but correlations were equal between the two invasive tests or in comparing echocardiography with either angiography or thermodilution techniques. Comparison of values for left ventricular volume between any two of the methods produced correlation coefficients in the range of 0.80 to 0.88. This simply emphasizes the fact that perfect correlation between two indirect measurement systems is seldom to be found and should not be expected.

Correlation with autopsy measurements: In a study of 24 subjects comparing postmortem left ventricular mass with echocardiograms performed just before death and measured using a local convention, it was found that a correlation coefficient of 0.36 occurred with a standard deviation of 29 g over the range of 100 to 500 g of heart weight. Studies of terminally ill heart transplant patients (generally dying from cardiac rejection) with a thick stiff myocardium showed that echocardiographically measured wall thickness was within 1 mm of the autopsy measurements. In vitro studies generally have shown excellent accuracy of echocardiographic data.

Reproducibility of measurements: Reproducibility of echocardiographic measurements is subject to problems in standardization of transducer position and selection of landmarks within the ventricle to guide the operator in consistently measuring the same spot within the ventricle on serial studies. Serial daily measurements of normal subjects show excellent reproducibility from day to day over long periods. In a recent study of the method in patients with cardiomyopathy, weekly outpatient echocardiograms were performed in subjects thought to be in a stable clinical situation. A second group of patients with cardiomyopathy were studied daily when measurement of pressure and flow with indwelling catheters showed them to be in hemodynamically stable condition. In the former group of patients, the mean of the standard deviations for diastolic left ventricular diameter was 4 mm and the 95 percent confidence interval was 8 mm. The mean of the standard deviations for fractional shortening (%FS) was 2.8 percent and the 95 percent confidence interval was 5.6 percent. Comparable results in patients studied daily showed a mean of the standard deviations of 2 mm for left ventricular end-diastolic dimension with 95 percent confidence limits of 1 mm. The %FS showed a mean of the standard deviations of 1.6 percent and 95 percent confidence limit was 3.2 percent. In other studies, the error of echocardiography for measuring either left ventricular end-diastolic volume or %FS was estimated to be 5 percent for acute changes in a given patient. The interobserver variability in measurement is rather small and is consistent with the foregoing values.

Global ventricular function versus segmental contraction abnormalities: From a qualitative sense, we must separate the accuracy of echocardiography (M mode) in patients with uniformly contracting left ventricles versus those with segmental contraction abnormalities typical of coronary artery disease and some
types of cardiomyopathy. In the former, the whole ventricle can be represented by M mode measurements and the estimates of ventricular function are accurate. This may also be true in some patients with coronary artery disease. Echocardiography is highly accurate in measurement of wall thickness and the ventricular dimension that is described by the ultrasound beam. The relation of the length of the ventricle to this dimension and the relation of the third dimension representing the orthogonal or short axis dimension not measured, are the factors that lead to absolute errors in calculating ventricular volume by M mode techniques. 12 If one assumes, for example, that the long to short axis ratio of the left ventricle is 2:1, when this ratio may vary anywhere from 2:3:1 to 1:3:1, then variation of the calculated volume from the true volume will be large in either of these extreme cases. These relations do not change a great deal in the same patient with a given intervention. In a single patient, used as his own control, the effect of drugs or other physiologic interventions can be reliably assessed with echocardiography. 26 This seems to be generally true for global left ventricular function, but alterations that are manifest by segmental myocardial changes cannot be well assessed with M mode techniques.

Assessment of pattern of mitral and aortic valve motion: Indirect indexes or signs of left ventricular function, such as changes in patterns of mitral or aortic valve motion, have their genesis in factors that are not completely understood. 26, 27, 28, 29, 30, 31, 32 Since situations that invalidate the observation are not fully understood, the signs have limited applicability. For example, the mitral valve B notch and prolonged P-R A C interval may occur in patients with acute myocardial infarction, aortic disease or hypertension with myocardial hypertrophy or in extreme degrees of ventricular abnormality. It is not an early sign of deteriorating function but is a good sign of ventricular dysfunction. Some ideas about the cause of this phenomenon have been put forth, but reasons for its general lack of specificity and sensitivity have not been clarified. An increased mitral valve R point-septal separation (greater than 7 mm) seems to be a relatively good indicator of reduced global left ventricular function manifest by a reduced ejection fraction (less than 50 percent). 27, 28 In some patients this sign seems to be a result of left ventricular dilatation; in other patients, with coronary disease or restrictive cardiomyopathy, left ventricular dilatation clearly is not necessary for the sign to occur. It might be assumed that reduced transmural flow reduces the excursion of the mitral valve and yet the mitral valve does not have unrestricted motion dependent solely on mitral flow for the excursion of the valve. 27 Thus, several factors may be interacting to produce a "sign" that is useful, but less useful than it might be if we understood all of the factors involved in its presence.

How is Echocardiography Used and How Should It Be Used?

One can see echocardiography being used in many ways. For example, it is possible, with this noninvasive technique, to screen all patients coming to a physician's office or all people working in an industrial plant or attending school. It is possible for all patients with certain diagnoses such as hypertension, congestive heart failure or valve disease to be "screened" with this method. One could choose to use the method solely for diagnosis of disease, or alternatively use it primarily for follow-up and serial studies of patients with known types of disease. It does not seem cost effective to screen all asymptomatic people or those coming to a physician's office for routine physical examinations with echocardiography. The echocardiogram should not be used as a substitute for the medical history or physical examination. Patients first suspected of or found to have valve disease, hypertension, congestive heart failure (and possible coronary artery disease) may benefit from a single echocardiographic study if the physician has assessed the patient and determined that something available from echocardiography would benefit his formulation of this patient's case. Echocardiography is probably the most accurate way to measure serially small changes in left ventricular size and left ventricular wall thickness. Therefore, serial follow-up studies of patients who have aortic or mitral regurgitation, congestive heart failure or hypertension may be beneficial as a guide to the effectiveness of a given therapy.

Clinical applications: These recommendations must take into account how the technique is used in the community in general and what is usually measured. Most laboratories measure wall thickness, cavity dimensions at end-diastole and end-systole and some variable of change in dimension such as %FS or ejection fraction, and some laboratories have the facilities to measure rate of change of these dimensions. Patients with normal left ventricular function can be separated from those with quite abnormal ventricular function, but this is not the problem in clinical practice. We desire a method of finding subtle degrees of left ventricular abnormality and/or means of observing when the left ventricle loses its "myocardial reserve," or both. This is especially pertinent to the timing of interventions for valve surgery or valve replacement. So far, clinical, electrocardiographic, angiographic, hemodynamic and radionuclide studies have not yielded variables that consistently accomplish this purpose. If we use the time-honored clinical observation of progressive dilation of the heart as an indication for surgery, then echocardiography can measure this at least as well as any technique. Recent studies have suggested that patients with aortic regurgitation who have a combination of an extremely dilated heart and reduced %FS do worse after surgery than those with the opposite situation. 28 From these data it has been suggested that patients who are minimally symptomatic or asymptomatic, but whose ventricle exceeds a specified echocardiographic diameter, should be considered for surgery. 29 Similarly, patients who are stressed with increased ventricular afterload or preload normally maintain or increase angiographic ejection fraction whereas a decrease in ejection fraction may indicate loss.
of myocardial reserve. Such patients have been shown
to do badly postoperatively. Echocardiography provides
a method to make these observations, but so far tests of
this type have not been proved in long-term or large
scale clinical trials. Therefore, we still assess each pa-
tient individually and do not propose that echocardi-
ographic variables themselves be the indication for
sending patients to surgery.

**Strengths of M Mode Echocardiography**

The most significant strength of M mode echocardi-
ography is our 15 to 25 years of experience with clinical
application of the method and the fact that many of
the diagnostic criteria developed for M mode echocardi-
ography have stood the test of time in the clinical arena.
The relatively low cost of the test (because of the rela-
tively low cost of the equipment) is an attractive feature
of M mode echocardiography. More and more labora-
tories are combining M mode and two dimensional
techniques because this often provides increased and
better information and because it may be more cost
effective than duplication of the tests in a high pro-
portion of patients. The conventional printout strip chart
records of cardiac motion are a rather unique way to
document cardiac dynamics and allow the observer to
assess how well the heart moves. This motion is mea-
sured with a very high sampling frequency, approxi-
mately 1,000 times/sec, giving a high time resolution
of motion. As mentioned, echocardiography is a relatively
fine tool for measurement of intracardiac structures.
Accuracy with echocardiography is in the range of a few
millimeters for ventricular dimensions or wall thickness
versus a centimeter or so with some other techniques
such as radionuclide imaging.

Echocardiography remains a noninvasive method
having no radiation hazard and so it is quite good for
serial studies. Such serial studies can be used to monitor
cardiac function with or without interventions. This
method for left ventricular observation has been stan-
dardized using empirical methods of measurement
and standards agreed on by a great many laboratories.
The method is available throughout the world. Finally,
M mode echocardiography provides an excellent time
reference in studying cardiac valve motion or measuring
dimensions in relation to pressure, flow or occurrence
of heart sounds. Simultaneous M mode recordings from
two or more areas of the same heart can be used to ob-
serve precise timing of motion of various valves or se-
gments of the left ventricle.

**Limitations of M Mode Echocardiography**

Limited visualization of ventricular walls: Standard-
ized M mode echocardiography is confined by trans-
ducer placement in the parasternal and subcostal
areas. This means that the yield of technically good to
excellent studies is relatively low. Up to 40 percent
of patients in the coronary care unit have technically
inadequate studies to assess left ventricular function fully.
When the parasternal ultrasonic window is small or in
an inappropriate place for standardized studies, it is not
easy to move the transducer to an alternative position
and still understand the M mode measurements. Even
in a perfectly standardized study of good quality, one
assumes geometry and dynamics for parts of the left
truncus that are out of the field of view of the M mode
transducer. Patients having significant coronary artery
disease and hypokinetic or dyskinetic segments at the
ventricular apex will not have these recognized with most
M mode studies. Similarly, apical aneurysms or large
akinetic segments generally will be missed with con-
ventional M mode echocardiography. These are im-
portant exclusions in most cardiologists’ and internists’
practices.

Resolution problems: The more “sophisticated”
variables derived from M mode studies, such as peak
date of wall thickness change or rate of diameter change,
require a method to digitize the record and a micro-
processor or computer to process the data as well as
graphic displays for optimal appreciation of the dy-
namics expressed. Such auxiliary devices are expensive.
Finally, the physics of ultrasonic recording yield a finite
resolution in the axis of the sound beam and a finite
resolution in the lateral dimensions. Thus, two
structures that are very close within the heart, such as
diaphragm tendineus and the left ventricular endocardical
surface, may not be resolved as two separate structures
and an ambiguity of measurement may thus be intro-
duced. Generally the ability to resolve two structures
next to each other is worse than axial resolution. The
width of the sound beam at any distance from the chest
wall determines the lateral resolution at that depth. Any
structures that are displaced laterally from each other
by less than the beam width cannot be reliably resolved
as separate structures. Again, this creates ambiguities
in choosing the echo to be measured and this may result
in systematic or sporadic errors.

**Requirement for extensive training:** Another
limitation of the method stems from the extensive
training usually required to perform and interpret the
studies properly. Several months of intensive training
are considered optimal (more than 3 to 6 months) in
fellowship programs. Fortunately there is now a sizable
group of such well trained people. It is much more dif-
ficult for the physician beyond his period of fellowship
to obtain optimal, or even minimal, training. This is
because he cannot leave his practice for sufficient time
periods and because few active laboratories offer such
training. There is also a shortage of training programs
for technicians (sonographers) when compared with the
expressed need for people with these skills. Each
echocardiographic laboratory should have an experi-
enced and technically capable physician serving as
medical director, even if a well qualified sonographer
is there on a daily basis. These matters truly limit the
usefulness of the technique because having any test
done badly may be worse than not having the test at all.
Finally, education of the general medical public of
physicians who refer patients for echocardiography is
a major task that limits most efficient and effective
application of this method for those patients who may
benefit most from its use.
References

Evaluation of Ventricular Function Using Two Dimensional Echocardiography

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Two dimensional echocardiography potentially offers several advantages over the standard M mode echocardiographic examination for the assessment of ventricular function. The major advantage of the technique is its ability to visualize an entire cross-sectional slice of the ventricle as opposed to a single linear dimension. These slice views of the ventricular cavity allow dimensions to be evaluated which are inaccessible by M mode examination. For example, an apical four chamber view allows the motion of the lateral and medial walls of the ventricles to be appreciated, a capability that is not available with M mode echocardiography. Because greater anatomic information is present in two dimensional views of the ventricle, it is also possible to identify and localize myocardial wall segments more accurately. However, these strong points of two dimensional echocardiography have not been fully realized, because the technique requires time-consuming data analysis in order to be quantitative. Instrumentation which either is being developed at present or anticipated in the near future should overcome much of this computational difficulty. The present discussion, therefore, will concentrate on the applications of two dimensional echocardiography to the analysis of ventricular function with use of techniques either currently available or anticipated in the next few years.

Instrumentation

Digital scan converters: The major instrumentation advance that allows a more quantitative assessment of ventricular function from two dimensional echocardiography is the incorporation of digital scan converters in current two dimensional equipment. The digital scan converter changes the sector scan image into a series of very small picture elements, known as "pixels" that, when displayed in video format on a standard rectangular television screen, recreate the two dimensional echocardiographic image. Because the precise location of each pixel is known, it is possible to identify specific points and to trace boundaries directly from the two dimensional image. Once specific points and boundaries have been identified by the user, the computer is able to determine distances and to compute volumes using standard area-length methods.

Analyzing two dimensional images: Two options are available for analyzing two dimensional images. One method involves performing the data analysis while the echocardiographic study is in progress. For example, the two dimensional transducer can be placed directly on the patient's chest and the resulting two dimensional images viewed on the instrument's video display in real time. From direct examination of the real time images, it is possible to determine whether wall motion abnormalities are present and to assess qualitatively the extent of any wall motion abnormalities that exist. At present, this method of direct visualization of the ventricular chamber in real time precludes a precise quantitative analysis of ventricular size or volume. This limitation can be partly overcome by using an electrocardiographic triggered method to freeze one frame of the two dimensional echocardiographic image on the video display of the instrument. If the electrocardiographic trigger is set at the onset of the QRS complex, the frozen frame would represent end-diastole. Ventricular volume could be estimated from this frame using either a manual method (that is, tracing the image onto a transparent overlay) or an electronic method (using a light pen or joystick to trace the boundary of the ventricle). By resetting the electrocardiographic trigger to a specified time after the onset of the QRS complex, it is also possible to freeze a frame near end-systole and estimate the end-systolic volume of the ventricular cavity.

This method has many shortcomings, including the fact that it usually requires the sequential analysis of diastolic and systolic frames that are not from the same cardiac cycle. Because of the time delay between freezing the diastolic and systolic frames, it is possible that the operator will have moved the transducer slightly causing a different two dimensional slice to be recorded. Moreover, the method requires that the computations occur while the patient is being imaged, thus requiring a longer time to perform the study. As a consequence, this method is discouraged.

The alternative method for evaluating ventricular function from two dimensional images is to record the data initially onto videotape for subsequent playback and analysis. If this method is to be fully utilized, the videotape recorder should have several features. These features include the ability to run the tape recorder in slow motion and to freeze a full frame or field of video during playback. An additional and desirable feature is the ability to run the recorder in slow motion in a reverse direction. This feature is not found on current recorders. If a tape recorder is available which provides both slow motion and freeze-frame capabilities, it is possible to record the two dimensional studies on vid-
cotape so that the videotape can be played back at a later time either through the same instrument or through a separate analysis instrument.

One advantage of this approach is that sequential frames can be analyzed from the same heartbeat. Another advantage is that the analysis can be done either with the same two dimensional instrument when it is not in patient use or with a separate analysis instrument, thereby allowing a more efficient utilization of equipment and minimizing patient examination time.

Video disc: An additional device that further simplifies the outlining of the ventricular cavity is the video disc. This device allows several seconds of two dimensional data to be recorded. These data can then be played back at various speeds in both the forward and reverse directions. In addition, stop-frame images from video discs are of excellent quality. Advances in the near future should allow longer recording times and random access to selected frames. This latter feature should be a particularly attractive operational feature.

Unique Measurements From Two Dimensional Echocardiograms

All dimensional measurements that can be obtained from M mode echocardiograms can also be derived from two dimensional echocardiograms, including left ventricular internal dimensions and myocardial wall thicknesses. Because two dimensional echocardiograms allow linear measurements to be made in directions oblique to the ultrasonic beam, it is possible to measure dimensions not available from M mode echocardiograms. It is also possible to measure the area of structures seen in the cross-sectional images. This ability to measure the area of the slices of cardiac structures is a unique feature of two dimensional echocardiography. Area measurement may have useful clinical applications such as the noninvasive measurement of mitral orifice area in patients with mitral stenosis. In regard to the evaluation of ventricular function, the ability to measure the area of a slice of the ventricular cavity may allow estimation of ventricular volume. Likewise, the ability to measure the area of a specific region of a myocardial wall might allow an estimation of the extent of myocardial damage or, more importantly, of the amount of remaining viable myocardium. The ability to obtain these additional measurements that cannot be obtained from M mode echocardiograms makes two dimensional echocardiography a particularly powerful tool for assessing global and segmental ventricular function.

Evaluation of Global Ventricular Function

Left ventricular volumes and ejection fraction: Global function of the left ventricle can be evaluated by placing a wide angle transducer in either the parasternal or apical position with the scan plane oriented parallel to the long axis of the left ventricle. With this approach, it is possible to visualize a cross-sectional slice of the long axis of the ventricle. If an 80 to 90° scan angle is used, the resulting images will extend from near the cardiac apex to the aortic root. If one then assumes that the ventricular cavity is circular in all cross sections perpendicular to the long axis, it is possible to estimate left ventricular volume at end-diastole and at end-systole and, thereby, estimate left ventricular ejection fraction. This approach of assessing global left ventricular function has significant advantages over the M mode technique particularly in diseases that produce irregular shapes of the left ventricle, such as hypertrophic cardiomyopathy or coronary artery disease. Qualitative evaluation: Although quantitative assessment of ventricular function is desirable, it is also possible to use two dimensional echocardiography to obtain a qualitative evaluation. Thus, the large and diffusely hypokinetic ventricle seen in patients with a dilated cardiomyopathy can be easily identified and distinguished from the ventricle seen in normal subjects or in patients with diseases in which ventricular systolic function is usually normal, such as aortic stenosis or systemic hypertension. Qualitative assessment is most useful in identifying gross abnormalities. However, identification of more subtle dysfunction requires a more quantitative approach.

Shortcomings: Like M mode echocardiography, two dimensional echocardiography has shortcomings. For example, it is necessary to have the scan plane parallel to the long axis of the left ventricle and to transect the left ventricle through the center of the left ventricular cavity. If the long axis plane used to estimate volume either is not parallel to the long axis of the left ventricle or does not pass through the center of the ventricular cavity, one will underestimate the volume of the left ventricle. In addition, the endocardial surfaces of the left ventricle must be clearly visualized in order for an accurate volume to be estimated.

Comparison with contrast ventriculography: The ability of two dimensional echocardiography to assess left ventricular volume accurately and evaluate global left ventricular function has been studied by comparing the ventricular volumes and ejection fraction derived from two dimensional images with those derived from standard contrast angiograms. Studies thus far indicate that although there is a reasonably close correlation between the two techniques, the two dimensional echocardiographic volumes are generally smaller than those estimated from the contrast angiographic studies. Whether this discrepancy is due to methodologic errors inherent in the two dimensional technique or is related to inaccuracies in the determination of ventricular volume from contrast angiography cannot be clearly determined at present. However, a good correlation has been found between left ventricular ejection fraction estimated from two dimensional echocardiographic images and that determined from contrast angiograms.

Studies during exercise: Radionuclide angiographic studies have clearly demonstrated that it is useful to
assess global left ventricular function during exercise. This is particularly true in the assessment of patients with suspected or known coronary artery disease. As a result, investigators have begun studying the feasibility of performing two-dimensional echocardiographic studies before and immediately after treadmill or handgrip exercise to determine if the technique can be used to estimate ventricular ejection fraction before and after stress. Preliminary studies indicate that it is feasible to estimate left ventricular systolic function both at rest and immediately after exercise. It has not been possible to analyze ventricular function at peak exercise because the rapid and deep breathing that accompanies maximal exercise prevents reliable ventricular visualization. However, studies performed with breathholding immediately after exercise appear technically feasible and may be clinically useful.

Clinical applications: The ability to image the left ventricle and assess its global function has important clinical applications. For example, it is very useful in routine patient management to determine whether left ventricular systolic function is normal or reduced. It is also important in those patients with reduced systolic function to distinguish the patient who has a dilated, diffusely hypokinetic ventricle from the patient with normal systolic function at the base of the heart but overall global dysfunction because of an aneurysm or a dyskinesis myocardial wall. The ability to distinguish patients with normal systolic function from those with decreased systolic function has important therapeutic implications in that patients with congestive heart failure who have a diffusely hypokinetic ventricle are best treated with an isotropic drug such as digitalis, whereas patients with congestive heart failure due to decreased ventricular compliance are more appropriately treated with diuretic therapy.

Evaluation of Segmental Ventricular Function

Imaging in multiple planes: One of the unique features of two-dimensional echocardiography is its ability to visualize virtually any segment of the ventricular walls. For example, the left ventricle can be imaged from multiple areas on the chest including the parasternal, apical and subcostal regions and can be imaged in three orthogonal planes. The left ventricle can be imaged from the parasternal region in either a short or long axis plane. From the apical region the ventricle can be imaged in either a long axis or a four chamber plane, whereas from the subcostal region it can be imaged in either the four chamber or short axis plane. Moreover, by rotating the transducer around its long axis, it is possible to image the ventricle from planes intermediate between these three general imaging planes. This ability to image the ventricle in multiple planes from several different regions on the chest, coupled with the ability to visualize intracardiac anatomy and thereby localize wall segments more precisely, allows two-dimensional echocardiography to be a powerful tool in assessing segmental left ventricular function.

Identification of wall segments and wall motion abnormalities: To facilitate the evaluation of segmental wall motion abnormalities, the American Society of Echocardiography recently adopted image orientation standards as well as standard nomenclature for identifying ventricular wall segments. The nomenclature for ventricular wall segments is based on identifying intracardiac structures, such as papillary muscles, and using them to subdivide the ventricle into approximately 15 segments. Recent studies of patients with coronary artery disease demonstrated that lesions in specific coronary arteries produce wall motion abnormalities in specific myocardial segments. For example, a myocardial infarct caused by a lesion in the left anterior descending coronary artery usually produces wall motion abnormalities in the anterior segments of both the ventricular septum and left ventricular free wall. These clinical observations are supported by studies in experimental animals demonstrating that sudden occlusion of a coronary artery will produce an immediate cessation of contraction and, consequently, the development of a wall motion abnormality in the corresponding myocardial segment supplied by that coronary artery. This ability of two-dimensional echocardiography to identify myocardial segments precisely should prove very useful in the evaluation and assessment of patients with both acute and chronic coronary artery disease.

Measuring wall thickness: In addition to being able to assess wall motion abnormalities, two-dimensional echocardiography also allows the thickness of various myocardial wall segments to be measured. This ability to measure wall thickness should prove useful in evaluating patients to determine whether dyskinetic myocardial walls are thin and therefore presumably consist of fibrous tissue, or are of normal thickness and presumably still contain viable myocardium. This distinction could have important therapeutic implications because surgical resection of wall segments seems to be most successful when the wall being resected consists primarily of fibrous tissue. In addition, the visual appearance of the myocardium may provide useful information for identifying either the presence of abnormal tissue, such as fibrous tissue or disorganized myocardial cells, or abnormal substances, such as amyloid or iron. It remains to be determined whether the visual appearance of the myocardium or a more quantitative assessment of the interaction between the myocardium and ultrasound energy will allow tissue characterization to be performed noninvasively.

Identifying abnormal cavity masses: An additional clinical advantage of two-dimensional imaging of the left ventricle is its ability to identify abnormal masses inside the left ventricular cavity. Recent studies have suggested that the incidence of intracardiac thrombi in the setting of an acute myocardial infarction is much greater than previously suspected. Although the therapeutic implication of detecting these clots is unclear, studies are now underway to determine whether these clots are associated with an increased number of embolic events.
or are a relatively benign accompaniment of an acute myocardial infarction.

**Evaluation of Ventricular Function in Conjunction With M Mode Echocardiography**

Because two dimensional echocardiography allows a clearer visualization of intracardiac structures, it is possible to use the two dimensional images to locate more precisely the region of the heart from which M mode echocardiographic tracings are being obtained. In the past, the T scan method has been used with M mode echocardiography in an attempt to assure that the ultrasonic beam was passing through the center of the left ventricular cavity. The use of two dimensional echocardiography to locate the ultrasonic beam provides direct visual confirmation of the location of the M mode beam and thereby allows greater measurement reliability and reproducibility.

In addition, two dimensional imaging allows patients with wall motion abnormalities to be identified and distinguished from those with either a normal or diffusely hypokinetic ventricle. Thus, a study that combines two dimensional and M mode echocardiography allows a more precise evaluation of ventricular function than a study using only the standard M mode echocardiographic technique. For example, if two dimensional images identify major wall motion abnormalities, then any assessment of ventricular function from M mode echocardiography should be viewed with considerable skepticism. In contrast, if two dimensional echocardiographic imaging demonstrates that a focal major wall motion abnormality is not present, then the M mode echocardiographic assessment of left ventricular function should be a reliable assessment of the systolic performance of the entire left ventricle. Moreover, two dimensional echocardiography can be used to ensure that the M mode beam is being reflected from the center of the left ventricular cavity below the tips of the mitral valve and above the papillary muscles. Therefore, M mode echocardiographic studies obtained in conjunction with two dimensional imaging should provide a reproducible and computationally simple method for evaluating the systolic and diastolic functions of the left ventricle.

**Strengths of Two Dimensional Echocardiography**

Two dimensional echocardiography allows a cross section of the ventricle to be imaged rather than a single chord. This has several potential advantages. One advantage is that a large portion of the ventricle is imaged so that it is easier to identify the myocardial segment being visualized. Also, the greater field of view allows abnormalities of ventricular configuration to be visualized. In addition, quantitative assessment is performed by measuring changes in an area of the myocardial cavity or wall rather than changes in a chord or the perimeter of the cavity. At least one study suggests that measurement of changes in the area of the ventricle can be made more reliably than changes in a perimeter or chord.

Because two dimensional echocardiography allows an improved visualization of the spatial relations of various myocardial walls, one can measure distances between myocardial walls in directions other than those parallel to a single ultrasonic beam. This allows chamber dimensions to be measured from many more regions on the chest and in directions not feasible with M mode echocardiography.

**Compared with other noninvasive techniques**, two dimensional echocardiography allows ventricular function to be assessed in an unlimited number of cardiac cycles and without the use of contrast agents, such as iodinated dye or radioactive tracers. Moreover, the method allows excellent spatial resolution and precise quantitative evaluation of segmental myocardial function.

**Limitations of Two Dimensional Echocardiography**

Although two dimensional echocardiography allows visualization of a cross-sectional slice of the ventricle rather than a single chord, it still cannot be used to assess global ventricular function unless certain assumptions are made or multiple views and complex computations are performed. Moreover, the same attention to technique required for M mode quantitation must be followed when recording two dimensional images of the heart so that oblique cross sections do not result in quantitative inaccuracies. Thus, the slice visualization of the heart makes two dimensional echocardiography an ideal method for assessing segmental function but it is less satisfactory for global function.

A second limitation of two dimensional imaging is that quantitative analysis of ventricular function requires a trained observer to outline the boundaries of the ventricular cavity and left ventricular walls. This requires considerable observer training and is time-consuming. Although it may be possible to automate this process, such methods are not yet available.

Another limitation of the two dimensional technique is that it is difficult to image the heart when the lungs are overinflated, as occurs in patients during exercise or in patients with obstructive lung disease. Recent studies have indicated that it may be possible to visualize the heart immediately after exercise, particularly if the apical transducer position is used. However, it remains to be determined whether this technique can be performed reliably in a large percentage of patients and in a large number of echocardiographic laboratories.

**Compared with M mode echocardiography**, the two dimensional approach has not yielded a large body of quantitative measurements. For example, the effect of body size and age on M mode measurements has been well described in a large group of normal subjects and regression equations have been developed to allow prediction of M mode echocardiographic measurements in a subject of known age and body weight. Such data allow subtle changes in cardiac dimensions to be identified. Similar data have not yet been developed from...
two dimensional echocardiograms. Until they are, this relative lack of normal quantitative data will be a limitation of the two dimensional echocardiographic technique.

Summary

Two-dimensional echocardiography is potentially a more accurate and reliable method for assessing ventricular function than the standard M mode echocardiographic technique. More widespread clinical application of this technique for the quantitative assessment of left ventricular systolic function has been limited by the fact that quantification was time-consuming. Recent advances in two dimensional instrumentation allow quantification to be performed with less diffi- culty and in a shorter time period. As a result, two dimensional echocardiography should find widespread clinical use in the evaluation of global and segmental ventricular function.

References

Evaluation of Ventricular Function Using Doppler Echocardiography

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In comparison with other techniques that utilize reflected ultrasound to assess ventricular function, Doppler echocardiography should probably be assigned secondary importance. Doppler techniques cannot evaluate ventricular geometry or dynamics directly; two dimensional and M mode echocardiography are better suited to such applications. However, the Doppler approach provides a novel method for assessing ventricular function, because (unlike two dimensional and M mode echocardiography) it does not depend on specification of, or assumptions about, ventricular geometry. Moreover, the Doppler investigation does provide data not always apparent from the anatomic findings, and this is a useful adjunct to conventional echographic studies. A Doppler examination should be done at the same time as an M mode or two dimensional examination (or both); when done in this fashion, the Doppler study requires about 15 minutes extra time and it entails no known risk or discomfort. Although costs for all procedures vary from hospital to hospital and city to city, a Doppler study invariably costs less than an M mode echocardiogram, so that it is relatively inexpensive. Indeed, M mode, two dimensional and Doppler echocardiography should probably be viewed as related but different diagnostic applications of reflected ultrasound, depending on the cardiac disease in question, one or another of these techniques may be more or less useful. For evaluating ventricular performance, Doppler echocardiography should at present be viewed in a supporting role.

When compared with noninvasive techniques that use energy modalities other than ultrasound to examine the heart, Doppler echocardiography shares the advantages and limitations of the other ultrasonic techniques. Doppler echocardiography does not use ionizing radiation; it is painless, thought to be harmless and provides data on a beat to beat basis. However, it is subject to the same limitations governing ultrasonic penetration as are other ultrasonic methods: when penetration is poor (due to air-filled lung, fat or excessive tissue depth interposed between the transducer and the region of interest), the technical quality of recordings is limited.

Some of the technical problems peculiar to pulsed and continuous wave Doppler echocardiography will be discussed here; many are well recognized, and solutions are being actively pursued. It appears that in the future, Doppler echocardiographic methods will be less restricted by technologic limitations and more amenable to quantitation of intracardiac blood flow. Doppler echocardiography is thus likely to play an increasingly important role in the assessment of ventricular function.

Doppler Techniques

Flow velocity and volume flow: The Doppler principle can be used to detect blood flow within the heart and great vessels. When an ultrasonic beam traverses blood, backscattering of ultrasonic energy from particles (primarily red cells) in the blood occurs. If a component of blood flow is oriented parallel to the ultrasonic axis, the frequency of ultrasound backscattered from moving red cells is altered so that it differs from that of the original incident beam. This frequency alteration is called a "Doppler shift." Under ideal conditions, one could compute actual flow velocity from the Doppler frequency shift if one could quantitate the Doppler shift accurately, and if one knew the angle between the ultrasonic beam and the axis of blood flow. One could also calculate volume flow through a cardiac chamber or great vessel by measuring the mean velocity of flow through, and the cross-sectional area of, that chamber or vessel. In practice, however, quantitation of the preceding variables requires a number of assumptions and approximations. It appears premature to consider Doppler echocardiography an accepted technique for measuring volume flow.

Detection of turbulence: Doppler echocardiography also can be used in a qualitative fashion as a turbulence detector. Normal blood flow is organized, and red cells move in an orderly, relatively parallel fashion. Adjacent red cells flow with similar velocities at any instant in the cycle, although flow velocities obviously change with time over the cardiac cycle. Accordingly, uniform Doppler frequency shifts will be recorded from red blood cells as they flow through a localized area of sampling. However, disorganization of flow occurs when blood traverses a stenotic orifice; under some circumstances, regurgitant flow is also disorganized. Under these conditions, adjacent red cells move with differing velocities in different directions, so that the corresponding Doppler shifts show a broad spectrum of frequencies. Using current Doppler instrumentation, one can evaluate intracardiac flow patterns to determine if they are normal or if they indicate disorganization ("turbulence"). Although this approach does not measure ventricular function directly, it is of use in
evaluating a patient with symptoms or signs suggesting ventricular dysfunction.

Continuous wave and pulsed Doppler techniques: Two related Doppler techniques should be described briefly. Continuous wave Doppler technique utilizes ultrasound that is emitted continuously from a piezoelectric transducer. Ultrasound backscattered from moving targets anywhere along the ultrasonic beam axis is detected and processed for Doppler shift information. Continuous wave Doppler technique can detect flow signals from across an entire cardiac chamber, but when a series of chambers are traversed by the ultrasonic beam, the continuous wave Doppler signals represent a composite, and it is not always easy to define from which chamber certain signals originated. Pulsed Doppler echocardiography can overcome this potential source of ambiguity. Brief pulses of ultrasound are emitted repetitively, and Doppler shifts in the return signal are analyzed from a brief time “window.” The time delay between emission of an ultrasonic pulse and the Doppler analysis window defines the distance between the ultrasonic transducer and the region from which the Doppler shifts are recorded. This region is referred to as the “sample volume.” The Doppler sample volume can be positioned at any desired distance along the ultrasonic beam to examine flow at specific intra-cardiac locations. More detailed descriptions of pulsed Doppler techniques and instrumentation can be found elsewhere.

Analysis techniques: Whether obtained using continuous wave or pulsed techniques, Doppler shift signals can be recorded as a waveform that resembles a flow velocity curve. Older Doppler instruments make use of a time-interval histogram technique that plots the inverse of time between successive zero-crossings in the Doppler signal as a function of time in the cardiac cycle. This analysis technique is inexpensive and, under ideal conditions, provides an accurate flow record. Unfortunately, it is quite sensitive to poor signal/noise ratios and to alterations in instrument gain settings, features that often limit its utility in the clinical setting. New techniques for real-time analysis of the frequency spectra contained within the Doppler shift signals have been implemented within the last few years. These techniques also display flow signals as a function of time in the cardiac cycle, but they are not as sensitive to poor signal/noise ratios or to instrument settings and so permit a degree of quantitation not always possible with the older graphical display.

Assessment of Ventricular Function

Doppler flow curves could be used to analyze ventricular function. Physiologists have long used systolic acceleration and peak flow rates, measured from directly recorded flow velocity curves, as sensitive indicators of ventricular contractile force. These variables, as well as many other measures of systolic mechanical performance, are dependent on ventricular loading conditions. The Doppler shift induced by flowing blood is related to the velocity of blood flow according to the formula \( \Delta F \propto V \cdot \cos \theta \), where \( \Delta F \) = Doppler shift, \( V \) = flow velocity, and \( \theta \) = the angle between the incident ultrasonic beam and the axis of flow. Accordingly, a graph of Doppler shift against time can be converted to a flow velocity curve if one can measure the angle between the ultrasonic beam and the flow axis. Alternatively, if the ultrasonic beam is oriented parallel, or nearly so, to the axis of flow, the angle \( \theta \) approximates 0°, its cosine approximates 1, and Doppler shift can be used directly as a reasonably close approximation of actual flow velocity. In clinical practice, the suprasternal notch approach has often been employed in order to align the ultrasonic beam with aortic flow, and while the parasternal approach has been used to study pulmonary flow.

Doppler velocity curves from aorta and temporal artery: On the basis of the preceding principles, clinical investigators have evaluated ventricular function directly from Doppler flow curves. Gardin et al. recorded aortic flow velocity curves from the suprasternal notch, employing a pulsed Doppler instrument coupled to a frequency spectrum analyzer, and evaluated them to determine peak flow velocity, systolic ejection time, acceleration and deceleration. With the exception of acceleration, these variables were found to change little on repeat determination in normal subjects. These same workers noted a reduction in peak aortic velocity in patients with constrictive cardiomyopathy as compared with normal subjects, reflecting impaired left ventricular muscle function in the group with cardiomyopathy. Finally, systolic time intervals such as the prejection period and ejection time have been measured from continuous wave Doppler recordings of temporal arterial blood flow, and have been found to correlate well with systolic time intervals derived from carotid pulse tracings. It appears reasonable to hope that time intervals measured from pulsed or continuous wave Doppler recordings of flow in the proximal aorta or main pulmonary artery will prove useful in evaluating the performance of the left and right ventricle, respectively, because systolic time intervals measured from external pulse tracings can be used to assess ventricular muscle function.

The preceding studies have involved limited numbers of patients. Additional confirmatory studies will be needed before direct analysis of Doppler flow curves can be considered an accepted clinical technique for assessing ventricular function.

Measurement of Stroke Volume

Doppler echocardiography has been used to quantify left ventricular stroke volume and to calculate cardiac output. An accurate determination of forward volume flow certainly does not in itself define whether ventricular function is normal or abnormal. For example, the dilated, hypokinetic left ventricle in a patient with constrictive cardiomyopathy may eject a relatively normal forward stroke volume and cardiac output despite marked increases in end-diastolic and end-systolic volumes and marked depression of systolic
indexes such as ejection fraction, rate of rise of left ventricular pressure (dP/dt), and mean velocity of circumferential fiber shortening (Vcf). However, a quantitative measure of stroke volume using Doppler echocardiography would provide a clinically important, noninvasive means of following the response of the failing ventricle to therapeutic interventions.

Doppler echocardiographic measurement of stroke volume requires knowledge of several variables. The rate of volume flow through the aortic valve is a product of the mean velocity of flow in the valve orifice and the cross-sectional area of this orifice. Both of these variables change during the cardiac cycle. Thus, it would be most accurate to state that volume flow at any instant is equal to the product of instantaneous mean flow velocity and instantaneous orifice area. Accordingly, the volume of blood ejected into the aorta during systole could be measured by integrating mean instantaneous aortic flow velocity over the period of systole, and multiplying this integral by mean systolic aortic orifice area.

**Technical Limitations**

Lack of simultaneous recordings: Unfortunately, Doppler instruments that are widely available do not allow simultaneous recording of Doppler and two-dimensional echocardiographic data, so that the variables needed to compute stroke volume cannot be measured simultaneously. It is necessary to assume that, at the same instant in the cardiac cycle, aortic orifice area and flow velocity are relatively similar from beat to beat. This assumption should hold for the case of sinus rhythm, so that flow orifice and flow velocity could be measured sequentially and used to estimate volume flow. However, the variability of flow velocity seen in the presence of rhythm disturbances such as ventricular arrhythmia or atrial fibrillation would invalidate this approach.

Overlapping of aortic root and cardiac chamber Doppler shifts: Either continuous wave or pulsed Doppler techniques could be used to measure aortic flow velocity. Because it is not range-gated, continuous wave Doppler ultrasound would record Doppler frequency shifts across the entire lumen of the aortic root. Unfortunately, if the continuous wave ultrasonic beam also traversed a flow field other than that of the aorta, the Doppler shifts recorded from the aorta would be contaminated by signals recorded from the second flow field. For example, continuous wave Doppler ultrasound passing from the precordium across the right ventricular outflow tract, aortic valve and left atrium would detect a composite of Doppler shifts from all three of these flow fields, and not specifically those frequency shifts representing aortic flow. This uncertainty would create no practical problem so long as aortic flow velocities were the highest recorded, as would usually be the case. However, the presence of high right ventricular ejection velocity (secondary to infundibular or valve stenosis) or low aortic flow velocity (in congestive cardiomyopathy, for example) might seriously restrict the ability to record accurate aortic flow velocity from the precordium. By using the suprasternal notch approach and directing the continuous wave ultrasonic beam to record only aortic flow, this restriction can be obviated.

Range-gated pulsed Doppler techniques could also be used to measure aortic flow velocity. Conventional pulsed Doppler instruments employ a single range gate and record Doppler frequency shifts from red cells flowing through a single small sample volume. The sample volume does not necessarily encompass the entire aortic orifice; its axial dimension is determined by the duration of the range gate, while its lateral dimension depends on the geometry of the ultrasonic beam (which in turn is a function of transducer size, focusing and range). Using a single sample volume of fixed dimensions, one would need to record flow velocity profiles across the entire aortic orifice and use these multiple recordings to estimate average instantaneous aortic flow velocity over systole. Such an approach would obviously be tedious. Moreover, accurate mapping of local flow profiles would ideally require that the sample volume "track" certain anatomic landmarks (such as the aortic walls) during systole, since the aortic orifice does move in relation to the chest wall during the cardiac cycle. Tracking devices have been described, but have not yet been widely implemented.

**Alternative approaches**: Several alternate approaches could be taken to determine average instantaneous velocities across the aortic lumen. It would be simplest to assume that the transverse profile of flow in the aorta is uniform, and that flow velocity measured in one region is representative of all regions. While this is the case in normal subjects, it would not pertain to patients with aortic stenosis or a valve prosthesis, for example. By matching the diameter of the aorta to the axial dimension of a variable sample volume, as described by Greene et al. and incorporated quite recently into commercial instrumentation, one could record average instantaneous Doppler shifts across the entire aortic lumen. Finally, multiple adjacent sample volumes spanning the aortic lumen could be employed to record Doppler shifts. A prototype digital multigate Doppler device has been constructed by Brandesfaini and co-workers and used in the clinical setting by Stevenson et al. This innovative pulsed Doppler approach would allow recording of flow across the aorta, but it is not yet available for widespread clinical use.

Accurate measurement of Doppler frequency shifts requires reliable, objective methods for calibrating these frequencies and for recording Doppler shifts without the directional ambiguity ("aliasing") caused by insufficient sampling rates. Recordings should also be relatively free of interference from electronic noise inherent in the Doppler instrument. In practice, aliasing and machine noise do impose limitations in the most widely used pulsed Doppler units, although solutions to these problems appear feasible.

The angle between the ultrasonic beam and the axis of flow must be known in order to convert Doppler shift to blood flow velocity. In the case of aortic flow, this angle changes as the aortic root moves over the cardiac cycle, and it would optimally be measured from real-time images recorded at the same time as Doppler flow signals. At present, the angle must be approximated.
either from sequential two-dimensional echo/Doppler studies, or by using the suprasternal or apical approach to align the ultrasound beam with flow in order to detect the apparent maximum Doppler shifts. Similar approaches must be used to study pulmonary flow.  

Measurement of aortic orifice area: Finally, flow orifice area must be measured. Previous workers have assumed that the aortic root was circular in cross section, and that its cross-sectional area changed little during systole. Accordingly, they calculated aortic cross-sectional area from aortic diameter measured by angiography or M-mode echocardiography. The preceding assumptions are not strictly true, however, and it would be preferable to image aortic (or pulmonary) cross-sectional area directly. Theoretically, flow orifice area could be measured using two-dimensional echocardiography. For example, the aorta could be imaged in the parasternal short axis orientation, or just above the aortic valve level, and its systolic cross-sectional area measured from sequential stop-frames over the duration of systole. Assuming high quality images, this would provide a series of instantaneous aortic areas at multiple points during systole, which could then be used in conjunction with Doppler flow velocity measurements to compute systolic stroke volume. However, such an approach seems tedious and its feasibility has not been validated.

It should be apparent from the preceding discussion that Doppler measurement of volume flow requires a number of assumptions and approximations. The magnitude of the error introduced by each individual assumption would appear to be small, and it is reassuring that Doppler estimates of volume flow in the clinical setting correlate reasonably well with independent measures of stroke volume and cardiac output. Nonetheless, the cumulative effect of all the necessary approximations is such that absolute values of velocity and volume flow may show substantial error in individual subjects. Future technologic improvement in signal/noise ratio, signal processing, sample volume tracking and control of sample volume dimensions should reduce the approximations inherent in current Doppler estimates of volume flow and thus increase the reliability of the method. Although it is not yet a time-proven, clinically accepted technique, Doppler echocardiographic measurement of left and right ventricular volume output should probably be awaited with cautious optimism.

Assessment of Lesions That Mimic Ventricular Dysfunction

Doppler echocardiography can be used to detect the presence of a variety of mechanical lesions that sometimes mimic left or right ventricular dysfunction. For example, elevated pulmonary venous pressures in a patient with predominant signs and symptoms of pulmonary venous congestion could be due to primary myocardial dysfunction (dilated cardiomyopathy). However, moderate or severe mitral regurgitation could cause similar elevations of mean pulmonary venous pressure, as well as similar signs and symptoms, in the absence of left ventricular dysfunction. This distinction has important therapeutic implications: mitral valve replacement might benefit the patient with the latter condition, but not the former.

Mitrail regurgitation: Moderate or severe mitral regurgitation can generally be detected without resort to Doppler echocardiography. A systolic murmur will usually be audible over the left precordium, the left ventricular impulse will be broad and hyperdynamic, and the left ventricle and atrium will appear large by chest roentgenogram. M mode and two-dimensional echocardiography will generally demonstrate left ventricular and atrial enlargement as well as anatomic derangements of the mitral apparatus (such as rheumatic involvement, myxomatous degeneration, vegetations, prolapse, etc.). Unfortunately, however, the murmur of mitral regurgitation is sometimes difficult to detect, obesity and emphysema may mask the physical findings and left heart chamber enlargement can be caused by conditions other than mitral regurgitation. Finally, echocardiographic documentation of structural abnormalities involving the mitral apparatus may explain the etiology of mitral regurgitation, but it does not prove the existence of mitral regurgitation.

Accordingly, an accurate noninvasive method for detecting if mitral regurgitation were present or absent would be useful in patients with suspected left ventricular dysfunction. Pulsed Doppler echocardiography appears to be such a method. Flow patterns can be examined just cephalad to mitral leaflet closure (that is, in the low left atrium) using either a single crystal transducer or a sequential sector scan/Doppler instrument. When the mitral valve is competent, net flow signals are not recorded during systole low in the left atrium. However, when mitral regurgitation is present, systolic flow from the left ventricle to the left atrium, often "turbulent" in nature, is recorded just superior to mitral leaflet closure. When selective left ventricular cineangiography is taken as the reference standard, pulsed Doppler echocardiography detects the presence of mitral regurgitation with a sensitivity of 96 percent and a specificity of 90 percent; the predictive accuracy of a positive test is 99 percent. Moreover, pulsed Doppler echocardiography can be used to estimate semiquantitatively the severity of mitral regurgitation. It has been hypothesized that the severity of regurgitation is reflected by its spatial distribution, so that severe mitral regurgitation is widely distributed in the left atrium while mild mitral regurgitation is localized to the region just proximal to the mitral valve. Thus, the examiner positions the Doppler sample volume at multiple locations within the left atrial cavity to determine if mitral regurgitant flow is localized or diffuse. Several investigators have used this approach to differentiate mild from severe mitral regurgitation. 

A pulsed Doppler study should be performed not in isolation, but rather as part of a complete echocardiographic examination including an M mode or two dimensional study, or both. From a practical perspective, pulsed Doppler findings may not add diagnostic information in a patient with clinically obvious mitral...
 incompetence and echocardiographic signs of left ventricular volume overload. On the other hand, clinical findings are not "classic" in all patients with mitral regurgitation and echocardiographic chamber abnormalities are absent in occasional patients with mitral regurgitation, and they may be caused by other disorders, even when the mitral valve is competent. Thus, a pulsed Doppler study should be seen as a useful adjunct to the echocardiographic evaluation of a patient with suspected left ventricular dysfunction, particularly when regurgitation cannot be demonstrated or eliminated otherwise.

**Aortic regurgitation:** Other lesions may also cause symptoms and signs of pulmonary venous congestion despite well preserved intrinsic myocardial function. Aortic regurgitation, one such lesion, can be detected by characteristic clinical, radiographic or echocardiographic changes. On occasion, however, the diastolic murmur of aortic regurgitation may be soft or inaudible, while radiographic or echocardiographic abnormalities of the aortic valve or root are not necessarily diagnostic of aortic regurgitation. Pulsed Doppler echocardiography can detect regurgitant diastolic flow from the aortic root into the left ventricular outflow tract with a high degree of accuracy, even when clinical findings have been nondiagnostic. Moreover, the spatial distribution of the regurgitant flow can be used to estimate the severity of aortic regurgitation.

**Combined lesions:** As an isolated lesion, neither mild mitral nor aortic regurgitation causes a major impairment. When superimposed on another lesion affecting the left ventricle, however, mild valve regurgitation could aggravate the hemodynamic burden imposed by the primary lesion and falsely suggest left ventricular dysfunction. For example, if a patient with mild to moderate aortic stenosis later manifested relatively mild mitral or aortic regurgitation as an additional lesion, exertional dyspnea might ensue and be attributed (erroneously) to aortic stenosis. Although cardiac catheterization would probably be needed to define certain the severity of aortic stenosis, detection of aortic regurgitation prior to catheterization might help in planning the catheterization procedure and might help explain the patient’s symptoms. Pulsed Doppler documentation of relatively mild mitral regurgitation might similarly be helpful in explaining the discrepancy between the presence of congestive symptoms and the absence of demonstrable functional impairment in a patient with coronary artery disease and symptoms of pulmonary congestion despite good left ventricular pump function by two dimensional echocardiography.

**Congenital defects:** Certain congenital defects may cause increased pulmonary blood flow and symptoms that mimic myocardial impairment. Lesions such as ventricular septal defect or patent ductus arteriosus have characteristic clinical features, but are occasionally clinically "silent" or inapparent. Pulsed Doppler echocardiography is highly reliable in detecting left to right shunting through a ductus arteriosus, even when no murmur is audible, and similarly accurate in detecting ventricular septal defect.

**Tricuspid regurgitation:** Pulsed Doppler echocardiography can also be used to evaluate patients with suspected right ventricular dysfunction. The systemic venous congestion and elevated right sided filling pressures that result from right sided myocardial impairment may be mimicked to some extent by tricuspid regurgitation, for example. Severe, long-standing tricuspid regurgitation causes right ventricular and right atrial enlargement detectable by chest roentgenogram or by an experienced observer at the bedside. However, these findings may be obscured by obesity or pleural fluid, absent when tricuspid regurgitation is of short duration or mild degree, or seen in the absence of tricuspid regurgitation. M mode or two dimensional echocardiography can demonstrate features of right ventricular volume overload as well as structural abnormalities involving the tricuspid valve apparatus, but these features are not specific for tricuspid regurgitation. Systolic regurgitant flow from the right ventricle to the right atrium can be demonstrated in patients with tricuspid regurgitation, even when clinical findings are absent, using either single crystal or combined two dimensional echocardiography/Doppler study methods. Its spatial distribution helps indicate if regurgitation is mild or severe. Accordingly, a pulsed Doppler study can document the presence of a mechanical lesion that may be clinically apparent yet mimic right ventricular dysfunction.

**Pulmonary regurgitation and atrial septal defect:** Two additional causes of right ventricular volume overload may on occasion suggest right ventricular dysfunction or aggravate preexisting right ventricular disease. Pulmonary regurgitation can be detected reliably by pulsed Doppler echocardiography, even when typical clinical features are absent. Atrial septal defect with left to right shunting can also be demonstrated; not all patients with atrial septal defect manifest flow across the atrial septum by conventional pulsed Doppler techniques, but improved sensitivity is possible with a multigate instrument.

**Summary**

Doppler echocardiography is closely related to M mode and two dimensional echocardiography, although it uses reflected ultrasonic signals to examine blood flow rather than to image cardiac anatomy. It is a useful adjunct to standard echocardiographic methods when one wishes to evaluate ventricular function, but at present it plays a supporting role. In theory, Doppler techniques can be used to assess global ventricular function directly and without regard to ventricular geometry, to calculate volume flow from both the right and left ventricles, and to follow changes in ventricular stroke volume induced by interventions. In practice, various technical limitations restrict the routine clinical application of Doppler echocardiography, but solutions to several of these problems should be forthcoming. Doppler echocardiography can properly be viewed as a useful method for evaluating mechanical lesions that may mimic ventricular dysfunction, and as a promising future method for analyzing ventricular function directly.
References


Future Applications for The Evaluation of Ventricular Function Using Echocardiography

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Echocardiography is intimately linked with developments in biomedical engineering. Thus, the future of this field is in the hands of both engineers and clinicians. Without knowing specific future changes, one can anticipate a number of probable developments that will be pertinent to the evaluation of cardiac function. A) There will undoubtedly be improvements in the current clinical echocardiographic examination. (1) One can anticipate significant improvements in instrumentation, especially with an increasing use of computers and microprocessors. (2) There will be greater efforts at quantitating two-dimensional echocardiography. (3) Greater emphasis will be made on the use of echocardiography with various forms of stress. (4) There should be major advances in the use of contrast echocardiography. (5) There could be increased interest in visualizing intracardiac blood. (6) One can anticipate increasing efforts to improve the echocardiographic technique of identifying types of myocardial tissue. (7) There will undoubtedly be significant improvements in Doppler echocardiography. (8) There will be several approaches to developing three-dimensional echocardiography. (9) Echocardiography will be used as an invasive tool together with catheterization and cardiac surgery.

Improvement in Echocardiographic Techniques

There is always room for improvement in what is currently being done in echocardiography. Much of the improvement will be linked to advances in instrumentation; however, there will also be new ways of using current instruments. For example, with the advent of two-dimensional echocardiography new echocardiographic windows, such as the apex, become increasingly useful. Other echocardiographic windows, such as the subcostal, suprasternal and right parasternal approaches, took on added significance with the introduction of two-dimensional echocardiography. Clinicians will undoubtedly develop additional ways of examining the patient. Maneuvers to enlarge the echocardiographic window are quite possible. Placing the patient in the left lateral position is an old technique that displaces some of the lung and facilitates the echocardiographic examination. There are other possible maneuvers, such as having the patient sit up and lean forward or even examining the patient in the prone position. The voluntary control of respiration is yet another possible approach to enhancing the examination.

There is the possibility that one might be able to alter the acoustic properties of the chest wall for better transmission of ultrasonic energy. For example, high quality echocardiograms are frequently obtained in the uremic patient. However, once dialysis occurs, the quality of the recording may decrease. Thus, there are apparently changes in the acoustic properties of the tissues through which the ultrasonic beam passes. For example, the uremic patient may have a higher water content in the chest wall permitting a better ultrasonic examination. It is conceivable that whatever these
factors might be, a better understanding of them might lead to an improvement in the quality of the echocardiographic images.

It is hoped that these changes, together with improvements in instrumentation, will decrease the proportion of technically unsatisfactory echocardiograms. Inadequate recordings are probably the most important limitation to echocardiography at the present time. The percentage of unsatisfactory echocardiograms ranges between 10 to 40 percent depending on the type of patient being examined. These percentages are clearly too high and eventually should be less than 10 percent of all patients.

**Advances in Instrumentation**

It is a foregone conclusion that echocardiographic instrumentation will steadily improve in years to come. This improvement is stimulated by many technical problems that persist with current echocardiographic examinations. The problem of technically unsatisfactory echocardiograms in as many as 10 to 20 percent of adult patients and the problem of echo dropout producing difficulty in analyzing the data will be of concern to all involved in developing new echocardiographic equipment. In addition, there is strong competition among the commercial companies and the impetus for improvement is ever present.

**Instruments with better signal to noise ratio and high frequency transducers:** Some of the more obvious advances that are already becoming available are instruments with better signal to noise ratios and echocardiograms that utilize higher frequency transducers. There are obvious advantages to having better signal to noise ratios and to using higher frequency transducers. These two developments enhance visualization of the weaker echoes, such as those from the myocardium and the intracardiac blood. The higher frequency permits better resolution in all dimensions and provides a more accurate cardiac image. The newer instruments will also have improved gray scale in order to differentiate between stronger and weaker reflecting interfaces.

Besides having higher frequency transducers, it is also conceivable that one may use lower frequency transducers in difficult cases. The deterioration in resolution that occurs with lower frequency transducers can possibly be recaptured with the use of computer processing of the returning signals.

**Improvement of ultrasonic beam and resolution by improved transducers:** There are many possible ways of improving the ultrasonic beam and the resolution in the echocardiographic systems. Besides merely increasing the frequency of the transducers one can also utilize various transducer designs. Multiple ring transducers and annular phased array transducers are already being used for ultrasonic imaging of other parts of the body. These types of transducers are usually considerably larger than those used for echocardiography. It is certainly conceivable that such transducers might be made small enough to be utilized for echocardiography. Annular phased array transducers permit excellent focusing of the ultrasonic beam in both X and Y lateral dimensions and thus should improve the accuracy of the ultrasonic information. If such transducers did become available for echocardiography, they would probably have to be incorporated into a mechanical scanner.

**Computer and microprocessor technology:** As with all other medical instrumentation the computer or microprocessor will undoubtedly play an increasingly important role in echocardiography. These devices are already in all phased array sector scanners and will be an integral part of almost all two-dimensional scanners. Most of the newer equipment displays the echocardiograms in a digital format so that the data can easily be manipulated by computers. There will be ongoing efforts using computer technology to improve the quality of the echocardiographic image. Computer technology will also be used to facilitate the analysis of echocardiographic data. Freeze-frame recordings timed to the electrocardiogram have already proved to be useful. One can anticipate using much of the computer technology that has already been developed for nuclear cardiology. Some of these features might include gated superimposition of multiple cardiac cycles in order to average the images. One could also display a sequence of images in whatever fashion one might desire. Computer technology used with computerized tomography and digital subtraction techniques could also be used for echocardiography.

The instruments will probably become smaller to facilitate portability. There has already been a significant decrease in the size of the larger sector scanners, such as those used for phased array sector scanning. Advances in microprocessor technology are permitting smaller packaging of the electronics.

**Video recording advances:** Developments in video recording technology will also have an impact on echocardiography. Both two dimensional and M mode echocardiography can be recorded in a video format. As tape recorders and disc recorders improve with an increasing number of convenience features, these advances will undoubtedly enhance the recording and analysis of echocardiographic data.

**Quantitative Two Dimensional Echocardiography**

To date, two dimensional echocardiography has principally been a qualitative examination. Aside from the measurement of mitral valve area and quantitating left ventricular volume, there have been relatively few efforts at using two dimensional echocardiography in a quantitative fashion. One of the reasons for the reluctance to make quantitative measurements of two dimensional echocardiograms has been the inconvenience of obtaining such quantitative information. The videotape recorders that have been used have not made it convenient to make such measurements. With the advent of newer videotape and video disc recorders, together with light pen and joystick systems for tracing video images, it is now becoming easier to obtain quantitative information.
Accurate quantitative measurements: Because of the inherent spatial accuracy of two dimensional echocardiography one should anticipate an increasing number of quantitative measurements from the two dimensional examination. These measurements will be particularly pertinent to the examination of the left ventricle. Although M mode echocardiography has excellent axial resolution and has the advantage of displaying the recording in a convenient strip chart format, there are significant limitations to the M mode measurements. Because the echocardiographic window is not the same in all persons, the M mode dimensions of the left ventricle vary from one person to another. In some patients the standard M mode left ventricular measurement approximates the minor axis; in others, because of a low echocardiographic window, the echocardiographic measurement is closer to the major axis. Actually, in the adult patient it is frequently impossible to place the transducer high enough on the chest to obtain a true minor axis of the left ventricle. M mode measurements obtained with the aid of two dimensional echocardiography don't correct this problem because such M mode recordings can only correspond to a raster line on the two dimensional display. Measurements taken directly from the two dimensional echocardiogram do not have this limitation. One can obtain any chord and a true minor or major axis on every individual irrespective of where the examination happens to be performed utilizing the spatially correct two dimensional examination. Admittedly, the two dimensional measurements would partially use lateral resolution, which is poorer than the axial resolution used with M mode measurements. However, the more accurate spatial orientation should outweigh the 1 or 2 mm difference between axial and lateral resolution.

Ventricular function quantitative measurements: As the basic advantages of quantitative two dimensional echocardiography become better appreciated and the convenience of making these measurements is improved, one can anticipate an increasing use of two dimensional echocardiography for quantitating left ventricular function. One should be able to measure more than merely volumes and ejection fraction. Measurements such as true circumferential shortening, functional infarct size or percent functioning muscle are certainly within the realm of possibility using quantitative two dimensional echocardiography. Because with two dimensional echocardiography one more easily sees the details of all areas of the left ventricle than is possible with the silhouettes obtained with contrast or nuclear angiography, measurements such as functional infarct size may be more accurate in the overall assessment of the ischemic left ventricle than data obtained in other currently available examinations.

Direct computer analysis: Most quantitation to date has utilized manual tracing of the desired echoes either on M mode or two dimensional echocardiograms. Considerable work is being done to use computers to recognize and analyze the desired echoes for measurements. Although there are major problems, such as incomplete records or "echo dropout," there is no reason to believe that they cannot be resolved. Even though the computer identification of cardiac echoes may be less accurate than the manual method, such an approach would certainly make quantitation much easier and more practical. Thus, direct computer analysis of echocardiographic images should probably be forthcoming in the not too distant future.

Stress Echocardiography

Exercise testing: There are increasing data indicating that one can use echocardiography to monitor cardiac changes with various forms of stress. The greatest interest has been trying to use echocardiography to assess the effect of exercise. There are many technical difficulties with obtaining an adequate echocardiogram while the patient is undergoing physical exertion. However, advances in this area have already been made and further resolution of the technical difficulties can be anticipated. Most echocardiographic laboratories are currently using bicycle exercise, either in the supine or sitting position. Technically satisfactory recordings are apparently possible with this technique in approximately 50 to 75 percent of patients. More recently, there has been increasing interest in examining the patient immediately after rather than during exercise. Myocardial ischemia produced with exercise frequently will last several minutes, especially if the patient is in a recumbent position. Thus, there is sufficient time for technically satisfactory echocardiograms to be obtained in the immediate postexercise period while the effects of ischemia are still present. Utilizing the post-exercise period one can obtain satisfactory echocardiograms in a high percentage of patients, possibly as high as 90 percent.

Other types of stress: Other forms of stress besides physical exercise—cold pressor stimulation and various pharmacologic agents—have been used with echocardiography. These forms of stress introduce less technical difficulty in the echocardiographic examination. Unfortunately, they are not quite as physiologic as bicycle or treadmill exercise and frequently may not be sufficiently severe to produce ischemia. Irrespective of which type of stress ultimately proves to be the most practical, one can be reasonably certain that stress echocardiography will eventually be a routine part of echocardiographic examinations in most laboratories.

Contrast Echocardiography

Contrast echocardiography permits the echocardiographer to look at the blood pool in a fashion somewhat similar to that of contrast angiography or radionuclide angiography. With echocardiography one is not detecting radiolabeled particles that absorb X-rays but rather imaging particles that scatter ultrasound. The contrast substance that has been used clinically consists of microbubbles that occur with the injection of fluid into the intravascular system. The microbubbles, probably those already suspended in the liquid, are introduced into a vessel. The length of time that these bubbles persist depends
principally on the surface tension of the liquid. Indocyanine green dye has been one of the most commonly used liquids for contrast echocardiography. Saline, Ringer's lactate or the patient's own blood are alternate solutions.

Newer contrast agents for echocardiography: There are many disadvantages to the current contrast substances. The bubbles formed are not uniform or reproducible. One cannot anticipate getting the same contrast effect with each injection. In some patients one might get a faint contrast effect with a peripheral venous injection. The small bubbles that are formed are also too large to pass through the pulmonary capillaries. Newer contrast agents have been proposed. Carbon dioxide gas, injected in small quantities, is one such agent. A very marked contrast effect will occur with such an injection. Gelatin encased micro-bubbles represent another new contrast agent being investigated. The advantage of the gelatin micobubbles is that they can be made uniformly and will persist for longer periods of time than do the bubbles formed by the injection of liquids. One obtains more reproducible and potentially quantitative contrast injections. The gelatin bubbles are still too large to pass through the capillaries, and their persistence raises questions with regard to their safety. Micro-bubbles can also be made using a coating of exotic sugars. The sugar bubbles are exciting in that they can possibly be made small enough to pass through the capillary beds. They also have some potential problems in that they may clump together and thus produce emboli. They also persist somewhat longer than the usual contrast bubbles or even the gelatin bubbles and could potentially have some adverse effect. Thus, the safety of all of the new contrast agents will have to be substantiated.

There will undoubtedly be further research in finding contrast agents that pass through the capillaries and are innocuous. The potential usefulness of such agents is tremendous. First of all, such a technique would permit studies similar to those obtained with contrast angiography or radionuclide angiography. Indoc-dilution or washout curves for the measurement of blood flow or cardiac output are certainly feasible. There are even theoretical techniques for using contrast echocardiography to measure intracardiac pressure. It is also possible that contrast agents could be utilized for visualizing myocardial perfusion, especially regional perfusion.

Doppler echocardiography: One can also use Doppler echocardiography to detect a circulating substance that reflects ultrasound and thus produces a contrast effect. In fact, Doppler echocardiography may be even more sensitive than either M mode or two-dimensional echocardiography for this purpose. For example, the Doppler signal originates from circulating red cells, and M mode and two-dimensional echocardiography have great difficulty in detecting reflected ultrasonic energy from red cells in the normal person. Thus, one could conceivably inject substances about the same size or even smaller than red cells and expect to get a “contrast” Doppler signal. These molecules virtually will traverse the capillary bed and therefore have an advantage over micro-bubbles.

Contrast echocardiography during cardiac catheterization: Contrast echocardiography can also be used in an invasive fashion, such as with cardiac catheterization. Some echocardiographers are already using contrast echocardiography instead of selective cineangiography, especially in young infants in whom angiographic dye injections represent a significant hazard. A contrast injection in the root of the aorta or even directly into the coronary arteries may be a useful technique for visualizing myocardial perfusion. Thus, it is conceivable that selective contrast echocardiography could be a useful adjunct to coronary cineangiography for determining myocardial perfusion.

Imaging of Intracardiac Blood

Although M mode and two-dimensional echocardiography normally do not record echoes from the intracardiac blood there is evidence that stagnant or slowly moving blood may, in fact, produce a cloud of echoes within the cardiac chamber. Such a cloud of echoes has already been noted as an indirect sign of a dyskinetic segment of the left ventricle. In a few clinical examples a smoke-like pattern of intracavitary echoes has been noted in patients with marked left ventricular dysfunction. With instruments that have better signal to noise ratios and higher frequency transducers it is possible that the myocardial intracavitary blood may be visualized more often. The significance of this observation with regard to left ventricular function is unclear, but it might raise the possibility of assessing "regional intracavitary blood flow."

Tissue Variable Identification

Calcification: Echocardiography already does a fairly good job of identifying certain alterations in cardiac tissue. The fibrosis and calcification associated with valve stenosis is readily seen in routine echocardiographic studies. In earlier work it was demonstrated that echocardiography was a more sensitive tool in detecting calcified mitral valves than was cardiac fluoroscopy. These observations have been utilized for the detection of a calcified mitral annulus and more recently in the detection of atherosclerotic plaque within the coronary arteries.

Myocardial scar: Another clinical area in which echocardiography detects alterations in cardiac tissue is in the identification of myocardial scar. Scoured areas of the myocardium are more echo-intense and thinner than normal muscle. The echocardiographic detection of scar using the acoustic changes and alteration in wall thickness is probably more accurate than relying totally on wall motion.

There are other entities in which the echocardiographic appearance of myocardial tissue is altered. Several investigators have noted an unusual speckled appearance of the interventricular septum in patients with hypertrophic cardiomyopathy. An alteration in the myocardial echoes has also been noted in patients with amyloid heart disease. It is suspected that these
Accurate quantitative measurements: Because of the inherent spatial accuracy of two dimensional echocardiography one should anticipate an increasing number of quantitative measurements from the two dimensional examination. These measurements will be particularly pertinent to the examination of the left ventricle. Although M mode echocardiography has excellent axial resolution and has the advantage of displaying the recording in a convenient strip chart format, there are significant limitations to the M mode measurements. Because the echocardiographic window is not the same in all persons, the M mode dimensions of the left ventricle vary from one person to another. In some patients the standard M mode left ventricular measurement approximates the minor axis; in others, because of a low echocardiographic window, the echocardiographic measurement is closer to the major axis. Actually, in the adult patient it is frequently impossible to place the transducer high enough on the chest to obtain a true minor axis of the left ventricle. M mode measurements obtained with the aid of two dimensional echocardiography don’t correct this problem because such M mode recordings can only correspond to a raster line on the two dimensional display. Measurements taken directly from the two dimensional echocardiogram do not have this limitation. One can obtain any chord and a true minor or major axis on every individual irrespective of where the examination happens to be performed utilizing the spatially correct two dimensional examination. Admittedly, the two dimensional measurements would partially use lateral resolution, which is poorer than the axial resolution used with M mode measurements. However, the more accurate spatial orientation should outweigh the 1 or 2 mm difference between axial and lateral resolution.

Ventricular function quantitative measurements: As the basic advantages of quantitative two dimensional echocardiography become better appreciated and the convenience of making these measurements is improved, one can anticipate an increasing use of two dimensional echocardiography for quantitating left ventricular function. One should be able to measure more than merely volumes and ejection fraction. Measurements such as true circumferential shortening, functional infarct size or percent functioning muscle are certainly within the realm of possibility using quantitative two dimensional echocardiography. Because with two dimensional echocardiography one can more easily see the details of all areas of the left ventricle than is possible with the silhouettes obtained with contrast or nuclear angiography, measurements such as functional infarct size may be more accurate in the overall assessment of the ischemic left ventricle than data obtained in other currently available examinations.

Direct computer analysis: Most quantitation to date has utilized manual tracing of the desired echoes either on M mode or two dimensional echocardiograms. Considerable work is being done to use computers to recognize and analyze the desired echoes for measurements. 1,3 Although there are major problems, such as incomplete records or “echo dropout,” there is no reason to believe that they cannot be resolved. Even though the computer identification of cardiac echoes may be less accurate than the manual method, such an approach would certainly make quantitation much easier and more practical. Thus, direct computer analysis of echocardiographic images should probably be forthcoming in the not too distant future.

Stress Echocardiography

Exercise testing: There are increasing data indicating that one can use echocardiography to monitor cardiac changes with various forms of stress. The greatest interest has been trying to use echocardiography to assess the effect of exercise. 2,12 There are many technical difficulties with obtaining an adequate echocardiogram while the patient is undergoing physical exertion. However, advances in this area have already been made and further resolution of the technical difficulties can be anticipated. Most echocardiographic laboratories are currently using bicycle exercise, either in the supine or sitting position. Technically satisfactory recordings are apparently possible with this technique in approximately 30 to 75 percent of patients. More recently, there has been increasing interest in examining the patient immediately after rather than during exercise. 7 Myocardial ischemia produced with exercise frequently will last several minutes, especially if the patient is in a recumbent position. Thus, there is sufficient time for technically satisfactory echocardiograms to be obtained in the immediate postexercise period while the effects of ischemia are still present. Utilizing the post-exercise period one can obtain satisfactory echocardiograms in a high percentage of patients, possibly as high as 90 percent.

Other types of stress: Other forms of stress besides physical exercise 13-15, cold pressor stimulation 16 and various pharmacologic agents 17 have been used with echocardiography. These forms of stress introduce less technical difficulty in the echocardiographic examination. Unfortunately, they are not quite as physiologic as bicycle or treadmill exercise and frequently may not be sufficiently severe to produce ischemia. Irrespective of which type of stress ultimately proves to be the most practical, one can be reasonably certain that stress echocardiography will eventually become a routine part of echocardiographic examinations in most laboratories. 18

Contrast Echocardiography

Contrast echocardiography permits the echocardiographer to look at the blood pool in a fashion somewhat similar to that of contrast angiography or radionuclide angiography. With echocardiography one is not detecting iodinated liquid that absorbs X-rays or ionizing particles that give off radiation. With echocardiography the contrast substance is some particulate matter that reflects ultrasound. 17 The contrast substance that has been used clinically consists of microbubbles that occur with the injection of fluid into the intravascular system. 18 The microbubbles, probably those already suspended in the liquid, are introduced into a vessel. The length of time that these bubbles persist depends
abnormal echoes reflect the pathologic changes that occur in these patients.

Myocardial ischemia and infarction: Many investigators have been looking at the acoustic changes with myocardial ischemia or infarction. There are several possible techniques for detecting the acoustic changes that occur with ischemia and infarction. The laboratory data are quite convincing that the acoustic properties of ischemic or infarcted muscle are different from normal. It is quite possible that a clinically useful method will be devised for using echocardiography to identify types of tissue in the not too distant future.

Quantitative methods: Thus far, most of the observations using echocardiography for the analysis of tissue type have been qualitative in nature. There is work in developing a quantitative method for identifying acoustic changes associated with alterations in tissue properties. One hopes that with the increasing use of computer analysis of echocardiographic data subtle changes in acoustic properties can be detected that would not be noted in a qualitative examination. With the developments already accomplished, it is not difficult to predict that echocardiography should be able to aid significantly in the diagnosis of myocardial ischemia, cardiomyopathy or myocarditis.

Doppler Echocardiography

Commercial Doppler echocardiographic instruments have been available to clinical investigators for the past 4 to 5 years. As noted in the section describing the current uses of Doppler echocardiography, many problems still persist with this technique, and it has not had the impact that two-dimensional echocardiography has had. However, there are reasons to expect an expansion in the interest of this ultrasonic technique. One might anticipate two major areas in the development of Doppler echocardiography with regard to assessing cardiac function.

Quantitative measurements of blood flow: The first area is in quantitating the Doppler signal so as to obtain quantitative measurements of blood flow. Although there have been many attempts at using Doppler echocardiography for quantifying blood flow, there have been many problems that prevent this technique from becoming an important clinical tool. There have been new developments that should overcome some of the problems. Fast Fourier analysis of the Doppler signal is giving a more accurate velocity measurement. Measurement of blood acceleration now becomes feasible as a measure of left ventricular function. In addition, by coupling the Doppler echocardiograph with the two dimensional echocardiograph, the angle between the moving column of blood and the ultrasonic beam can now be assessed and the diameter of the vessel through which the blood is flowing can be measured. Combining the velocity, angle and diameter permits a quantitative measure of blood flow. Thus, the quantitative analysis of blood flow using Doppler echocardiography is a more likely possibility than it was in the past.

Imaging of blood flow within the heart: The other exciting area of Doppler echocardiography is in the imaging of blood flow within the heart. There have already been preliminary studies using multigated Doppler techniques that have produced recordings of blood flow within the heart. This Doppler imaging technique makes the prospect of gaining clinically useful information about blood flow patterns within the heart a real possibility. This development is just another example of how much of the future work in echocardiography will be centered on the intracardiac blood rather than the walls and valves, which have been the principal areas of interest in echocardiography to date.

Three Dimensional Echocardiography

Echocardiography has basically developed from M mode or single dimensional echocardiography to two dimensional echocardiography. The next logical step would be three dimensional echocardiography. There have already been many attempts at constructing three dimensional echocardiograms. Problems associated with this effort are certainly present, but not insurmountable. There are several techniques available for assessing the position and angle of the ultrasonic transducer, which is all that is necessary for the reconstruction of multiple two dimensional images into a three dimensional display. There are also several ways in which the reconstructed image can be displayed on a television screen or in some other manner. It is also conceivable that by a fairly elaborate transducer design one could even send out a three dimensional beam that could produce a real time three dimensional image of the heart. Such an effort would, of course, be far more complicated than merely reconstructing a two dimensional echocardiogram into a three dimensional image.

Irrespective of how a three dimensional echocardiogram is obtained, it theoretically should provide a more accurate spatial image of the heart and thus provide more accurate quantitative and qualitative information. Such a three dimensional display should improve on our ability to quantitate aneurysms, infarcts or residual myocardium. Three dimensional echocardiographic devices will undoubtedly be undergoing clinical investigation in the fairly near future.

Invasive Echocardiography

Substitute for contrast angiography: Although echocardiography is almost synonymous with noninvasive cardiology, there is no need to limit the echocardiogram to merely noninvasive applications. As noted in the discussion of contrast echocardiography, many physicians have used contrast echocardiography in the cardiac catheterization laboratory to obviate the need for selective cineangiography especially in pregnant women, patients with iodine allergies or patients in whom the osmotic load of the contrast agent would be hazardous. It may also be useful for studying myocardial perfusion with selective contrast injections in the root of the aorta or coronary arteries.

Esophageal echocardiography: Ultrasonic transducers have also been placed in an esophageal catheter. Esophageal echocardiography has been used both with M-mode and real-time sector scanning. Such
techniques obviously have some discomfort and disadvantages; however, some of these problems could be overcome with newer transducer designs. Esophageal echocardiography does provide an unobstructed view of the heart including the left ventricle.

Catheter ultrasonic transducer: It is also possible to place an ultrasonic transducer on the tip of a cardiac catheter. An older technique whereby a small Doppler transducer was placed at the tip of the catheter has already been reported. Studies with this technique demonstrated the ability to record the velocity of blood flow at the origin of the coronary arteries. It would also be possible to place a very high frequency transducer within a catheter so as to analyze the myocardium. For example, a 100 megahertz transducer at the tip of a catheter might give an excellent histologic diagnosis when placed against a myocardial wall. Such a high frequency ultrasonic examination might provide information equivalent to that obtained by biopsy.

Application during cardiac surgery: Yet another invasive approach to echocardiography would be the use of the ultrasonic examination at the time of cardiac surgery. Some investigators have already used echocardiography to evaluate the mitral valve after mitral commissurotomy. With the use of more advanced instruments one can also use an intraoperative approach for analyzing the coronary arteries prior to the insertion of bypass grafts. One might also use such a technique to further explore cardiac function at the time of surgery while the chest is open.

Summary

It is almost impossible to anticipate all of the potential technological and clinical advances in echocardiography; however, the development of new clinical techniques, new instrumentation, stress echocardiography, contrast agents, the ability to identify tissue types, improved ultrasonic information from the circulating blood, Doppler echocardiography, three dimensional echocardiography, the ability to obtain ultrasonic information using catheters or surgical exploration and especially improved techniques for quantitating echocardiographic data, make the potential usefulness of echocardiography in assessing cardiac function, and specifically left ventricular function, very exciting. We should be able to use the advances in echocardiography to improve our understanding of normal cardiac function and pathophysiology, as well as to enhance our ability to make precise diagnoses.

References


Nuclear Cardiology: Introduction

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Nuclear cardiologic techniques have been used widely since 1975 in the practice of noninvasive clinical cardiology. There are three classes of procedures that can be performed: (1) The radionuclide ventriculogram measures the size and function of the cardiac chambers at rest and with interventions. (2) Exercise myocardial perfusion imaging or exercise radionuclide ventriculography may detect otherwise latent coronary artery disease, particularly when patients' symptoms or the results of other tests are nondiagnostic. (3) Myocardial infarct-avid tracers may supplement standard tests in defining acute myocardial infarction. In addition to aiding cardiac diagnosis, radionuclide ventriculography and infarct avid scintigraphy provide important prognostic information; ventriculography may also be used in directing and assessing results of therapy. Because these techniques are relatively new, their best use is dictated not only by the clinical question to be answered, but also by the depth and breadth of experience of the laboratory performing the study, as well as the familiarity of the practicing clinician with a given test. One aim of this Conference is the familiarization with and education about what these procedures can and cannot do. Additionally, the clinical certainty an individual physician requires in decision making is highly relevant to any test's utility. For example, for the physician requiring coronary angiography as the standard for diagnosis in all patients with suspected ischemic heart disease, noninvasive testing would be relatively unproductive. However, if some probability of disease or its absence without arteriographic confirmation suffices, a procedure such as noninvasive radionuclide exercise testing, for example, can assist in decision making about the need for coronary angiography.

It is clear that nuclear cardiology will continue to grow and change rapidly. Improved radiopharmaceuticals, tomographic or three dimensional imaging, and more direct study of cardiac metabolism are in the offing and described in the final article of this series, “The Future of Nuclear Cardiology.” The methodology and its application as defined in the initial three articles is meant to reflect the current state of the art - that is, the techniques and measurements that should be available and of high quality in most nuclear cardiology laboratories.

Radionuclide Angiography

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After intravenous administration of a radionuclide, cardiac chamber size and function can be measured by recording the amount and distribution of the radiolabel in the heart throughout the cardiac cycle. Once the radionuclide mixes with the flowing blood, changes in the number of events recorded from a cardiac chamber or great vessel during the cardiac cycle are proportional to the changes in blood volume in that area. As a result, global chamber volume and related measurements such as ejection fraction, rates of emptying and filling, and regional variables such as regional wall motion or regional ejection fraction can be readily calculated. In addition, the distribution of tracer in the lung as recorded during routine cardiac imaging provides added information about left heart function.

Nuclear techniques are particularly useful in measuring the most useful single variable of ventricular function, ejection fraction. The proportionality of counts and volume largely eliminates assumptions about the geometry of the ventricle used with contrast angiographic and echocardiographic ejection fraction calculations. This is especially useful in the setting of...
regional contraction abnormalities\textsuperscript{5,6} and for the right ventricle where geometric assumptions are difficult. Furthermore, because several measurements can be performed at a specific examination, cardiac function can be determined both before and after an intervention such as exercise or pharmacologic stress to define both basal cardiac function and the impact of the intervention on function, a measure of reserve capacity.\textsuperscript{1,11}

Techniques

There are two methods for recording nuclear images of cardiac function: (1) first transit, where only the initial passage of the radionuclide through the heart and great vessels is recorded; and (2) equilibrium, where a minimum of 100 cardiac cycles must be recorded, usually with physiologic gating, to provide information about cardiac function. The two methods differ in several areas: (1) number of cycles sampled, (2) number of measurements that can be made after a single injection of radionuclide, (3) the type of radiopharmaceutical employed, and (4) the time required to record a measurement of ventricular function.

First Transit Method

The first transit approach requires a separate injection of radiopharmaceutical for each determination. To record meaningful data in the 20 to 40 ms intervals required to measure cardiac function at stress or rest, a dose of at least 8 to 10 milliliter (mCl)/measurement must be used. The radiopharmaceuticals used for the first transit measurement of ventricular function should clear from the vasculature after each determination to permit the next measurement of the series to be made with a minimal background (thereby providing the greatest precision for each determination). The agents commonly used are technetium-99m-labeled sulfur colloid (clearly the reticuloendothelial system, primarily in liver and spleen), technetium-99m-labeled diethylthiobenzylcadetionate (clearly by glomerular filtration in the kidneys), and technetium-99m peroxidase or red blood cells. The requirement for a separate injection for each measurement places a practical limit on three measurements of cardiac function that can be made at any one examination (when technetium-99m is employed as the radiopharmaceutical).\textsuperscript{4} The radiation burden from these injections, even if different radiopharmaceuticals are used for each injection, usually results in a dose of up to 5 rads to an organ from the three injections. As a result of these constraints, the first transit method is commonly used for basal measurements in several views, or for a single measurement of cardiac function at rest and a single measurement at the peak of exercise.

Ventricular volumes and ejection fraction: The total time required to record a first transit study (after placement of the intravenous line and positioning the patient in front of the scintillation camera) is less than 1 minute. Ejection fraction data are obtained from the recorded data by placing a region of interest over the area of the left ventricle and defining the changes in counts in the chamber versus time (after background correction) during the cardiac cycle. The difference between a peak in counts (end-diastole) and a valley (end-systole) provides the stroke volume in count units, which allows calculation of the ejection fraction. Because any one cardiac cycle has relatively few counts, it is common practice to add data from several cycles together. To assist with this addition, the electrocardiogram may be recorded in conjunction with the nuclear data to provide a precise marker of the beginning of each cardiac cycle. Because the injected activity enters the cardiac chambers and lungs sequentially, both right and left ventricular ejection fraction and pulmonary transit time can be readily calculated. Similarly, the same geometric approach used in contrast angiography (that is, defining the edges of the ventricle at end-diastole and end-systole, and measuring the enclosed areas and lengths) can be used to calculate left ventricular volumes.

Equilibrium Technique

The equilibrium approach records data gated (synchronized) with the cardiac cycle from a minimum of 100 up to a practical maximum of 1,000 beats for analysis. This approach can record valid data if the patient is in a steady state during the time of data collection. This is usually accomplished by labeling the patient's red cells in vivo and recording data in 30 to 50 ms frames (matrices) for each cardiac cycle, synchronized by the patient's electrocardiogram to achieve additional data from each successive cycle in phase. The calculation of ejection fraction is performed by defining the change in counts in the left ventricle from end-diastole to end-systole as described for the first transit approach. As few as 100 cycles will provide a sufficient number of counts to permit the calculation of ejection fraction to be made with less than a 10 percent interobserver variation.\textsuperscript{15} The equilibrium technique of data collection permits data to be recorded for several hours after tracer injection; measurements can be made at rest, during stress or after a pharmacologic intervention.

Choice of technique: Although the first transit and equilibrium techniques are different, they are both valid approaches for the subjective and quantitative determination of both right and left ventricular ejection fractions, ventricular volumes and ejection rates when compared with the results obtained at cardiac catheterization. Both techniques can readily define the changes in left ventricular ejection fraction from rest to exercise. No systematic difference in the sensitivity or specificity of the data for the detection of compromised ventricular function or reserve has been observed. As a result, either technique may be employed to measure ventricular function.

Clinical Applications

The general clinical situations in which determination of ventricular function by nuclear techniques is useful in adult patients can be divided into: (1) Definition of
the nature and severity of clinically suspected ventricular dysfunction (for example, the differentiation of diffuse hypokinesis from a focal ventricular aneurysm). (2) Evaluation of the cause of a systemic embolus. (3) Determination of right or left ventricular functional reserve in patients with suspected or known coronary, valve or myopathic disease. (4) Serial determination of the impact of a therapeutic intervention. The following sections review these applications in several cardiac disorders.

**Coronary Artery Disease: Acute Unstable**

**Right versus left ventricular infarction:** In patients with acute unstable coronary artery disease (acute myocardial infarction or unstable angina), the nuclear measurements of ventricular function can be readily performed at the bedside to (1) differentiate right from left ventricular impairment; (2) define global ventricular function; (3) determine the location and extent of a regional wall motion abnormality; and (4) evaluate the complications of a myocardial infarct such as ventricular septal defect, aneurysm or intracardiac shunts. Differentiation of predominant right ventricular infarction may be of therapeutic importance in the setting of cardiogenic shock. Although right ventricular infarction may be suspected clinically, the diagnosis is difficult to make, but is usually apparent from the nuclear image.

**Defining global and regional left ventricular function:** Because prognosis after acute myocardial infarction is largely a reflection of global left ventricular function as well as the presence of additional coronary artery disease remote from the site of infarction, determination of ejection fraction and the site and extent of regional wall motion abnormalities can assist in formulating a plan of management. Assessment of regional wall motion is important in understanding the mechanism of heart failure after myocardial infarction—whether due to a localized abnormality such as an aneurysm or a more diffuse process. This differentiation is often not apparent clinically, but has important implications for management. For example, in a patient with a suspected aneurysm the differentiation of true aneurysm from pseudoaneurysm is important. A true aneurysm may be treated with resection in a nonurgent manner, whereas a pseudoaneurysm should be operated on more expeditiously. A diffuse wall motion abnormality that has adequate thallium-201 redistribution and suitable coronary anatomy may be treated with coronary bypass surgery, while a diffuse wall motion abnormality with evidence of scar on the thallium scan may reflect myocardium that is beyond surgical help, and therefore catheterization may not be indicated.

**Defining complications of myocardial infarction:** When a postmyocardial infarction ventricular septal defect is suspected clinically, detection and quantification of the left to right shunt may be performed by the measurement of recirculation of tracer in the lungs. These shunt detection measurements are capable of reliably detecting pulmonary/systemic flow ratios of 1.3:1. Detection of intracardiac thrombus at the time of acute infarction would generally indicate the need for anticoagulation, although the accuracy of the radionuclide angigram in the detection of thrombus is not yet well defined (see later).

**Identifying multivessel coronary artery disease:** The identification of coronary artery stenoses in arteries distant from a known infarct has had limited study to date. Exercise angiography in the post myocardial infarction period might theoretically identify patients with two or three vessel disease by further worsening of left ventricular function with exercise, whereas those with isolated infarction and otherwise normal coronary arteries might show improvement in ventricular function with exercise. Pending further study, electocardiographic exercise testing alone or in combination with thallium-201 imaging appears at present the best noninvasive means of identifying coronary disease at a site remote from infarction.

**Coronary Artery Disease: Chronic**

**Detection of occult coronary disease:** The concept of using the nuclear measurements of ventricular function at rest and stress to detect occult coronary artery disease grew from the initial promising observations of a failure of ejection fraction to increase by more than 5 percent from rest to exercise in patients with disease, while in all normal subjects ejection fraction increased by more than 5 percent. The nuclear measurement of changes in ventricular function from rest to exercise was suggested to be not only highly sensitive but also specific. The physiologic basis for the detection of occult coronary disease with this technique was that areas of underperfused myocardium could not contract effectively at stress and would therefore cause either a detectable wall motion abnormality or a decrease in ejection fraction. This acute decrease in ventricular function also appeared to produce changes in the pulmonary blood volume from rest to exercise. Acute increases in pulmonary blood volume during exercise were observed in patients with coronary artery disease, even in those who did not have a decrease in ejection fraction during exercise. This increase has been shown to correlate with an acute change in pulmonary capillary wedge pressure during exercise. However, all these changes may occur with any heart disease because they reflect an inappropriate response to stress (that is, an increase in end-diastolic volume over stroke volume and an increase in pulmonary capillary wedge pressure). It has been shown with aortic regurgitation and with cardiomyopathy (not due to coronary artery disease).

**Sensitivity and specificity of the method:** Clearly, then, the major limitation of exercise radionuclide measurements of ventricular function is that it is not a specific procedure for the detection of coronary artery disease, especially when a large, unselected group of patients are subjected to the procedure. Furthermore, the effect that common cardiac therapy such as administration of propranolol and the level of fitness have on the response to be expected in normal subjects has not been fully defined. A recent review by Okada et al. suggests that the resting and stress radionuclide ven-
tricular function determinations are more sensitive than the stress electrocardiogram in detecting occult coronary disease but, as expected, the results are not specific. Often, patients with other cardiac diseases that can alter cardiac functional reserve can be identified on the basis of history or physical examination and therefore do not present a problem in clinical application of the procedure. However, in patients in whom this differentiation is not made as readily the procedure’s lack of specificity can be a problem. If one is seeking a specific diagnosis of ischemic heart disease, then a thallium scan with injection at stress and immediate imaging followed by a redistribution study, as described in the myocardial imaging section, is indicated. However, if a patient can exercise adequately without cardiac therapy and has a normal ejection fraction and wall motion response, then the likelihood of coronary artery disease is small and the likelihood of left main or three vessel coronary artery disease is virtually nonexistent. One important disadvantage of supine equilibrium radionuclide studies is the absence of hypotension with exercise in patients with severe disease. Recent studies suggest that sitting bicycle studies are feasible, and may be preferable for exercise studies.

Evaluation of Unexplained Dyspnea

Dyspnea is a common complaint. At times the etiology is obvious and at other times it is not. Often it is ascribed to heart failure and digitalis and diuretic therapy is empirically begun. Radionuclide angiography is useful in clarifying the etiology of such a “congestive heart failure equivalent” (an enlarged heart size on chest radiograph, dyspnea on exertion of uncertain cause, or peripheral edema of uncertain etiology). A noninvasive approach is desirable early in the management, when catheterization would not be appropriate.

The differential diagnosis includes: pulmonary disease, pericardial disease, valve disease, restrictive cardiomyopathy, hypertrrophic cardiomyopathy in addition to a congestive cardiomyopathy (reduced ejection fraction). These disorders have characteristic scan patterns. For example, patients with obstructive airways disease and dyspnea have a dilated right heart with a small left ventricle, whereas patients with pulmonary venous congestion secondary to left ventricular failure also have a dilated left ventricle and left atrium. The precise definition of right and left ventricular function helps to define the pathophysiology of the dyspnea and thus direct appropriate therapy. Although ultrasonic methods have superior resolution and can visualize valves and pericardial effusion, the nuclear technique is almost always technically satisfactory in defining the cardiac chambers. Among patients with chronic airways disease, who are often difficult to image with ultrasound, nuclear studies may be particularly useful.

Valvular Heart Disease

The role of radionuclide scans in valve disease is uncertain. The presence and severity of the valve disease can often be determined clinically without scans. Nuclear procedures are also not necessary when surgery is obviously indicated and the patient is scheduled for catheterization. Furthermore, the echocardiogram is generally the procedure of first choice because of its resolution. However, nuclear methods may be useful in (1) determining the degree to which heart failure is due to myocardial problems known to be associated with valve disease. This is particularly important in postoperative patients; (2) substituting for left ventricular angiography in a sick patient; (3) evaluating right ventricular function in mitral valve disease; and (4) prognostic determination based on ventricular performance.

The most widespread application of nuclear methods has been in determining the appropriate time for surgery in patients with known aortic regurgitation. Borger et al. suggested that in patients with aortic regurgitation an “abnormal” ejection fraction with stress may identify persons with a worse prognosis after aortic valve replacement (due to irreversible depression in ventricular function). The evidence to substantiate this concept fully is not available at this time. Furthermore, this approach may be limited by other factors that affect ejection fractions such as changing preload and afterload. Although the ability to assess cardiac function during exercise may prove to enhance the early detection of left ventricular dysfunction, results at present are preliminary and should be studied in combination with a careful clinical evaluation. In patients with proved or suspected regional contraction abnormalities, the radionuclide technique may provide a more precise measure of global left ventricular function than that obtained with echocardiography.

Evaluation of Patients With Systemic Embolism

In patients who have an unexplained systemic embolus, investigation is usually directed toward a possible cardiac source. The primary causes for an embolus arising from the heart include left atrial myxoma, left ventricular aneurysm with mural thrombus from recent infarction, and atrial enlargement with mural thrombus. Both the nuclear procedures and the two-dimensional echocardiogram can be helpful in assessing each of these conditions. However, because the relative sensitivity of each method for detecting lesions in the same patients has not been evaluated, it is difficult to define which procedure should be used in the initial evaluation of a patient with systemic embolization.

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Of notice...
Myocardial Perfusion Imaging

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This discussion will consider the use of myocardial perfusion imaging in the setting of chronic coronary artery disease, that is, not at the time of acute myocardial infarction. The aim of such imaging is straightforward—namely, the noninvasive measurement of regional coronary blood flow or perfusion. Because that theoretical aim has been incompletely realized, this review will discuss current clinical uses and limitations of myocardial perfusion imaging based on available experimental and clinical data. Position emitting radionuclides, although offering great research and possible clinical applications, will not be considered. The extraluminal requirement for most position radiochemicals makes their widespread availability uncertain. This analysis will concentrate on the current gamma emitting radionuclide of choice, the potassium analog thallium-201 (201Tl). It is intended that these comments will be similarly applicable if 203Tl should be replaced with newer perfusion agents possessing more favorable imaging characteristics.

Experimental Data

Myocardial thallium distribution as a reflection of myocardial blood flow: At low or tracer concentrations as are employed in clinical nuclear medicine. 201Tl is taken up by cells in a fashion similar to potassium via the sodium-potassium adenosine triphosphatase pump. After intravenous injection, 88 percent of what isotope is extracted by the heart is taken up during the first pass or first circulation through the
should then reflect regional coronary flow. Isotope distribution is detected and recorded externally by imaging with a gamma scintillation camera. In patients with frank ischemia at rest, such as those with 100 percent coronary occlusion secondary to coronary arterial spasm, the acute reduction of blood flow is demonstrable in an image from an injection at rest.5

In clinical practice, 201TI imaging can be simply incorporated into conventional upright bicycle or treadmill testing. Before exercise is begun, an intravenous line is placed, and the patient is asked to identify a point 30 to 60 seconds before exercise termination, at which time the isotope is injected. Imaging then begins 5 to 10 minutes after exercise. Thus, if diagnostic testing is planned, the addition of 201TI exercise perfusion imaging does not require a separate test. Pharmacologic means of increasing myocardial blood flow, such as intravenous dipyridamole, have been employed with 201TI imaging as an alternative to exercise.65 Pharmacologic “stress” has inherent appeal as a more standardized and universally applicable form of testing; isotope extraction fraction may be relatively lower and net 201TI deposition may not parallel coronary flow as closely as that after exercise.

**Myocardial thallium redistribution:** Although the initial distribution of 201TI reflects regional flow, absolute quantitation of this distribution, and thus regional flow, has not been possible. Following its initial distribution, myocardial 201TI deposition is dynamic. After an injection of 201TI during exercise there is both an immediate and prolonged period of so-called “redistribution.” As coronary perfusion returns to baseline levels after stress testing, ongoing myocardial washin and washout of 201TI continue to occur, and over time a new equilibrium reflecting basal flow is reached. Delayed or late imaging, typically performed 3 to 6 hours after isotope injection, provides additional information on the state of basal perfusion.6 However, this redistribution phenomenon limits stress imaging in several respects. Because a clinical observation period after exercise testing is required, isotope redistribution may start before imaging begins and continue as multiple images are acquired. Some perfusion abnormalities may be masked if imaging is delayed more than a few minutes after stress, or they may change during the course of imaging. Additionally, the rapidity and magnitude of redistribution depend on the blood concentration of 201TI, when blood levels of isotope are relatively high, as they might be if the period of exercise maintained after 201TI injection is brief, the rapidity and extent of redistribution is relatively greater.69

**Limitations:** Current gamma camera resolution as well as the imaging characteristics of 201TI also limit perfusion imaging. Thin lines of 201TI activity spaced 1 cm apart are just resolvable in a simulated clinical imaging situation.11 Because of its low energy, 201TI is substantially absorbed and scattered by soft tissue or contiguous myocardium as the gamma camera and the region of interest. Mueller et al.12 employing a canine model, showed that 1 to 6 g ischemic...
ventricular segments with flow reductions of 40 to 60 percent were inconsistently detected by qualitative or visual image analysis, whereas larger perfusion defects were regularly seen. Additionally, the gamma camera employs multiple views or two-dimensional images to assess the three-dimensional distribution of isotope within the body. Because some isotope is taken up by nonmyocardial structures overlying the heart, and because the region of a myocardial perfusion defect may be superimposed over a region of normal myocardium, planar or standard imaging cannot be quantitative in an absolute sense. Tomographic approaches to imaging may partially resolve this problem.13,14

In sum, the initial myocardial distribution of 201TI parallels regional coronary perfusion. Because of overlapping of structures, limited resolution of the gamma camera, and some uncertainties in the timing of isotope injection and the subsequent dynamic state of myocardial isotope wash-in and washout, only semiquantitative or semiquantitative indexes of perfusion are obtained from external gamma camera images.

Clinical Applications

Given the experimental and theoretical limitations inherent in 201TI perfusion imaging, certain clinical uses have evolved. Specifically, 201TI perfusion imaging may help answer the following clinical questions: (1) Among patients with possible coronary artery disease, such as patients with chest pain syndromes, is coronary artery disease present or absent? (2) Among patients with known coronary artery disease, such as those in the period after a myocardial infarction, what is the extent of disease?

Diagnosis of Coronary Artery Disease

Sensitivity and specificity of testing: In addressing the first of these questions, 1 TI perfusion imaging has been extensively compared with exercise electrocardiographic testing in patients with a chest pain syndrome and suspected coronary artery disease. In general, these studies have shown moderate and statistically significant improvement in the detection of disease when present (sensitivity of testing) and exclusion of disease when absent (specificity of testing) compared with those of exercise electrocardiography.15–20 In a review summarizing data on 1,817 patients in 24 published series,21 overall sensitivity in the detection of exercise-induced perfusion defects by 201TI was 82 percent and specificity 91 percent. For the exercise electrocardiogram the corresponding sensitivity was 60 percent and specificity 81 percent. Both the sensitivity and specificity were significantly higher for 201TI than for exercise S-T depression (p < 0.0001 and p < 0.05, respectively).

The higher sensitivity of 201TI imaging over that of exercise electrocardiography derives in part from that subset of patients whose exercise tests are nondiagnostic with either: (1) an abnormal resting electrocardiogram in which ischemic S-T segment changes cannot be defined, or (2) failure to achieve 85 percent of predicted heart rate when no ischemic S-T segment changes are noted. In a multicenter study,15 for example, 13 of 16 patients with coronary artery disease and left bundle branch block or digitalis effect in the baseline electrocardiogram were identified with 201TI exercise testing, whereas ischemic S-T segment changes were uninterpretable. In four other series,16,22 a total of 168 patients with nondiagnostic exercise tests were reported. In each, the sensitivity and specificity of 201TI imaging in this subset were not significantly different from those of patients with exercise tests and diagnostic end points. Sensitivity ranged from 70 to 100 percent and specificity from 69 to 100 percent. Thus, among patients with an exercise test that is not diagnostic, the 201TI exercise study retains its diagnostic accuracy and is uniquely helpful.

Application of Bayes' theorem of conditional probability: Generally, most of the reported series comparing exercise testing and 201TI imaging have included large numbers of patients with typical exertional angina. In this clinical subset, likelihood of disease is sufficiently high that any diagnostic test that is not 100 percent sensitive and specific will add relatively little certainty to the diagnosis. Bayes' theorem of conditional probability shows that the positive predictive accuracy of a test (the ratio of true positive/true positive and false positive results), and generally the most useful clinical index, is highly dependent on the underlying or pretest probability of disease in a given patient population. Assuming that the average sensitivity for 201TI stress imaging is 80 percent and specificity 90 percent, and considering a hypothetical population of 1,000 patients with a low disease prevalence of 5 percent, 40 of the 50 patients with disease would have a truly positive 201TI study (sensitivity X number of patients with disease, or 0.80 X 50 patients). Of the remaining 950 disease-free patients, 95 would have a falsely positive test (specificity 0.90 percent or misidentification of 10 percent of patients without disease). Overall then, only 40 of the total 135 positive TI studies or 30 percent of the positive studies would correctly identify disease (positive predictive accuracy = 40 true positive results/40 true positive + 95 false positive results = 40/135 or 30 percent). In a second example of moderate disease prevalence of 50 percent in 1,000 patients, 400 of the 500 patients with disease would be detected by imaging, while 50 of those without disease would have a false positive result. Thus, 400/450 or 89 percent— that is, the vast majority of all positive studies— would correctly predict disease. A negative test would similarly reduce the probability of disease to 18 percent.

It is in this mid range of disease prevalence that a positive (or negative) test optimizes the difference between the pre- and post-test probability of ascertaining disease. At very high disease prevalences, such as those seen in middle-aged men with typical angina pectoris, 201TI imaging can add relatively little in the diagnosis of disease per se, because about 80 to 90 percent of such patients can be identified as having disease on the basis of symptoms alone.23,24
Studies in patients with low prevalence of coronary disease: The application of Bayes' theorem requires that the sensitivity and specificity of the involved tests be uniform at any disease prevalence. Although early studies with $^{201}$Tl were taken from high prevalence patient samples, four studies have now demonstrated similar specificities and sensitivities among patients in the low to mid range prevalence of disease (disease prevalence ranging from 15 to 60 percent). That is, even among such subsets as air force pilots with asymptomatic exercise S-T depression and a prevalence of 15 percent, the sensitivity and specificity of $^{201}$Tl testing are preserved. A judicious application of Bayes' theorem to optimize clinical decision making then requires clinical pretest assessment of the probability of disease. Recent clinical-pathologic and epidemiologic studies have accurately described the disease prevalence in clinical subsets from an analysis of conventional risk factors as well as patient age, sex and the presence or absence of typical anginal chest pain. For example, among men over the age of 40 with typical angina, the likelihood of coronary artery disease is greater than 80 percent based on history alone, and further testing can increase this likelihood only slightly. On the other hand, among women under the age of 50, even with typical angina, the likelihood of disease is 70 percent or less, and $^{201}$Tl imaging would be of relatively more value. Among both men and women with atypical chest pain, the prevalence of disease ranges from 20 to 60 percent, depending on age and other risk factors, and it is particularly in such a subset of patients that $^{201}$Tl imaging would most optimally separate patients with disease from those without. This was illustrated earlier in the example showing a 50 percent disease prevalence and is shown graphically in Figure 2.

Among asymptomatic men and women, the prevalence of coronary artery disease is relatively low throughout all age ranges and, in general, exercise thallium imaging would be of much less value. However, additional stratification based on risk factor analysis can identify patient subsets with a pretest probability of disease as high as 20 percent, a population in which imaging would be of some additional value. Similarly, the prior identification of exercise S-T depression in asymptomatic patients further categorizes them into a higher risk subset in which thallium stress testing has clearly been shown to be helpful. In summary, $^{201}$Tl imaging, when employed to determine whether coronary artery disease is present or absent, adds the most diagnostic information in the following broad categories: (1) patients in whom the pretest probability of disease, based on clinical information, is intermediate or moderate, and (2) patients in whom the exercise electrocardiographic response to exercise is nondiagnostic.

**Diagnosis of One, Two or Three Vessel Coronary Disease**

Because mortality from coronary artery disease is associated directly with the magnitude and extent of disease, a related question that diagnostic imaging might ask is, "How much disease is present?" To date, thallium exercise imaging has been less helpful in this regard than in the diagnosis of disease per se. In the study of Rigo et al., the extent of disease identified for individual vessels was 63 percent for the left anterior descending coronary artery, 50 percent for the right coronary artery and 21 percent for the left circumflex coronary artery. Similarly, Lamas detected disease of the left anterior descending coronary artery in 88 percent of cases, the right coronary artery in 63 percent of cases and the left circumflex coronary artery in 48 percent of cases. The data of Massie et al. are similar. Additionally, in each of these series, high grade stenoses of 80 to 100 percent were more commonly detected than were stenoses of lesser magnitude. Dash et al. in a small series of patients with left main coronary disease and a larger series with three vessel coronary artery disease, showed that a pattern suggestive of extensive disease, that is, either left main or three vessel disease, was identifiable in only 43 percent. Similarly, Leppo et al. studied a group of 30 patients with three vessel
coronary disease and exercise electrocardiographic signs of ischemia and showed that only two thirds of this subset had perfusion abnormalities.

Given current practice with planar imaging with or without computer processing, it seems reasonable to conclude that, in general, myocardial perfusion imaging does not fully define the number of vessels diseased. Recent studies employing semiquantitative, computerized measurements of $\text{F}^{13}\text{N}$ washout at two or three points in the 4 to 6 hours after injection suggest that the accuracy of detection of individual stenotic arteries will be improved; however, this remains to be widely confirmed.

**Identification of Diseased Vessels Distant from Regions of Infarction**

A question closely related to the identification of individual coronary arterial stenoses in patients with suspected disease is the following: "In a patient with known coronary artery disease manifested by myocardial infarction, can imaging detect disease of other vessels distant from the infarction?" Of asymptomatic patients with acute myocardial infarction, more than half have multivessel disease. Although the presence of coronary artery disease is known in this group, $\text{F}^{13}\text{N}$ imaging has been shown to be useful in identifying those with two or three vessel disease. Turner et al. employed submaximal exercise imaging 3 weeks after acute infarction in 32 patients, 90% of whom were asymptomatic. Among those with jeopardized myocardium, defined as a 70% stenosis distant from the infarction, $\text{F}^{13}\text{N}$ imaging detected 67% whereas 62% had exercise S'T depression. Combined, the two tests detected 83% of such patients. In a similar study, Dunn et al. studied patients with prior transient myocardial infarction at an average of 30 months after infarction. A reversible $\text{F}^{13}\text{N}$ exercise perfusion defect distant from the infarction was present in 85% of patients with multivessel disease and in only 12% of those with single vessel disease. Although exercise S'T depression identified 80% of patients with multivessel disease in the study of Dunn et al., it was nonspecific and was seen in 44% of those with single vessel disease. Thus, in these early series, exercise $\text{F}^{13}\text{N}$ imaging appears complementary to exercise electrocardiography in identifying multivessel disease in patients with prior myocardial infarction.

**Other Uses**

**Coronary bypass graft patency:** Thallium-201 exercise imaging has been studied in patients after coronary bypass surgery. In this subset of patients the underlying coronary anatomy was defined before surgery, and the location of grafts is known; postoperative exercise imaging has predicted graft patency reasonably well. For example, in a patient with isolated left anterior descending coronary artery disease and a single graft to that vessel, the presence of a postoperative exercise perfusion defect in that region would be expected to predict graft occlusion or stenosis. In general, among several reported series, exercise perfusion defects have predicted graft occlusion, stenosis or sites of ungrafted native disease. Additionally, the demonstration that a preoperatively identified perfusion defect resolved after surgery has similarly predicted graft patency. 12, 13

**Ischemia versus infarction:** Other occasional uses of $\text{F}^{13}\text{N}$ imaging include the differentiation of perinfarctional ischemia from infarction alone in postmyocardial infarction patients manifesting S'T segment elevation on exercise testing. The presence of exercise perfusion defects has also been noted to infer hemodynamic significance to stenoses of questionable angiographic importance, although direct validation is lacking.

**Cost effectiveness:** Extensive study of the impact of nuclear medicine procedures on patient management or cost effectiveness has yet to be performed. In the only such study available, Goldman et al. employed two independent reviewers to address such questions. Among the 48 patients with clinically ordered exercise $\text{F}^ {13} \text{N}$ images, these reviewers believed that in 11 (23 percent) the studies had a direct impact on patient management and that, by eliminating the need for cardiac catheterization in some patients, resulted in a net economic saving.

**Summary**

Thallium-201 exercise imaging may be of clinical value generally as a supplement to the exercise electrocardiogram. It is particularly useful when the exercise electrocardiogram cannot be interpreted because of electrocardiographic abnormalities at rest or failure to achieve a diagnostic end point. In addressing the question, "Is coronary artery disease present or absent?" imaging is most useful in patient subsets in which clinical information predicts a moderate or intermediate likelihood of disease. Adult men with atypical chest pain or women less than 50 years old with typical angina are examples of such groups. Exercise imaging adds little diagnostic information in the study of men with typical angina, because their likelihood of disease is very high based on the history alone. Similarly, exercise imaging adds little in patients with a low likelihood of disease, such as asymptomatic men or women without risk factors. However, exercise imaging is helpful among asymptomatic patients previously shown to have exercise S'T depression because disease prevalence in this subset is moderate.

In answer to the question, "How much disease is present?" exercise imaging does not now correctly identify all diseased vessels and cannot be used to categorize patients as having one, two or three vessel disease. Among patients with prior myocardial infarction, exercise imaging improves the utility of exercise electrocardiography in distinguishing multiple from single vessel disease. Exercise imaging may also help assess bypass graft patency after coronary bypass surgery.
References

40. Turner JD, Schwartz KN, Logan JR, et al. Detection of residual jeopardized myocardium 3 weeks after myocardial infarction by exercise testing with thallium-201 myocardial scintigraphy. Cir-
Myocardial Infarct Imaging

Myocardial scintigraphy provides a map of regional function, and therefore has potential clinical and research application in patients with acute infarction. When performed with technetium-99m Tc pyrophosphate as the tracer, myocardial scintigraphy detects the presence and extent of myocardial necrosis. Alternatively, myocardial scintigraphy with thallium-201 provides a regional map of myocardial perfusion.

Infarct-Avid Scintigraphy

Infarct avid scintigraphy is based on the principle that the radiopharmaceutical will sequester within the acutely damaged myocardium (Fig. 1). The initial successful application of infarct avid scintigraphy with 99mTc-tetracycline in human subjects was followed rapidly by the development of other radiopharmaceuticals, the most promising of which was 99mTc-pyrophosphate. At present, 99mTc-pyrophosphate is still the radionuclide of choice for imaging acute myocardial infarction in human beings.

Pharmacokinetics: Uptake of pyrophosphate by the myocardium is dependent on (1) acute necrosis, (2) time after onset of symptoms, (3) blood flow, and (4) the calcium concentration within the myocardium. The 99mTc-pyrophosphate concentration appears to result from selective adsorption of the tracer on various forms of tissue calcium stores, including amorphous calcium phosphate, crystalline hydroxyapatite and calcium complexes within myofibrils and other macromolecules. While the uptake of 99mTc-pyrophosphate is directly related to the degree of tissue damaged, the pharmacological must get to the damaged tissue to be extracted; consequently, uptake is inversely related to the extent of the reduction in blood flow. After acute coronary occlusion, increased concentrations of 99mTc-pyrophosphate are found in regions with only minimal reduction in blood flow. The highest concentration ratios between damaged and normal myocardium occur when local blood flow is 20 to 40 percent of normal. As flow is reduced further, the concentration ratio begins to fall until, in regions of minimal flow, 99mTc-pyrophosphate concentration may be normal.

Accuracy of the Test

The value of infarct-avid scintigraphy depends on several factors: (1) the accuracy with which acute infarction can be detected, (2) the timing between onset of symptoms and optimal concentration of the radiotracer within the necrotic tissue, (3) the accuracy with which acute infarction can be differentiated from old infarction and scar tissue, and (4) the prognostic value of the scintigraphic images.

Accuracy with which acute infarction can be detected: Initial efforts to determine the sensitivity of acute infarct scintigraphy overestimated its value because the study populations did not correspond to the patient group undergoing this examination in the clinical setting. In most series, patients were studied consecutively as they appeared in the coronary care unit. As acute infarct scintigraphy came into clinical practice, however, it was primarily for diagnosing acute infarction in patients whose condition was a clinical entity, usually suspected nontransmural infarction. As a result, the sensitivity for the detection of acute myocardial infarction, based on 24 studies with a total patient population of 1,143, was 89 percent. In a similar group of 19 different studies and 1,489 patients with no evidence of acute infarction, the 99mTc-pyrophosphate scans were normal in 86 percent. Thus, there appeared to be a 14 percent false positive rate.

These results may be deceiving, however. The low false positive rate may be due to the patient mix, which frequently involved a spectrum of pain syndromes. The diagnostic problem usually involves the distinction of
unstable angina pectoris from acute infarction, however. Many patients with unstable angina have abnormal scintiscans. Thus, in 374 patients with a clinical diagnosis of unstable angina pectoris and without clinical evidence of acute infarction, 132 (41 percent) had positive $^{99m}$Tc-pyrophosphate scans. It has generally been assumed that these abnormal scintiscans in patients with unstable angina pectoris represent false positive results. In a small number of patients with unstable angina pectoris or with symptomatic ischemic heart disease after myocardial infarction who were studied at autopsy, however, those patients with abnormal scintigrams had histopathologic evidence of multifocal irreversible damage. Patients with clinical evidence of unstable angina pectoris who were studied with both $^{99m}$Tc-pyrophosphate and with sequential determination of serum MB creatine kinase (CK) activity, 22 of 36 patients with abnormal images had elevated total plasma CK and MB CK activity. These studies would suggest that, at least in some patients with unstable angina and abnormal scintigrams, there is underlying tissue necrosis accounting for the pyrophosphate uptake. Furthermore, patients with abnormal images but without clinical evidence of acute infarction have a poorer prognosis than those patients with normal scintigrams.

During the 1st week after infarction, the complication rate is higher (26 percent) in patients with abnormal scans and with acute infarction than in patients with abnormal scans but without infarction by other criteria (6 percent). After discharge, however, the complication rate rises in the latter group to 26 percent compared with 5 percent for patients with normal scans, suggesting that patients without infarction but with abnormal scans have continuing ischemia that results in further deterioration of their clinical course.

Another diagnostic problem that is overlooked when composite results are reported is the difference in sensitivity in transmural and nontransmural infarction. Infarct scintigraphy with $^{99m}$Tc-pyrophosphate is most sensitive in patients with transmural infarction. However, in these patients the diagnosis can usually be made without the aid of infarct scintigraphy. It is in patients with nontransmural infarction that the diagnosis is frequently in doubt at the time of hospital admission.

The diagnosis of nontransmural infarction may be difficult to confirm because the accompanying electrocardiographic changes are nonspecific. Nontransmural infarction frequently occurs during surgery or in other clinical settings characterized by hemodynamic instability. Furthermore, when patients present with nonspecific S-T segment or T wave abnormalities several days after a prolonged episode of pain, it may be impossible to diagnose acute myocardial infarction using currently available techniques.

Although initial reports suggested that myocardial scintigraphy with technetium-$^{99m}$ pyrophosphate is a very sensitive method for detecting nontransmural myocardial infarction, subsequent evidence indicates a substantially lower accuracy. Berman et al. observed that, although 76 of 81 patients with transmural infarction had a definitely abnormal scintigram and the remaining 5 patients had a diffuse pattern, only 7 of 18 patients with nontransmural infarction had an unequivocally abnormal scintigram. Two patients had a normal pattern while 9 had diffuse uptake. Cowley et al. obtained similar results. Six of 13 patients with nontransmural infarction had discretely localized activity. Thus, the sensitivity of the technique was high in patients with nontransmural infarction, if one is willing to accept a correspondingly low specificity, because approximately 50 percent of these patients had diffuse uptake indistinguishable from that obtained in

![Graph showing complication rates versus myocardial infarction in patients with acute myocardial infarction and focal myocardial uptake of $^{99m}$Tc-pyrophosphate.](image_url)
many patients with unstable angina pectoris without clinical evidence of infarction. When rigid criteria were used, and faint diffuse uptake was considered a normal finding, the sensitivity for the detection of nontransmural infarction was 40 to 50 percent.\(^{7,11}\)

The incidence of diffuse uptake in patients with nontransmural infarction may be dependent on the spatial resolution of the imaging equipment. Recent studies suggest a lesser incidence of diffuse uptake than has been reported previously. Massie et al.\(^{13}\) found diffuse uptake in only 19 percent of patients with nontransmural infarction and in 10 percent of those with stable angina pectoris. While Jaffe et al.\(^{7}\) found that, in more than 95 percent of patients with unstable angina pectoris and elevated MB CK activity, the pyrophosphate uptake was focal.

The reduction in the number of patients with diffuse myocardial uptake and acute myocardial infarction with higher resolution instrumentation and the improvement in the specificity of infarct avid scintigraphy by delayed imaging\(^{2,3}\) (3 or more hours after injection) suggests that diffuse uptake is due to persistent blood pool activity. Other techniques have also been suggested to improve the specificity of diffuse pattern.\(^{12}\)

Timing between onset of symptoms and optimal radiotracer concentration in necrotic tissue: While the technique is most sensitive between 16 hours and 6 days after onset of symptoms, acute infarction can be detected as early as 4 hours after the onset of symptoms.\(^{13}\) The detection rate is somewhat lower with early imaging. Eleven of 15 patients with acute infarction had abnormal scintigrams between 4 and 8 hours after the onset of symptoms. In all cases, the uptake was faint to moderate in intensity and focal in distribution. In 5 of 11 cases, the serum CK activity within normal limits at the time scintigraphy was performed.

Patients with uncomplicated acute myocardial infarction show peak \(^{99m}\)Tc-pyrophosphate uptake between 48 and 72 hours after the onset of symptoms. At this time, the intensity of uptake decreases, reaching normal levels after 1 to 2 weeks. There are many patients in whom the scintigraphic pattern returns to normal very slowly, however. Olsen et al.\(^{14}\) observed a return to normal in only 43 percent of patients 6 to 37 weeks after acute infarction. In those patients with persistently abnormal scintigrams, the pattern was usually mildly diffuse. Only 28 percent of those patients had focal activity. While a ventricular aneurysm had developed in some of these patients, the majority of such patients studied postmortem had evidence of fibrosis, myocyte loss and significant myocardial degeneration.

Recurrent versus old infarction: The failure of \(^{99m}\)Tc-pyrophosphate scintigrams to return to normal within 1 to 2 weeks in the majority of patients with acute infarction limits the specificity of the technique in patients with recent myocardial infarction and recurrent symptoms. In those patients with infarction who return with recurring symptoms, a single study is of value only if it is negative or intensely positive. Sequential scintigraphy is of value if the scintigraphic pattern follows a classic course after the recurrent symptoms. If the intensity of pyrophosphate uptake increases for the first 48 to 72 hours with a subsequent rapid decrease in intensity, the probability of reinfarction is high. In all other cases, recurrent acute myocardial infarction cannot be distinguished from recent infarction without a baseline study at the time of initial infarction.

Other causes for increased myocardial tracer uptake: Although previous myocardial infarction and unstable angina pectoris are the most frequent causes for increased myocardial uptake with \(^{99m}\)Tc-pyrophosphate, there are other causes. Focal uptake may be seen in patients with valve calcifications,\(^{15,16}\) repeated high energy cardioversions,\(^{17}\) ventricular aneurysm,\(^{18}\) myocardial contusion\(^{19}\) or metastatic carcinoma to the heart. Because myocardial scintigraphy with \(^{99m}\)Tc-pyrophosphate would be a useful technique in evaluating patients for acute infarction after resuscitation, the initial case reports and animal studies\(^{20}\) that reported significant myocardial uptake after direct current cardioversion in the absence of ischemic heart disease were discouraging. However, when patients were looked at systematically after cardiopulmonary resuscitation with cardioversion, the incidence of pyrophosphate uptake in patients without myocardial infarction was only 13 percent.\(^{20}\) With an imaging accuracy of 80 percent it would appear that false positive scintograms after electrical cardioversion are infrequent. Similarly, valvular calcification must be extensive and focal uptake in patients with such calcification without evidence of infarction is unusual. Focal uptake in patients with ventricular aneurysm may represent calcification within the aneurysm. or, as with patients with recent infarction, may represent persistent and ongoing cell necrosis and damage. Pericarditis alone does not result in increased uptake of pyrophosphate.\(^{21}\) One exception is patients with hypercalcemia with pericardial calcification.\(^{22}\)

Because pyrophosphate is a bone seeker, increased uptake may be seen in overlying ribs in regions of focal disease. This may be seen, for example, in patients with rib fracture due to recent vigorous cardiac massage. Rib uptake can be differentiated from myocardial uptake by demonstrating that the increased activity remains with the ribs rather than the myocardium in multiple projections. A more troublesome problem is the increased uptake that can be observed in calcified costochondral cartilage. This is seen in 1 percent of patients and makes the interpretation of underlying myocardial activity hazardous without computer processing. Rarely, costal cartilage calcification may mimic the doughnut-shaped appearance seen in massive infarction.\(^{23}\) Uptake in calcified skin lesions\(^{24}\) and breast tumors\(^{25}\) has also been observed and can be differentiated from myocardial activity by multiple views.

Diffuse uptake in nontransmural acute infarction: Diffuse patterns of increased \(^{99m}\)Tc-pyrophosphate have been observed in patients with nontransmural acute myocardial infarction, idiopathic cardiomyopathy,\(^{20}\) unstable angina pectoris,\(^{20,22}\) stable angina pectoris,\(^{20,21}\) and in patients with no apparent
heart disease. The high incidence rate of diffuse uptake in nontransmural infarction and its occurrence in many other conditions would suggest that the primary cause for the diffuse pattern is persistent blood pool activity. Most patients with nontransmural infarction have focal necrosis and even in those patients with global subendocardial infarction, an area of reduced radioactivity corresponding to the left ventricular cavity is rarely seen. This pattern would be observed if the uptake were primarily in the left ventricular wall, but it is seen only in patients with a massive transmural infarct. Persistent blood pool activity will be seen if imaging is performed too soon after injection and in patients with poor renal clearance and enlarged cardiac chambers with poor ejection fraction. Some patients may have persistent blood pool activity without apparent explanation. In these patients there is probably some dissociation of the $^{99m}$Tc from the pyrophosphate with subsequent binding to either a protein or red blood cell fraction.

Drugs may also result in increased retention of the label within the vascular compartment. This probably accounts for the reports of diffusely abnormal pyrophosphate scans in patients with adriamycin toxicity. Patients taking adriamycin have altered tracer kinetics with increased activity outside of the intravascular component when in vivo red cell labeling is performed with $^{99m}$Tc-pertechnetate after pyrophosphate injection and they have delayed clearance in the blood when $^{99m}$Tc-pyrophosphate is used for myocardial scintigraphy. Other drug-radiotracer interactions probably occur.

It is possible, however, that processes that affect the myocardium diffusely and result in tissue necrosis may result in diffuse myocardial uptake. One such example has been demonstrated in the animal model of an experimental viral myopericarditis. Extensive experience with pyrophosphate imaging in myocarditis in human beings has not been reported. Similarly, processes that result in extensive calcification of the myocardium may result in diffuse pyrophosphate uptake.

**Prognostic value of myocardial scintigraphy:**

Although the diagnostic significance of myocardial scintigraphy with $^{99m}$Tc-pyrophosphate is at times unclear, the scintigraphic pattern of myocardial uptake provides clues to the patient's future course, both in-hospital and long-term. The complication rate, particularly during the hospitalization, is directly related to the size of the pyrophosphate uptake in patients with acute infarction (Fig. 1). In fact, patients with clinical evidence of infarction and small foci of $^{99m}$Tc-pyrophosphate myocardial uptake have complication rates comparable with those of patients without acute infarction. Nevertheless, when the extent of uptake is moderate, morbidity is high (67 percent), and when the extent of uptake is high, mortality is high (87 percent).

Other observations that reflect extent and intensity of pyrophosphate uptake also have prognostic value. Thus, 67 percent of patients with a scintigraphic doughnut pattern, intense peripheral uptake and relatively less central uptake manifested left ventricular failure with infarction. The doughnut sign is seen in patients with a very large infarct, usually anterior, with a central photopenic area due either to marked reduced in blood flow or to the left ventricular cavity or to a combination of the two. In another series, late complications developed in all patients with the doughnut pattern, compared with 43 percent of the patients with focal uptake and 12 percent of the patients with diffuse uptake. The extent of tracer uptake correlates directly with elevated pulmonary arterial pressure as well.
Clinical Applications

Myocardial infarction with nondiagnostic laboratory tests: Myocardial scintigraphy with $^{99m}$Tc-pyrophosphate is useful in patients with suspected acute infarction in whom clinical and laboratory evidence is otherwise nondiagnostic. Thus scintigraphy is very helpful in patients who present more than 48 hours after the onset of symptoms when very sensitive serum enzyme levels such as MB and creatine kinase may have returned to normal. The probability of acute infarction is high in patients with focal uptake, provided they did not sustain a recent infarct before their acute event. The size and persistence of uptake may provide predictive information as well. However, usefulness of the test in the face of faint diffuse uptake is limited.

Diagnosis of right ventricular infarction: Myocardial scintigraphy can be used to diagnose right ventricular infarction. Although a disproportionate elevation in right ventricular filling pressure may indicate right ventricular involvement, it may also occur in the presence of cor pulmonale. Myocardial scintigraphy with $^{99m}$Tc-pyrophosphate provides more direct evidence of acute right ventricular infarction. Sharpe et al. observed right ventricular involvement in 6 of 15 patients with inferior infarction. Five of these patients had right ventricular functional abnormalities. These included elevated right ventricular filling pressure and right ventricular dilation or wall motion abnormalities.

Diagnosis of myocardial infarction after cardiac surgery: This technique is also of value in evaluating patients after cardiac surgery. The diagnosis of myocardial infarction after cardiac surgery is complicated because chest pain, serum enzyme elevation and electrocardiographic changes may result from the operation itself. In the initial report of Platt et al., all patients with postoperative infarction diagnosed by standard criteria had an abnormal $^{99m}$Tc-pyrophosphate scintigram. These investigators also suggested that the incidence of postoperative infarction has been underestimated, since 31 percent of bypass patients had abnormal scintigraphy after surgery. Subsequent reports have confirmed the accuracy of $^{99m}$Tc-pyrophosphate scintigraphy in the postoperative patient but demonstrate an incidence rate of infarction much closer to 10 percent. Because a significant number of patients undergoing bypass surgery will have a positive infarct scintigram preoperatively, it is probably wise to obtain a preoperative scintigram in those patients with recent infarction and to disregard faint diffuse myocardial uptake on the postoperative study.

Diagnosis of infarct extension or reinfarction: Extension or reinfarction can be determined if a baseline scintigram is available. It has been observed, for example, that the abnormalities on infarct scintigraphy may become more prominent in the absence of clinically suspected infarct extension during the first 24 to 48 hours after the onset of symptoms. If serial infarct scintigrams are performed, certain sequential abnormalities are suggestive of infarct extension. If there is a marked increase in the size of the scintigraphic abnormality obtained during the baseline examination, or reappearance of an abnormality that had cleared or appearance of a regional abnormality in an area that was previously normal, reinfarction is likely.

Estimation of infarct size: Because myocardial scintigraphy with $^{99m}$Tc-pyrophosphate is a technique that directly visualizes the necrotic myocardium and may therefore permit accurate estimation of infarct size, the technique may also be useful for estimating infarct size. In the animal model, there is no correlation between the size of the acute myocardial infarction and the extent of the scintigraphic abnormality when the infarct is transmural and anterior in location. Computer estimates of infarct size and gross infarct area correlate well by linear regression analysis in most studies when the left anterior descending artery is occluded. Poor correlation between scintigraphic and histologic infarct size has been reported by Siemens et al., however, with overestimation by the scintigraphic method. When a second occlusion is applied to create infarct extension, correlation between histologic and scintigraphic infarct size is poor, probably because the infarct in the region of extension is patchy.

When this technique is applied to human beings, a significant relationship has been reported between the area of $^{99m}$Tc-pyrophosphate uptake and the maximal serum CK elevation in patients with acute anterior infarction. Other investigators have found a poorer correlation between scintigraphy and infarct size in inferior wall infarction.

Emission computed tomography for estimating infarct size: Accurate sizing of the acute infarction by measuring the extent of the radiotracer uptake is limited primarily by the geometric constraints of standard two dimensional imaging. Single photon emission computed tomography provides a three dimensional map of radionuclide distribution and may yield more accurate assessments of infarct size. Initial studies in the animal model have demonstrated an excellent correlation between infarct size and measured uptake of $^{99m}$Tc-pyrophosphate.
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Diagnosis of myocardial infarction after cardiac surgery: This technique is also of value in evaluating patients after cardiac surgery. The diagnosis of myocardial infarction after cardiac surgery is complicated because chest pain, serum enzyme elevation and electrocardiographic changes may result from the operation itself. In the initial report of Platt et al., all patients with postoperative infarction diagnosed by standard criteria had an abnormal $^{99m}$Tc-pyrophosphate scintigram. These investigators also suggested that the incidence of postoperative infarction has been underestimated, since 31 percent of bypass patients had abnormal scintigraphy after surgery. Subsequent reports have confirmed the accuracy of $^{99m}$Tc-pyrophosphate scintigraphy in the postoperative patient but demonstrate an incidence rate of infarction much closer to 10 percent. Because a significant number of patients undergoing bypass surgery will have a positive infarct scintigram preoperatively, it is probably wise to obtain a preoperative scintigram in those patients with recent infarction and to disregard faint diffuse myocardial uptake on the postoperative study.

Diagnosis of infarct extension or reinfarction: Extension or reinfarction can be determined if a baseline scintigram is available. It has been observed, for example, that the abnormalities on infarct scintigraphy may become more prominent in the absence of clinically suspected infarct extension during the first 24 to 48 hours after the onset of symptoms. If serial infarct scintigrams are performed, certain sequential abnormalities are suggestive of infarct extension. If there is a marked increase in the size of the scintigraphic abnormality obtained during the baseline examination, or reappearance of an abnormality that had cleared or appearance of a regional abnormality in an area that was previously normal, reinfarction is likely.

Estimation of infarct size: Because myocardial scintigraphy with $^{99m}$Tc-pyrophosphate is a technique that directly visualizes the necrotic myocardium and may therefore permit accurate estimation of infarct size, the technique may also be useful for estimating infarct size. In the animal model, there is good correlation between the size of the acute myocardial infarction and the extent of the scintigraphic abnormality when the infarct is transmural and anterior in location. Computer estimates of infarct size and gross infarct area correlate well by linear regression analysis in most studies when the left anterior descending artery is occluded. Poor correlation between scintigraphic and histologic infarct size has been reported by Siemers et al., however, with overestimation by the scintigraphic method. When a second occlusion is applied to create infarct extension, correlation between histologic and scintigraphic infarct size is poor, probably because the infarct in the region of extension is patchy.

When this technique is applied to human beings, a significant relation has been reported between the area of $^{99m}$Tc-pyrophosphate uptake and the maximal serum CK elevation in patients with acute anterior infarction. Other investigators have found a poorer correlation between scintigraphy and infarct size in inferior wall infarction.

Emission computed tomography for estimating infarct size: Accurate sizing of the acute infarction by measuring the extent of the radiotracer uptake is limited primarily by the geometric constraints of standard two dimensional imaging. Single photon emission computed tomography provides a three dimensional map of radionuclide distribution and may yield more accurate assessments of infarct size. Initial studies in the animal model demonstrated an excellent correlation between infarct size and measured uptake of $^{99m}$Tc-pyrophosphate.
Emission tomography can be performed in human beings, providing a three-dimensional map of $^{99m}$Tc-pyrophosphate uptake within the heart (Fig. 2). In patients with acute anterior infarction we have observed uptake within the anterior wall of the left ventricle with frequent extension to the septum. Patients with acute inferior infarction may have uptake in the posterior wall of the right ventricle, posterior septum and posterior-lateral wall of the left ventricle as well.

The ability to measure infarct size in both the animal model and in human beings suggests an important future application of infarct-avid scintigraphy. Currently there is much interest in actively limiting infarct size by both pharmacologic and surgical intervention. Infarct sizing by emission tomography provides a measure of infarct size up to at least 1 week after infarction and assesses the total extent of infarction, advantages over both the creatine kinase and electrocardiographic methods.

New Infarct-Avid Agents

Bone agents: Several biologic constraints have limited the practical application of acute infarct scintigraphy with $^{99m}$Tc-pyrophosphate. Improvement in radiopharmaceutical design may increase the clinical value of infarct-avid myocardial scintigraphy. Other bone agents, such as $^{99m}$Tc-carbamylyphosphate, have demonstrated infarct/normal myocardium concentration ratios equal to that of $^{99m}$Tc-pyrophosphate. $^{99m}$Tc-gluceroheptate accumulates within the acutely necrotic myocardium with concentrations of approximately half that of pyrophosphate, but appears early within the infarct. Whether its concentration at these early time periods is greater than pyrophosphate has not been tested.

Tetracycline analogs and radioabeled antibodies: More promising are agents such as $^{99m}$Tc-tetracycline analogs and purified radiolabeled antibody against cardiac myosin, both of which distribute in a manner that is inversely related to reduction in blood flow, and is therefore an improvement over pyrophosphate, which shows decreased avidity for necrotic myocardium in regions of severely compromised flow. At present, both tetracycline and radiolabeled antibodies have poor target to background ratios when injected intravenously, and further improvements in the design of these radiopharmaceuticals are necessary before they can be considered as alternates to $^{99m}$Tc-pyrophosphate.

Myocardial Perfusion Scintigraphy

Perfusion abnormalities in myocardial infarction: Myocardial perfusion scintigraphy performed at rest has been used to differentiate patients with previous myocardial infarction from other patients with coronary artery disease and from normal patients. The area of decreased radioactivity observed in regions of previous myocardial infarction results from a combination of factors: (1) The distribution of radioactive tracer is flow dependent, and flow in these regions is markedly reduced; and (2) there is greatly reduced myocardial cell mass in the infarcted region, with dead myocardial cells replaced by a cellular collagen scar that is unable to take up and retain the radiouclide.

Thallium-201 imaging: In most patients with previous myocardial infarct, regions of decreased activity are seen on the scintiscan that correspond to the location of the previous infarct. A high degree of accuracy has been observed in the detection of myocardial infarction using radioactive potassium or its analogs. Thallium 201 is the potassium analog of choice for myocardial scintigraphy because it has better spatial resolution than potassium and other gamma-emitting potassium analogs and because imaging can be assessed with a scintillation camera.

Acute myocardial infarction: When perfusion scintigraphy with thallium-201 was used to detect the presence of acute myocardial infarction, defects were detected in 16% of 200 patients (82 percent). This technique is most sensitive soon after infarction. When imaging was performed between 6 and 24 hours after chest pain, 88 percent of patients had perfusion defects, while only 72 percent of patients studied after 24 hours had abnormal images. Of the patients with a biochemically large infarct, 131 (94 percent) had a positive scan; of the patients with a small infarct, 35 (57 percent) had a positive scan. In patients with a transmural infarction, 55 percent had abnormal images, whereas only 63 percent of patients with a nontransmural infarction had focal regions of reduced activity. Defects also appeared to decrease in size with time, particularly when the initial study was performed within 24 hours of infarction.

Unstable angina and reversible ischemia: Because perfusion defects can be seen at rest in some patients with unstable angina and during spasm in patients with Prinzmetal's angina, perfusion scintigraphy cannot always distinguish between infarction and reversible ischemia. The technique is of greatest value when a normal scintigram is obtained within 24 hours of suspected infarction, greatly lowering the probability that the patient sustained acute infarction. Patients with unstable angina pectoris have abnormal perfusion at the time of chest pain, but may also have an abnormal scintigram during pain-free periods.

Other causes of perfusion abnormalities: Perfusion abnormalities at rest have been seen in conditions other than acute infarction and unstable angina. Congestive cardiomyopathy with an associated dilated ventricular cavity and septal hypertrophy are examples. Increased right ventricular uptake may be seen in patients with restrictive pulmonary disease, while segmental left ventricular defects may be seen in sarcoidosis as well. Focal perfusion defects are also seen in patients with aortic valve stenosis.

Limitations of thallium-201 infarct imaging: Since the right ventricle is not visualized by thallium-201 under resting conditions, right ventricular infarction cannot be diagnosed from the thallium-201 image. Therefore, $^{99m}$Tc-pyrophosphate myocardial imaging or radionuclide angiography is required to diagnose right extension of the infarct into the right ven-
tricle or predominantly right ventricular infarction. Myocardial infarct imaging with thallium-201 has serious drawbacks: (1) Acute and old myocardial infarction cannot be distinguished because unstable angina may result in perfusion defects that are indistinguishable from those of acute myocardial infarction, (2) the sensitivity of the technique decreases with time after the onset of symptoms, and (3) the test is of limited value for the diagnosis of acute myocardial infarction and for patient triage. Although it has been observed that abnormal scans predict a complicated course in patients with unstable angina, 24 percent of patients with a complicated course had a normal scintigram and 32 percent of patients with an uncomplicated course had an abnormal scintism.54

Myocardial scintigraphy with TI-201 has been advocated to assess prognosis in patients with acute myocardial infarction.55 The size of the perfusion defect is directly proportional to the mortality rate both in the hospital and after discharge. The principle advantage to this approach is that imaging can be performed and prognosis predicted within the first hours after onset of symptoms. Furthermore, the size of the perfusion defect can be assessed serially, at least within the limitations of the 3-day half-life of the tracer. This approach does not measure acute infarct size, however, because previous infarction and unstable angina may produce perfusion defects.

Future applications of myocardial perfusion scintigraphy: Although myocardial perfusion scintigraphy is of limited utility at present, it has the potential for providing critically important information concerning acute infarction. With use of short-lived radiotracers, such as rubidium-82 (75 second half-life), the course of myocardial infarction can be assessed sequentially. By applying transaxial tomographic techniques, it may be possible to measure the extent of the perfusion abnormality56 (Fig. 3) and compare it with the extent of necrosis, as defined by 99mTc-pyrophosphate. With use of these models, the effects of pharmacologic interventions aimed at limiting infarct size may at last be amenable to routine noninvasive in vivo testing.

References


The Future of Nuclear Cardiology

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Trying to predict the future can be a lot of fun and, if successful, quite profitable; but we must remember that 44 years ago President Roosevelt commissioned a study on technologic trends. Among the developments the experts failed to foresee were helicopters, jet engines, radar, computers, nuclear weapons, missiles, satellites and nuclear submarines.

The growth of nuclear cardiology has followed the S-shaped curve characteristic of most growing systems. Figure 1 illustrates the growth of thallium-201 and gated blood pool studies performed at The Johns Hopkins Hospital from 1975 to the present.

What factors produced these growth curves? The latent phase of nuclear cardiology occurred between 1970 and 1975, during which time several important events were taking place. First, scintillation (Anger) cameras were spreading throughout the United States and abroad. They were able to portray the distribution of radioactive tracers within the body during time intervals as short as a fraction of a second. This made them suitable for studies of heart and circulation. Second, during the same period, the use of technetium-99m was becoming widespread. The improvement in image quality compared with the results obtained with iodine-131 permitted cardiovascular structures to be recognized as a bolus dose of intravenously injected tracer passed through the heart and great vessels. Third, computers were beginning to be used in nuclear medicine. In the late 1960s, a recurrent theme was: cameras versus scanners? In the 1970s there was a new theme: Do computers have a role in nuclear medicine?

Considerable skepticism greeted the initial efforts at “nuclear angiocardiology,” serial imaging with the scintillation camera of the passage of a bolus dose of tracer through the heart and great vessels. At an early symposium, an experienced nuclear physician stated that he “couldn’t see any of the things that he was supposed to be seeing,” when presented with studies of patients with transposition of the great vessels, single ventricle and other congenital abnormalities. A pediatric cardiologist concluded that “these studies are a step in the wrong direction.” Although the images were far inferior in quality to those of contrast angiography and ventriculography, it was possible to distinguish heart disease from lung disease in cyanotic newborn infants, and to decrease the time required subsequently at cardiac catheterization. Later, echocardiography performed this task more effectively, but nuclear angiocardiology paved the way for the use of radioactive tracers in coronary heart disease, their most important clinical use in cardiology today.

The techniques of nuclear cardiology were able to bridge many of the gaps between the problems of patients with coronary heart disease and their solutions. To a large extent, the growth of nuclear cardiology paralleled the growth of coronary arterial bypass surgery. Just as angiono scanning was invented to provide a means for rapid diagnosis in patients with massive pulmonary embolism who were to be operated on with the use of the newly developed extracorporeal pump oxygenators, so also was nuclear technology used to help select patients for coronary arterial bypass surgery. Exercise electrocardiography was helpful but not totally adequate in the diagnosis of coronary artery disease. Zaret and his colleagues combined the use of the new technique of potassium-43 imaging of the left ventricle with exercise electrocardiography, thereby improving the accuracy of the diagnosis. Subsequent advances included the substitution of thallium-201 for potassium-43, the replacement of the rectilinear scanner by the scintillation camera, and the use of computers to aid in interpretation of the images.

The evolutionary character of technologic advances is illustrated by gated blood pool imaging, which developed from potassium-43 imaging of the myocardium. The relatively poor images of the myocardium produced with potassium-43 were attributable in part to the motion of the heart during the imaging process. To get around this problem, Natarajan had developed a gating device that permitted imaging during particular parts of the cardiac cycle. Although gating is not widely used today for myocardial imaging with thallium-201, the ability to produce images during end-diastole and end-systole led Pitt to conceive of gated

![Figure 1. Thallium-201 (Tl) and gated blood pool imaging studies performed at The Johns Hopkins Hospital.](image)
blood pool imaging.6 At that time blood pool imaging was being used only for the diagnosis of pericardial effusion, the first clinical application of nuclear imaging in cardiology. Pitt realized that, although contrast ventriculography provided important diagnostic information, its usefulness was restricted because it required cardiac catheterization.

What advances are likely to be made in the future? The most important advances are likely to be totally unexpected, the result of giant leaps forward. Other less spectacular advances are more easily predictable: (1) Increasing use of computers for acquisition, processing and display of data. (2) The use of Bayes' theorem to relate the masses of data in cardiac diagnosis. (3) Improved radioactive tracers for quantitative metabolic studies of the heart. (4) Beat to beat monitoring of ventricular volumes, work, power and efficiency, as an adjunct to pressure and pulse monitoring only.

The Use of Computers

The computer will dominate the future of nuclear cardiology. In addition to making possible single photon and positron emission tomography, computers will permit three dimensional display of data by holography. They will permit the use of imaging consoles to facilitate comparison of nuclear with other imaging data from transmission computerized tomography, digital radiography, nuclear magnetic resonance imaging and anatomic drawings. Automated interpretation of the data is likely to become commonplace. We have already successfully automated serial determinations of left ventricular ejection fraction, a procedure that greatly improves the precision of the measurements.

Special collimators such as the seven pinhole and slant hole collimator may achieve use in the future, but initial results suggest that ring or transaxial detectors will be required in order to provide an adequate number of views. It is predictable that rotating the gamma camera around the patient will become widespread. Images in transaxial, coronal, sagittal and long-axis projections are reconstructed using conventional filtered back-projection techniques. Some systems use two detector heads that are directly opposite each other.

Problems that need to be overcome include problems with the cameras themselves. Problems of uniformity of field and linearity that can be overlooked to some degree in conventional imaging produce ring artifacts when the camera is rotated around the patient. Furthermore, the amplification produced by the photomultiplier tubes may be affected by the orientation of the camera in the earth's magnetic field. A reference flood source for uniformity correction obtained in one orientation may not be appropriate in another.

The Use of Bayes' Theorem

Hard on the heels of the widespread use of computers in diagnostic imaging has come the use of computers in medical diagnosis. As we increase the amount of information about a given patient, we also increase the problem of analyzing an unbelievably large amount of data. The facts that can be collected concerning a patient's health are practically limitless. How is the physician to select which are important? Every question the physician asks, every maneuver he performs in the physical examination and every test he performs should be selected in light of the likelihood that the new data will alter the estimate of the probability that the patient has a particular disease or diseases.

Physicians are beginning to recognize that an essential feature of the diagnostic process is its statistical or probabilistic nature. They are more aware of decision-making under conditions of uncertainty. They are more familiar with computers. They recognize that just as the diagnostic process cannot be conducted in a completely standardized fashion for every patient, nuclear medicine procedures cannot be applied selectively. For example, which procedures we perform in nuclear cardiology depend on the patient's problems and a priori diagnoses. We do not perform the same procedures to evaluate chest pain, determine the cause of dyspnea or assess the response to an antiarrhythmic drug.

Given a complicated diagnostic problem, we view the diagnostic process as proceeding along two pathways: (1) to increase progressively the probability that a patient's illness can be classified as a particular disease or diseases and (2) to decrease progressively the probability that the patient is suffering from other diseases. In 1961 I presented a logical system of medical diagnosis based on Bayes' theorem (Fig. 2).5 First proposed as a possible basis for medical diagnosis in 1950 by Ledley and Lusted, it in 1961 Bayes' theorem seems to be an idea whose time has come.

The essence of Bayes' theorem is:

\[ P(D_j|S) = \frac{P(S|D_j) \times P(D_j)}{\sum_j P(S|D_j) \times P(D_j)} \]

This equation states that the probability (P) that a patient with a given syndrome (S) has a particular disease (D) is directly proportional to the probability of occurrence of his syndrome in that disease multiplied by the a priori prevalence of that disease and inversely proportional to the probability of occurrence of his syndrome in all diseases times the prevalence of those diseases.

In the application of Bayes' theorem, the term P(D) refers initially to the prevalence of disease in all patients who enter the diagnostic process with a given problem or problems. Thereafter the a priori diagnosis at each stage becomes the a posteriori diagnosis after each stage is completed. Working diagnoses are modified at several stages: after speaking to the patient, after the physical examination and after each type of ancillary examination, including nuclear medicine procedures. The physician waits to make a decision regarding treatment until there is sufficient certitude to warrant a decision.

At any stage of the process he may make a therapeutic decision or defer until more information is obtained.

In 1977 an important result was described by Rifkin and Hood, who evaluated a Bayesian approach to the interpretation of electrocardiographic exercise stress...
testing, a procedure with increasing relevance in nuclear cardiology. They examined the accuracy of predicting the angiographic evidence of coronary heart disease from a quantitative analysis of the degree of exercise-induced S-T segment depression. They found the predictive value when assessed by a Bayesian approach to be quite accurate.

Another important advance in the application of Bayes' theorem was reported recently by Diamond and Forrester, who have developed a commercially available program based on an extensive review of published data on clinical and laboratory manifestations of coronary heart disease. Their approach pools the diagnostic experience of nearly 100 studies and integrates fundamental pretest clinical descriptions with many varying test results to predict the probability that a patient will have angiographically proved coronary heart disease. As Diamond stated, we may be standing at the threshold of a perceptual upheaval in medicine . . . “Our perception of apparently simple categorical questions of diagnostic judgment can be expanded from a lean, dimensionless point into a rich three dimensional whole.”

Computers help solve the problem of intellectual indigestion, the problem of keeping up with the tremendous amount of information published every year in the field of cardiology. Without them, not only do we also have trouble keeping up with scientific papers, we also have trouble keeping up with the journals themselves.

**Positron Emission Tomography**

The greatest advances in nuclear cardiology will come through chemistry. A revolution in pharmacology is occurring today, including the invention of innumerable drugs to improve the function of the heart. The modern cardiologist must select from among a host of new drugs being developed in all fields of pharmacology, from receptor agonists and antagonists to antiarrhythmic agents. Even morphine, long a standby as a cardiac sedative, is in the forefront of pharmacologic research that is likely to have important consequences in cardiology.

As pharmacology and chemistry increase their impact on medicine in general and on nuclear medicine in particular, we can benefit from recalling the dictum of Paracelsus of Hohenheim, who said:

“The body is a conglomeration of chemical matters: when these are deranged illness results, and sought but chemical medicines may cure the same.”

**Measuring regional blood flow with nitrogen-13 ammonia:** In the heart as well as other organs, abnormal function often reflects one or more abnormal biochemical events. The development of new ways of labeling important substrates plus the more precise localization and quantification of the distribution of radioactive tracers within the heart have made it possible to begin the biochemical assessment of heart muscle in living patients. This assessment begins by measuring regional blood flow. Nitrogen-13 ammonia is a suitable agent for measurement of coronary blood flow, about 90 percent extracted on first pass through the coronary artery. With microsphere techniques under resting conditions, it has been shown that uptake of nitrogen-13 ammonia by the myocardium is proportional to flow measured. The disadvantage of nitrogen-13 ammonia is that a cyclotron is required for its production. Although this is an important limitation at present, small cyclotrons designed for hospital use are now commercially available.

**Study of regional myocardial metabolism:** The most important advantage of positron emission tomography is its potential to permit detection of derangements in regional metabolism. The two agents that have been used most to date are carbon-11 palmitate and fluorine-18 2-fluoro-2-deoxyglucose (FDG) which permit tracing of fatty acids and glucose, the primary energy substrates of the heart.

Initial results indicate that as regional perfusion decreases, there is a proportional decrease in fatty acid
utilization and images of regional myocardial fatty acid uptake closely resemble images of perfusion. Images of regional myocardial glucose utilization do not always correspond to those of regional perfusion. During ischemia, glucose becomes the preferred energy fuel for production of adenosine triphosphate (ATP) through aerobic and anaerobic pathways. Rath and his associates at the University of California at Los Angeles suggest that the reduction in the rate of beta oxidation of fat in the ischemic myocardium results in a shift from free fatty acid to glucose utilization through either an anaerobic pathway or residual oxidative capacity. Evaluation of local glucose metabolism may prove useful in estimating the mobility of the ischemic myocardium. When administered intravenously, FDG rapidly leaves the blood, is converted by the action of the enzyme hexokinase to FDG-6-phosphate and becomes trapped within the cell because it cannot take part in subsequent steps in the glycolytic pathway. A compartmental kinetic model that represents the transport and phosphorylation of FDG will be used increasingly with positron emission tomography to measure quantitatively the rate of regional glucose utilization in the myocardium in patients with proved or suspected coronary artery disease.21

Other available radioactive tracers: Other tracers that are currently being used in research are:

1. Oxygen-15 (half-life of 2 minutes) to measure regional metabolism; and, when incorporated into carbon monoxide or dioxide, to measure regional blood volume and blood flow, respectively.

2. Nitrogen-13 (10 minute half-life) incorporated into a variety of amino acids in order to study protein metabolism. In the form of nitrous oxide, it is being used to estimate blood flow.

3. Carbon-11 (20 minute half-life) has been used as a label for carbon monoxide and dioxide, various alcohols and ethers, acetate, palmitate, methyl albumin, glucose, deoxy-d-glucose, thymidine, norepinephrine, dopamine, and the drugs, pinoxide, etorphine, flumazenil and phenytoin.

In the heart, ventricular work can now be measured by monitoring both volume and pressure changes within the ventricle; power can be calculated by relating work to the duration of systole. When methods for measuring glucose and fatty acid metabolism in the heart have been further perfected, we will be able to measure efficiency.

The specialized equipment required for these studies, a cyclotron and positron emission tomograph, will be limited to certain university medical centers and research laboratories for the next decade, but the fruits of their research should be translatable into the practice of cardiology as a result of new knowledge and, perhaps, by translation of the research findings, into the development of tracers labeled with iodine-123 and technetium-99m.

Monitoring Ventricular Function

Concurrent with the development of complex technology, including positron emission tomography and
FIGURE 5. The electrocardiograms (top) and time-activity curves (bottom) in a patient with orthostatic hypotension. Left, the legs have been lowered at the point indicated and there is pooling of blood in the dependent legs. The end-diastolic and end-systolic volumes decrease two beats later. Right, same patient as his legs are elevated. The end-diastolic and end-systolic volumes increase.

cyclotron-produced tracers, is the development of simpler devices for beat to beat monitoring of left ventricular function. While nuclear techniques permit detection of hypertrophy, diffuse and focal decreases in myocardial blood flow, valve regurgitation and the presence of shunts, I believe that the major contribution of nuclear techniques in cardiology is to permit measurement of cardiac volumes. Cardiology has been dominated since the turn of the century by pressure measurements. If we can measure both pressure and volume as a function of time, we will have all the information necessary to characterize the thermodynamic state of the heart.23

We are now able to monitor the volume changes within the left ventricle on a routine basis. The upper curve in Figure 3 is a beat by beat tracing of activity from technetium-labeled red blood cells within the left ventricle. This type of monitoring of ventricular activity, when converted to volume, may some day be the means to monitoring ventricular work, power and efficiency in a manner similar to monitoring pulse, blood pressure and respiration.

Automated selection of ventricular fields of interest: An important question in the field of nuclear cardiology is whether the Anger camera will remain the predominant imaging device. Modern Anger cameras have spatial resolution capabilities that are adequate to permit selection of regions of interest such as the left or right ventricle. Background activity remains a problem since, when one uses labeled red blood cells, they are not restricted to the cardiac chambers, but are also present in the lungs, chest wall and so forth. Cinematic display of serial images of the heart and great vessels is commonplace in nuclear cardiology. Most people divide the cardiac cycle into a minimum of 16 frames/cardiac cycle; others use 32 frames. For subjective interpretation of wall motion, 16 frames are adequate, but to derive all the information from a ventricular function curve, 32 frames are preferable.24 When we are concerned only with the diagnosis of coronary artery disease, manual selection of regions of interest is adequate, but interobserver variability in manual selection of regions of interest such as the left ventricle is about 10 percent. Several computer companies have devised semiautomatic systems for the selection of region of interest, but the observer has to interact at several stages. We have recently been able to automate the selection of the left ventricular region of interest to the point where only the patient's identifying number needs to be entered.25 Automation greatly improves the reproducibility of the studies, which is especially useful in the study of the effects of drugs on the heart. Some produce changes of the order of only 5 percent. To be able to measure these, we have to have better precision than that associated with subjective determination of the region of interest. Ejection fraction can vary within 15 or 20 ejection fraction units by variation in the manual selection of the region of interest.

Beat to beat monitoring (the nuclear stethoscope): We are moving more and more in the direction of beat to beat monitoring. Particularly when one looks

FIGURE 6. The left ventricular time-activity curve (top) and a simultaneously obtained electrocardiogram (bottom) in a patient with premature ventricular complexes.
at the diastolic part of the cardiac cycle, variability in the R-R interval causes problems if we derive composite or average cardiac cycles as is done with scintillation cameras. Several groups, including our own, believe that there is considerable information in the diastolic part of the cardiac cycle that can best be looked at if ventricular volume is measured on a beat by beat basis.

Since 1975, I have been developing a monitoring device known as a nuclear stethoscope (Fig. 4). This device is more sensitive than the scintillation camera. It is difficult to do beat to beat monitoring with an Anger camera that has a collimator designed to study regional wall motion. The sensitivity of the camera is too low. With the nuclear stethoscope, we can get enough counts for beat to beat monitoring. Figure 5, left, is a time-activity curve from a patient with orthostatic hypotension when lying down; we can see that when we lower his legs so that there is pooling of blood in the legs, there is a reduction in the end-diastolic and end-systolic volumes. Then when we elevate his legs from a down to an up position (Fig. 5, right), end-diastolic and end-systolic volumes increase.

We have been particularly concerned with using this type of hemodynamic monitoring to study patients with arrhythmias. The tracings in Figure 6 are from a patient who had two premature ventricular beats after three normal beats. The premature ventricular beats occurred within an R-R interval shorter than normal. This was followed by another premature beat that decreased the end-systolic volume to a very low level. Then there was a compensatory pause during which time the patient’s heart filled with blood; when the next beat occurred, there was a supernormal stroke volume. This type of monitoring is particularly useful in differentiating the hemodynamic events associated with different types of arrhythmias. Some arrhythmias, particularly those associated with syncope, are associ-
ated with a very low stroke volume; while patients who do not manifest syncope in association with ventricular tachycardia can be shown to have a good stroke volume.

In patients with atrial fibrillation, we can get an indication of the type of hemodynamic dysfunction associated with the arrhythmia and that due to disease of the ventricular muscle itself. Figure 7 is from a patient with a myocardial infarction and atrial fibrillation. Ejection fraction on a beat by beat basis varied from 18 to 56 percent. When the patient was treated with lidocaine and his rhythm reverted to a normal sinus rhythm, each beat had an ejection fraction equal to that of the strongest beat during fibrillation.

A major use of the nuclear stethoscope is in evaluating the effect of specific drug therapy in a given patient. Figure 8 is from a patient with aortic stenosis and catheter-proved coronary artery disease. When the patient's heart failed, the question was whether the patient's condition would be improved by vasodilator therapy. Within 2 minutes of afterload reduction, there was an increase in ejection fraction in association with the decrease in arterial pressure. The study indicated that this patient would be benefited by afterload reduction. In 22 patients studied after myocardial infarction in Venezuela (Beer J, personal communication), when nifedipine was administered, there was a decrease in arterial pressure, the relative cardiac output did not change, while ejection fraction and end-diastolic volume both increased without a significant change in stroke volume. Thus, it was concluded that nifedipine did not impair hemodynamic function. Monitoring a patient's response to drugs is one of the most important areas of research in nuclear cardiology today.

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Cardiac Computed Tomography

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Technique: The basic computed tomographic image of the heart consists of a transverse tomographic section constructed by computer from approximately 90,000 X-ray attenuation measurements. The X-ray pulses are produced by an X-ray tube that is supported by a circular gantry that also carries a detector array. The patient is placed in the center of the gantry which for one scan rotates 360°. The advantages of this somewhat complicated method of making a cardiac image are briefly that very small differences in radiodensity can be detected and that the spatial location of the picture elements, the so-called pixels, which measure approximately 1 by 1 by 10 mm, is exactly known. This allows for high fidelity reconstruction of imaged structures on the basis of a single or multiple, cardiac sections.

Presently available computed tomographic scanners require a scan time of 2 to 5 seconds. In terms of cardiac motion this is a long time, which would seem to preclude sharp images of the heart. However, the scanner computer deals with the confusing signals surprisingly well and useful cardiac images can be obtained both in the native state and after intravenous injection of contrast medium; the picture reproducibly represents a graphic cardiac phase slightly smaller than that of end-diastole. The myocardium and the cardiac chamber cavities can be identified after intravenous injection of contrast medium. Without contrast enhancement the cardiac structures cannot be identified, although it has been shown that reduced myocardial density resulting from myocardial infarction can be detected in dogs.

Acute myocardial infarction imaging: Overlapping of cardiac structures during the passage through the heart of contrast medium, so deleterious to planar imaging, is eliminated by computed tomography. The contrast medium concentration in the myocardium after intravenous injection of contrast medium is too low to be detected by conventional radiographic technique; by computed tomography useful images of the myocardium can be obtained, allowing detection of coronary perfusion abnormalities including myocardial infarction.

Figure 1 shows the manifestation of acute myocardial infarction in a patient. Contrast medium has entered the infarcted area and can be seen 15 minutes after the completion of the injection of 35 ml of Renografin-76®. The behavior of contrast medium in relation to myocardial infarction as seen on computed tomographic scans has been studied by several workers. Figures 2 and 3 show in schematic form how the images vary with age of the infarction and with time from the start of the contrast medium injection. One manifestation is a filling defect in the myocardium. The size of this filling defect is time-dependent; it becomes smaller as the infarct is healing and it diminishes in size as the time from the injection of contrast medium increases. Another computed tomographic manifestation of myocardial infarction is the contrast enhancement of the peripheral

![Figure 1](image-url)
**FIGURE 2.** The evolution of a left anterior myocardial infarction in a dog during the first 3 weeks after ligation of the left anterior descending coronary artery, showing the diminishing total size of the infarction and the relation between filling defect and contrast enhancement on the computed tomographic image of one cardiac section. The upper row of sections represents the early phase of the contrast medium injection and the lower row the infarction phase. In the 3rd week the filling defect has disappeared and has been completely replaced by the contrast enhancement. The contraction of the scar has resulted in a thin myocardial wall.

zone of the infarction. This zone grows relatively larger with time both in terms of the start of the contrast medium injection and in terms of infarct age. An infarct older than 36 days appears only as an enhancement in relation to the normal myocardium; the scar is clearly seen as late as 150 days after the event. At this time the scar volume is approximately one third of the initial total infarct size. Myocardial wall thinning and aneurysm formation can be quantitatively assessed by computed tomography. The former has been shown to correlate closely with total infarct size reduction during the first 30 days after the event (Carlsson B, Palmer R, Masuda Y, unpublished data).

**Ventricular volume measurements:** Ventricular volume including ejection fraction and regional motion measurements are potentially possible by currently available machines if equipped with an electrocardiographic triggered gating program and by future scanners with scan times in the millisecond range and multilayer capability. Model studies have shown the superior reconstructive power of the computed tomographic approach as compared to planar imaging. Computer analysis of isodensity curves of the left ventricular cavity on single scans may also allow motion analysis by deconvolution of the several integrated systolic and diastolic images which constitute the single scan. Pericardial computed tomographic volume measurements combined with pericardial pressure measurements for evaluation of the effect of the pericardium on the intraventricular diastolic pressure-volume curve have yielded significant clues to the interpretation of such curves in normal and failing hearts.9

**Other applications:** Myocardial mass measurements of cardiac structural components such as the ventricular septum have yielded consistent results in normal and hypertrophic dog hearts.10 Central and regional blood flow measurements on the basis of indicator time-concentration curves can, to some extent, be performed with available scanners.11 However, the low sampling rate of one measurement every 3rd second is a disadvantage that limits the usefulness of such measurements. With the advent of dynamic multilayer scanners extensive blood flow measurement will become possible at low cost in time and money. With currently available scanners practically useful results have been obtained in the demonstration of coronary bypass graft patency.12 Dissecting aortic aneurysm, which may be difficult to differentiate from ischemic heart disease, can be accurately demonstrated by intravenous, contrast-enhanced computed tomography without need for selective catheterization.13

The radiation dose needed for total cardiac reconstruction although not low (approximately 1 rad/scan) is well within acceptable limits for patients with ischemic heart disease. Direct comparison with other radiologic procedures such as cineradiography are difficult because of different dose distribution within the body but the dose from each of the approximately 300 X-ray pulses needed for a complete scan is approximately 1/10 of the dose of a cineradiographic pulse. Also, the coun-
Computertomographic X-ray pulse is well collimated to a 1 cm thick slice, whereas the cineradiographic pulse covers a larger part of the chest.

**Comments**

Present clinical status: The clinical use of currently available scanners as a noninvasive method of cardiac imaging is limited. Because of the need for intravenous injection of contrast medium, cardiac computed tomography is not strictly a noninvasive method. However, selective catheterization can be avoided and this is the major consideration in the logistics of cardiac imaging. Practically useful procedures have been developed only for diagnosis of dissecting aortic aneurysm and for demonstration of patency of coronary bypass grafts. Demonstration of myocardial infarction in patients has not been uniformly successful probably because of inadequate contrast medium administration or motion degradation of the image, or both. The latter is presumably most pronounced when the posterior portion of the left ventricular wall is examined, as this segment, which is more or less parallel to the transverse plane, moves in and out of the scanned section during the 2 to 3 second scanning period. The shortcomings relate to the lack of multilayer capability, the low sampling rate and the relatively long scanning time required for reconstruction of a single transverse section.

**Prospective and retrospective gating:** Electrocardiographic triggered gating of the prospective type, that is, X-ray exposures limited to the desired cardiac phases, improves image quality to some extent and it may allow myocardial motion studies including ventricular volume measurements. Retrospective gating, that is, selection of desired cardiac phases from a series of consecutive, complete scans, is less attractive because of the large radiation dose required for this technique. Even if successful gating could be accomplished the only motion that would be controlled is that of the heart itself; single pass contrast medium motion through the heart would not.

**Future potential of method:** When the motion problem is solved by the introduction of dynamic scanners with scan times in the millisecond range, the unmatched reconstructive power of computed tomography as well as its high density resolution capability can be fully utilized. Noninvasive imaging of the heart requiring only intravenous injection of contrast medium will then, it is hoped, provide a complete quantitative evaluation of the myocardial structures as well as of the cardiac chamber lumens. In addition, the rapid rate recording of the contrast medium concentration changes with time will permit intracardiac, intravascular and myocardial blood flow estimates on the basis of time-concentration curves after a single intravenous injection of contrast medium. The experimental work on dogs and in patients with currently available scanners and the developmental work now underway on a dynamic, electronic scanner strongly supports this assessment of the potential of cardiac computed tomography.

**References**

Intravenous Angiography Utilizing Digital Video Subtraction Techniques

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A prototype video-digital subtraction system has been developed capable of imaging major cardiovascular structures after the intravenous injection of radiocontrast. The image acquisition system consists of a specially designed X-ray image intensifier-video chain with which images are obtained. Images are acquired at the rate of 1 frame/s after the intravenous injection of radiocontrast agent, converted into a digital format by means of an analog to digital converter, and stored on a digital disc. Images before the appearance of the radiocontrast material are then subtracted from those obtained after its appearance so that the resultant image contains contrast medium only. The image is then electronically contrast-enhanced and the final image of arterial structures is then viewed on a televised display.

Description of System Image Acquisition Chain

The system is outlined in Figure 1 and shows the major components of the system and the data pathways. A high flux, high heat load X-ray source is required so that relatively short exposures can be performed with sufficient photon influence for cardiac examinations. Our calculations indicate that a 1 milliampere exposure to the intensifier face is needed per exposure to detect 2 percent contrast levels in 1 mm structures. The image intensifier has been redesigned to accept the 1 milliamp exposure in a 5 ms pulse width without significant loss of resolution or contrast.

The video system consists of an Amperex frog's head plumbicon incorporated into a Sierra Camera, optically coupled to the image intensifier. Its most important feature is a high signal output of 2.5 to 3 microamps with a preamplifier noise of 1 to 2 nanovolts, at a 5 megahertz video bandwidth, so that the measured signal to noise ratio is in excess of 80dB. This is required so that there is no degradation of the signal emanating from the image intensifier. The camera was modified to improve the sweep stability, which is of utmost importance for the exact temporal subtraction of sequential images. The camera has been converted to operate in the non-interlaced mode. This is necessary to preserve resolution and prevent motion degradation which occurs in the integrated interlaced mode of operation.

The analog to digital converter is a high speed instrument capable of 10 megawords/s at 13 bit accuracy. This allows us to digitize in real time with 512 by 512 pixels and to trade off improved resolutions for slower raster rates as needed. At present we are only utilizing 8 bits, but we expect to expand this to 10 bits.

The digital image store is a 512 X 512 X 8 bit charged coupled device memory built in this laboratory. (This is to be expanded in the near future to a 2048 X 2048 display with up to 16 quantization levels.) In addition, it has a mapping memory so that in the display mode any portion of the 256 gray levels can be expanded or compressed on the cathode ray tube display. This allows for considerable contrast enhancement of the displayed image.

The computer in use is a VAX 11/780, which was chosen for its relatively high data rate utilization capabilities. Digitized images can be obtained at 1 frame/s and stored on a digital disc within the computer as presently formatted. Any image can be subtracted from any other image and redisplayed on the cathode ray tube within 1 to 2 seconds; both binary and logarithmic subtractions are conventionally performed. An Oktel video disc recorder is incorporated into the system
for display purposes as well as real time subtraction studies. This allows for dynamic display with freeze-frame capabilities.

The Bell and Howell digital magnetic tape recorder is used for real time (30 frames/s) digital data acquisition, for cardiac examinations. It has the capacity to acquire raw data at $512 \times 512 \times 13$ bits at 30 frames/s or $1024 \times 1024 \times 13$ bits at 7.5 frames/s without data compression. This allows complete postprocessing of the data. Other video subtraction systems use analog storage systems.\(^6\)

**Clinical Applications**

Studies to date have produced excellent results in visualizing the carotid arteries, renal arteries, aorta and peripheral arteries.\(^7\) The system has also proved extremely useful to surgeons in following up postoperative patients, who ordinarily would not be studied angiographically unless complications occurred.

Progress has been achieved to the point where we are now using intravenous angiography as the primary X-ray examination to study the extracranial carotid circulation in patients who have bruises or positive oculoplethysmography or ophthalmosonometry studies. These patients are usually older and many have significant cardiac and vascular disease.

Another primary use of this procedure is in the evaluation of renovascular hypertensive disease.\(^8\) Currently, any patient under 40 years of age with significant hypertension or any patient with recent onset of hypertension undergoes this examination.

The third major category of use is the immediate follow-up of surgical or radiologic interventional vascular procedures.

The current major research effort is to incorporate this technique for the examination of left ventricular function and wall motion studies into clinical use. Animal studies to date have had very satisfactory overall image quality.

**Discussion**

Conditions required for successful examination:
The success of intravenous angiography at this time depends on three factors: (1) It is imperative that the subject be motionless so that satisfactory subtraction can be performed. Because this requires an alert, cooperative patient, the procedure cannot be universally used. (2) A sufficient bolus dose (40 to 50 cc) of intravenous contrast agent must be delivered so that the arterial structures can be visualized after the considerable physiologic dilution that occurs. We are currently placing a pigtail catheter into the superior vena cava to ensure a good bolus injection and to preclude rupture of veins. (3) An X-ray system must be capable of delivering an X-ray dose of 0.5 to 1.0 millirads per exposure to the intensifier face to provide sufficient flux to discern these low contrast arterial images. Results in animal experiments and now in patients indicate that these conditions can be met successfully in more than 80 percent of patients examined.
Quantification of atherosclerotic lesions: The original impetus for developing such a system was to provide a means for detecting and quantifying atherosclerotic lesions in asymptomatic but high risk patients. At the present time it is very difficult to quantitate atherosclerotic lesions in the human arterial system unless (1) angiography is performed, or (2) the lesions are so severe that secondary effects occur. These include high blood pressure, angina, transient ischemic attacks, or (as happens too often) more serious sequelae such as stroke or myocardial infarction. It would be very desirable to identify significant atherosclerotic lesions before they cause symptoms so that appropriate prophylactic therapy can be instituted. Because direct catheter angiography is an invasive procedure and does require hospitalization, it is not a feasible method for identifying atherosclerotic lesions in the asymptomatic patient. The intravenous angiographic procedure has been developed, therefore, as a screening method to identify clinically important but latent disease and to follow up patients serially to determine the effects of treatment on demonstrated atherosclerotic lesions. However, during the course of development and implementation, it became obvious that the procedure could be used for any contrast examination of large vessel (greater than 2 mm) disease.

Advantages of method: The primary advantage of intravenous angiography is that it can be performed on an outpatient basis and requires only a simple venous cannulation rather than the sometimes more difficult arterial catheter placement. It is also a faster procedure, requiring only 15 to 60 minutes per examination and demands fewer personnel in comparison with an angiographic procedure. These features tend to a more rapid and potentially cheaper examination. However, the catheter angiographic technique does produce higher resolution images, and it is not significantly degraded by patient motion or overlapping vessels.

In comparison with ultrasonic examinations, this is not a completely noninvasive procedure. Because radiation is used—although in diagnostic amounts and less than that used in a standard angiographic procedure—there is a potential hazard. Finally, there is the risk of the reaction to the intravenous contrast medium which, although small, is present. In view of the initial success, it is anticipated that intravenous angiography will become the primary examination for evaluating large vessel disease.

Ventriculography: future developments: Experimental animal work has laid the foundation for clinical cardiac examinations. We have examined both normal and abnormal ventricles in the experimental model and have been able to produce excellent ventriculograms. These ventriculograms were performed at 30 frames/s and clearly demonstrate abnormal areas of ventricular contractility. We are now working on software programs to develop a semiautomated method, or interactive method, to outline the contrast-filled ventricle and perform ejection fraction analysis. Future hardware development will include the incorporation of a direct current coupled video preamplifier so that video densitometry can be performed accurately. It is hoped that with the addition of this piece of equipment and expansion of the dynamic range to 10 bits, volumetric studies as well as flow rate studies can be performed.

With future development this technique will likely compete with nuclear imaging techniques and two dimensional echocardiography as a method of performing wall motion analysis in a relatively noninvasive examination.

Further experiments will be performed to evaluate the ability of this procedure to visualize the coronary arteries in their entirety. This is a difficult project. However, new processing techniques are being developed, and it is hoped that in the near future diagnostic coronary examinations can be performed.

References


Case Presentations

Introduction
The first day of this 1½-day Bethesda Conference was devoted to the presentation and discussion of position papers on various noninvasive methods for the evaluation of left ventricular function in human beings. An effort was made to reach a consensus relative to the value of various tests in different clinical conditions. The last morning of the Conference was devoted to the consideration of nine individual patients chosen to represent common clinical problems in which noninvasive diagnostic methods may be of special value. Although the thrust of the conference was directed toward the evaluation of left ventricular function, other aspects of cardiac diagnosis could not reasonably be ignored when the discussion was directed toward individual clinical problems.

Before the Conference, each participant was provided with the case material, and individual cases were assigned to two or three participants to lead off the discussion. After their reports, the floor was opened to all those attending the conference. An effort was made to reach a consensus on the diagnostic approach to each patient and the order of test selection with cost and resource containment as a consideration. The case discussions were open, vigorous and relatively good natured. During 4 hours, many pages of discussion were accumulated. The material was initially edited by one of the primary discussants and secondarily by the chairman and co-chairman. We have attempted to capture the essence of this interesting morning in the brief summaries that follow.

Case Discussions

Case 1
An asymptomatic 50 year old man has moderately severe aortic regurgitation by physical examination. Blood pressure is 170/50 mm Hg; moderate cardiac enlargement is present on the chest roentgenogram, and left ventricular hypertrophy and strain are demonstrated on the electrocardiogram.

The problem: The evaluation of a 50 year old asymptomatic patient with known aortic regurgitation of moderate severity by clinical criteria is a challenge to the cardiologist. Such patients usually manifest an enlarged heart on chest radiography and left ventricular hypertrophy and strain on electrocardiography. However, in spite of evidence of severe disease and the likelihood that valve replacement will be required in the future, the decision to operate has to be made in light of the opposing risks of the morbidity and mortality of currently available valve prostheses versus the occurrence of progressive deterioration of ventricular function as the result of an uncorrected severe mechanical lesion.

Noninvasive methods to assess aortic regurgitation: There is general agreement that noninvasive methods can identify patients with aortic regurgitation who are likely to have a poor result after surgery. The two most common measurements that suggest a poor postoperative prognosis are an end-systolic left ventricular dimension of greater than 55 mm on M mode echocardiography and an ejection fraction of less than 50 percent obtained with radionuclide angiography. Therefore, the need is to identify patients whose measurements are approaching these limits and to offer them early valve replacement.

Both serial echocardiographic and radionuclide methods can be used to follow up such patients. In addition, the echocardiogram can be used to evaluate the aortic valve and the aortic root for possible causes of the patient's aortic regurgitation. The valve leaflets can be investigated to determine if these causes are present and the aorta examined for possible cystic medial necrosis. The wall motion and thickness of the ventricle can be assessed with a two dimensional echocardiogram. The analysis of wall motion becomes important in the older patient, who may have both aortic valve disease and coronary artery disease. In the past, the M mode echocardiogram alone was employed to evaluate these patients. Because serial measurement of end-systolic diameter of a large left ventricle by M mode echocardiography may result in substantial observer variability, it is clearly preferable to use M mode in conjunction with two dimensional echocardiography.

Alternatively, the nuclear imaging determination of left ventricular function can be helpful in evaluating this patient. Radionuclide determination of left ventricular ejection fraction is an excellent way to evaluate these patients and the measurement can be made repeatedly with very low interobserver variability. In addition, the end-diastolic and end-systolic volumes of the left ventricle can be estimated, and the regurgitation fraction approximated by comparing the left ventricular stroke volume with that of the right. Although left ventricular size by chest roentgenogram alone is not a good index of left ventricular function, when coupled with an initial estimate of left ventricular size by either echocardiographic or nuclear techniques, a progression of heart size on chest roentgenogram usually signifies a deterioration in left ventricular function.

Identification of the onset of irreversible ventricular damage as an indication of the time for surgical intervention: This is one of the major goals of noninvasive procedures. Symptoms and exercise
capacity are not sufficiently sensitive indicators, because patients with moderately depressed left ventricular function may continue to have acceptable exercise tolerance. Recently, it was suggested that, in patients with aortic regurgitation, a normal left ventricular ejection fraction at rest that becomes abnormal during or after exercise is indicative of reduced functional reserve and persistent abnormal ventricular function after surgery. Although these observations require further evaluation, at this time, it seems clear that if the patient is asymptomatic and has a normal ejection fraction at rest that increases with exercise, it is reasonable to delay surgical repair. However, whether all patients who have a depressed ejection fraction with exercise require valve replacement remains an open question. Because the data on depression of ejection fraction with exercise are not completely understood, this observation should not be the sole criterion for surgical intervention. Additional data gleaned from the nuclear scan, such as the alterations in stroke volume, end-diastolic volume and regurgitation fraction from rest to exercise, may be useful in assessing the patient's cardiac reserve. Evaluation of the performance of the ventricle from rest to exercise becomes more useful when it is employed serially to follow up a patient. The optimal frequency of such reevaluation will depend on the patient's clinical performance. If the patient begins to manifest symptoms, the chest roentgenogram, electrocardiogram and either the echocardiogram or nuclear examination should be repeated at rest. If these studies are unchanged and a baseline measurement of resting and exercise ejection fraction was performed, it should be repeated. In the absence of clinical symptoms, the patient should be reevaluated annually.

Because echographic and the nuclear imaging measurements of the left ventricle are not interchangeable, it is advisable to choose one of these two techniques and use it serially to follow up the patient. The choice of method will depend primarily on the expertise in each method available to the patient's physician.

**Case 2**

A 50-year-old man had symptoms of acute myocardial infarction 2 days before admission. The electrocardiogram and serum enzyme levels were not diagnostic. What is the role of noninvasive testing in the diagnosis and quantitation of myocardial infarction?

**Infarct scintigraphy:** In this case, in which 2 days elapsed between the onset of symptoms and admission and the electrocardiogram is not diagnostic, infarct scintigraphy would play its greatest role. It would be appropriate to use technetium 99m pyrophosphate scintigraphy as the first step. If the scan revealed focal uptake, the probability of acute myocardial infarction would be high. The question is, would one need further tests?

**Role of echocardiography and radionuclide ventriculography:** If this were an uncomplicated case, as suggested here, one would probably not perform a wall motion study with echocardiography or radionuclide ventriculography at this time. However, if complications developed, it might be important to determine the extent of left ventricular dysfunction. Although there is some information from the initial pyrophosphate study about the size of the acutely necrotic myocardium, one might want additional information. Of the two methods, some prefer the radionuclide ventriculogram to echocardiography because it provides information on both right and left ventricular function.

If the results of the pyrophosphate test were normal or indeterminate because of diffuse uptake, what next? There are four options: (1) no further diagnostic test; (2) thallium myocardial imaging; (3) radionuclide ventriculography; or (4) two-dimensional echocardiography. It is easiest to dismiss thallium imaging because the sensitivity of the test decreases with time, and by 48 hours it is likely that the thallium study will provide no additional information if the results of the pyrophosphate study are normal.

Let us assume that the patient had symptoms 2 days ago and no longer has significant chest pain. The radionuclide ventriculogram or echocardiogram could provide information concerning regional wall motion abnormalities and might be useful from a diagnostic point of view. In most cases, however, one would not perform further tests because, even though pyrophosphate imaging has a lesser sensitivity in the presence of transmural infarction, we know that the amount of pyrophosphate uptake correlates directly with the complication rate. If the results of the pyrophosphate study are normal, the likelihood that the patient will get into serious trouble is small.

**Assessing unstable angina, subendocardial infarction and coronary artery disease:** Eventually, it is important to establish if the patient had unstable angina or subendocardial infarction or, in some instances, if he has any coronary artery disease. The percent of patients with a focal pattern of tracer uptake and with unstable angina and no tissue necrosis is probably small. In most patients with focal uptake, serum MB CK activity is elevated. Only a small fraction of patients have focal uptake in the pyrophosphate study and normal serum MB CK. Many of these patients had a recent infarct. Eventually it may be important to determine the presence, extent and severity of coronary artery disease by coronary arteriography. Among patients who have unstable angina, 10 to 15 percent will not have significant coronary artery disease. In most of these patients, the clinical event is probably precipitated by coronary arterial spasm.

**Case 3**

The 50-year-old man just discussed is now 6 weeks past a myocardial infarction. The resting electrocardiogram is normal and he has no symptoms.

The patient who sustains an acute myocardial infarction and then becomes asymptomatic presents a common clinical problem. For the purposes of this discussion, we will consider transmural and nontransmural infarction together, ignoring the question as to whether the latter is more malignant.

**Defining left ventricular function:** Epidemiologic data show that about half of the patients who are
asymptomatic after a myocardial infarction have coronary artery disease in vessels other than that serving the area of infarction. Because long-term mortality in coronary disease is closely related to the severity of the left ventricular dysfunction and the presence of additional coronary arterial stenoses, rational planning after myocardial infarction should probably include the measurement of left ventricular function, either immediately or late after infarction. Because regional contraction abnormalities are anticipated, the radionuclide ventriculogram with ejection fraction/wall motion analysis would be a good first test. Alternatively, two-dimensional echocardiography employed at rest will qualitatively define left ventricular function.

Indications for coronary arteriography: Which additional tests are performed largely depend on whether the individual physician believes that coronary bypass grafting would be performed in this patient. Because few data are available about coronary bypass surgery in the asymptomatic patient, this discussion will assume that individual practice varies. If one intended to operate on most patients with significant coronary artery disease in regions distant from the site of infarction, the standard would be coronary arteriography, which one might perform in all patients. Alternatively, if one intended not to operate on asymptomatic patients, relatively few or no further tests might be performed for diagnostic purposes. Coronary arteriography will identify no additional disease in about 50 percent of patients. Hence, if noninvasive measures could predict most patients with two or three vessel disease, catheterization could be avoided in 50 percent, even if one desired to operate on those with additional disease.

Predictive role of further exercise stress testing with radionuclide imaging: Exercise testing alone, radionuclide study of ventricular function at rest and during exercise, and exercise thallium imaging are noninvasive studies that might be performed. Electrocardiographic exercise testing alone was recently shown to identify patients with the highest likelihood of early risk of coronary events and use of such testing is the current practice in many institutions. The addition of thallium-201 imaging appears to improve the predictive accuracy in defining two or three vessel disease over that of exercise variables alone and might reasonably be employed, although data are limited and long-term follow-up is not available. Because the myocardial infarction in itself has identified a subset of patients with an intermediate (about 50 percent) likelihood of disease in the noninfarcted beds, the use of a second test will substantially increase (or decrease) the post-test probability of disease to the 80 to 90 percent confidence level. Resting and exercise evaluation of ventricular function has obvious theoretic appeal—that is, patients with the most jeopardized myocardium would be expected to show the least reserve—however, in the immediate postmyocardial infarction setting, almost no data are available, and this approach awaits further study. The predictive value of any of these tests in identifying left main coronary artery disease in this setting is not defined. However, it is agreed that in clinical practice, most patients identified with left main coronary disease are symptomatic and unlikely to fall into the category under discussion.

Summary: In the asymptomatic patient after recovery from acute myocardial infarction, a measurement of resting left ventricular function and exercise testing, possibly combined with thallium-201 imaging or isotope ventriculography, will define patients at highest risk. As such, these noninvasive studies serve as a screening mechanism to identify patients deemed most appropriate for invasive study.

Case 4

A 70 year-old man with mild exertional angina and a grade 3/6 basal systolic ejection murmur is referred for evaluation of possible aortic stenosis.

Role of echocardiography: In patients with suspected aortic stenosis, echocardiography can often provide a good deal of information about the aortic valve and the left ventricle. When studies are of good technical quality, the anatomy and motion of the aortic valve leaflets can be defined. Two-dimensional echocardiography can demonstrate the number of leaflets, their size, thickness and systolic mobility. M mode echocardiography can measure the leaflet separation during systole and document the present or absence of fine systolic leaflet flutter (an indicator that the leaflets are pliable). Either technique is quite good at detecting calcification (as an increase in echo reflectance) or its absence, although two dimensional echocardiography is better for studying the distribution of calcification.

In the patient with suspected aortic stenosis, assessment of left ventricular structure and dynamics is also important. Both M mode and two dimensional echocardiography can be used to define left ventricular cavity size and wall thickness and to estimate global systolic left ventricular performance. Either technique can also be used to estimate left ventricular mass. The superior spatial sampling of two dimensional echocardiography provides the most thorough view of the left ventricle and permits analysis of regional systolic wall motion. However, M mode tracings are more easily measured and are still more widely available.

Ideally, a two dimensional echographic examination is performed first. If the aortic leaflets are thin and separated widely during systole, aortic stenosis is not present. Other disorders that can mimic aortic stenosis, such as hypertrophic cardiomyopathy or mitral valve prolapse, can also be evaluated. If the aortic valve is abnormal, careful recording of the leaflets and their degree of separation is needed. This can be done directly by two dimensional echocardiography or it can be used to direct an M mode cursor to record maximal systolic leaflet separation. If left ventricular contraction is uniform by two dimensional imaging, analysis of an M mode recording is sufficient to define accurately left ventricular size, wall thickness and systolic function. However, if regional contractile abnormalities are apparent, analysis of two dimensional images will provide more accurate information.
Echocardiography is good in distinguishing patients with a normal or severely diseased aortic valve, but it is less helpful in patients with mild or moderate disease. When the aortic valves are thickened and separate poorly by two dimensional echocardiography (or by M mode echocardiography, when one is sure that maximal leaflet separation has been recorded), significant aortic stenosis is a real possibility. However, some patients with only mild aortic stenosis will have similarly reduced aortic leaflet separation, particularly when left ventricular contractile performance is reduced. In one recent study, a systolic aortic leaflet separation of 8 mm or less by two dimensional echocardiography had a predictive accuracy of 82 percent in detecting significant aortic stenosis (valve area less than 0.75 cm²). The sensitivity of this criterion was 91 percent, but the specificity was only 65 percent.

In adults, calculation of the transvalvular gradient from the degree of aortic leaflet separation (measured by either two dimensional or M mode echocardiography) does not accurately predict the left ventricular-aortic gradient at cardiac catheterization, although results in children have been more encouraging. Similarly, computation of peak systolic left ventricular pressure from echocardiographic estimation of wall stress has not been reliable in predicting the left ventricular-aortic gradient in adults. Direct planimetry of the aortic orifice area seen on short axis two dimensional echocardiographic images may be more helpful, but images of adequate quality cannot be recorded in a substantial percent of adult patients. Moreover, it is important to emphasize that, for a fixed level of transvalvular flow, large changes in the transvalvular gradient can accompany only small changes in orifice area, and these small changes may be at or below the level of resolution of echocardiography.

Role of Doppler echocardiography: Doppler echocardiography should also be considered as part of a comprehensive echocardiographic evaluation. Ideally, Doppler methods could be used to measure both the peak velocity and the degree of disorganization of flow (both are related to the degree of stenosis). Several groups of researchers have studied patients with varying degrees of aortic stenosis. They used peak flow velocities estimated from Doppler recordings to predict left ventricular-aortic gradients, and found these calculated gradients to compare well with those measured at cardiac catheterization. Before this is considered a clinically accepted method, these observations must be confirmed in larger groups of patients, and the relative strengths and limitations of different Doppler approaches must be defined. However, Doppler evaluation of transaortic flow has the exciting potential to add important diagnostic information in patients with suspected aortic stenosis. This could be particularly helpful when the anatomic findings by M mode or two dimensional echocardiography indicate that the aortic valve is diseased, but cannot define its severity.

Role of radionuclide procedures: The role of nuclear cardiology procedures is more limited in the patient with suspected aortic stenosis. The nuclear tests do not provide any detailed information about the aortic valve itself. A gated blood pool scan could be used to document resting left ventricular function, but an isolated measurement of left ventricular systolic performance might not be particularly useful. Thallium myocardial perfusion images could help evaluate the presence or absence of associated coronary artery disease, but that does not address the primary question. Moreover, the presence of a myocardial perfusion defect in a thallium image obtained at exercise is not a reliable indication of coronary disease in a patient with aortic stenosis and left ventricular hypertrophy. Thus, the nuclear techniques are reserved for the noninvasive evaluation of left ventricular function in the patient whose echocardiographic images are of poor quality.

Summary: The noninvasive evaluation of the patient in this case should start with a two dimensional echocardiogram. If the aortic leaflets were normal or if they were minimally abnormal but separated well during systole, the likelihood of significant aortic stenosis would be extremely low. The physician could turn his attention to defining alternate causes for the patient's symptoms. However, if the aortic leaflets were thickened, calcified and immobile, and the left ventricle showed good contraction and substantial hypertrophy, the likelihood of significant aortic stenosis would be high. If aortic leaflet separation were reduced but associated with abnormal left ventricular contractile performance, significant aortic stenosis could not be ruled out with certainty. If the echocardiographic findings showed that significant aortic stenosis were highly likely or significantly possible, one would then want to obtain invasive documentation of the degree of aortic stenosis by measuring the left ventricular-aortic gradient and calculating the aortic valve orifice area. Coronary angiography could be performed at the same time.

Case 5

A young woman in her mid 20s has dyspnea on exertion of recent onset. She has no prior history or evidence of hypertension or of heart disease. There is moderate cardiac enlargement, an S4 gallop and no cardiac murmurs on physical examination. The chest roentgenogram reveals generalized cardiac enlargement and normal pulmonary vasculature. The electrocardiogram shows mild hypervoltage, normal axis and nonspecific T wave changes.

Differential diagnosis: The young woman has cardiomegaly. There is a definitely abnormal electrocardiogram, which is not diagnostic of left ventricular hypertrophy. She has an S4 gallop and dyspnea on exertion. Her left ventricle seems to be causing the difficulty, with cardiomyopathy the most likely diagnosis. The echocardiogram will give a fairly good assessment of her left ventricular function. She could also have pericardial effusion. Echocardiography would define each of these conditions. Cated blood pool studies are also very helpful in this situation. If the patient has a thin-walled dilated ventricle, she would probably not have focal motion abnormalities, and the probability of her having
coronary heart disease would be extremely small. You may be occasionally surprised by the results of the radionuclide angiogram indicating that the patient has a congenital abnormality. One can observe and measure the bolus dose of radioactivity as it travels through the heart and determine whether the structures are in the right places and the flow in the right sequence. Of course, if she has a diffuse cardiomyopathy, the right as well as the left ventricle will be dilated. She could also have primary pulmonary hypertension, in which case her left ventricle would be normal. The radionuclide angiogram will also identify a large but not a small pericardial effusion.

Because the patient is in her mid 20s, pregnancy is always a possibility. After a screening history, if pregnancy is likely, a nuclear study would not be done and echocardiography would be the technique of choice. In certain situations, it may be necessary to do a radionuclide study in a pregnant patient. This most often occurs when a pregnant woman has a high likelihood of having a pulmonary embolus and a decision about the use of anticoagulation must be made.

Editorial note: Although in further discussion there was some difference of opinion, most participants favored echocardiographic evaluation for initial evaluation and serial follow-up to assess the course of therapy.

Case 6

A 50 year-old woman presents with progressive dyspnea. On examination, a pulmonary flow murmur and a widely split S2 are heard. The chest roentgenogram shows enlarged pulmonary arteries, and the electrocardiogram shows a right ventricular conduction defect.

The differential diagnosis in this case would surely start with atrial septal defect, although other conditions that could conceivably present this way would include mitral stenosis with pulmonary hypertension or primary pulmonary vascular disease.

Radionuclide imaging studies: Radionuclide studies in a patient with suspected atrial septal defect can provide important information. A first-pass blood pool study, using technetium-labeled red cells injected in a bolus dose, is a reliable method for detecting the presence of a significant left to right shunt. By documenting recirculation of tracer from the left heart chambers into the right atrium, this test would indicate that the shunt occurred at the atrial level. Moreover, the magnitude of the shunt can be reliably estimated. Echocardiographic gated images can also be obtained (after complete mixing of the tagged red cells in the circulating blood pool) to define right and left ventricular systolic performance. These findings are useful in assessing the influence of the diastolic volume overload on right ventricular systolic function and predicting surgical outcome.

Echocardiographic studies: Echocardiographic tests are also helpful, but in slightly different ways. Either an M mode or a two dimensional echocardiogram can be used to assess chamber size, dynamics and associated valve function. If right ventricular enlargement is present and associated with paradoxic motion of the interventricular septum during systole, a lesion causing right ventricular volume overload is likely. Unfortunately, these findings are not specific for atrial septal defect. Paradoxic septal motion has many other causes, including abnormal septal activation (left bundle branch block or certain types of Wolff-Parkinson-White syndrome, for example), abnormal contraction (septal ischemia or cardiomyopathy) and abnormal cardiac motion (absent pericardium). Other causes of right ventricular volume overload, such as tricuspid or pulmonary insufficiency, can cause similar echocardiographic features, so that the specificity of M mode echocardiography for the diagnosis of atrial septal defect is not high, although it is very sensitive. In a combined series of more than 200 patients, 96 percent of patients with an atrial septal defect and left to right shunt had right ventricular enlargement by M mode echocardiography, and 87 percent had paradoxic systolic septal motion. As a corollary, if the right ventricle is not dilated on M mode echocardiography, the likelihood of an atrial septal defect is extremely low.

Two dimensional echocardiography can demonstrate an atrial septal defect directly in many cases. In patients with a large defect, good quality images from the subcostal examining window can demonstrate a hole in the atrial septum and can differentiate a primum from a secundum defect. Unfortunately, echocardiographic "dropout" can cause an apparent defect in the region of the fossa ovalis in some normal patients, especially when parasternal or apical approaches are used. The combination of contrast injection with two dimensional echocardiography appears to improve the predictive accuracy in detecting an atrial septal defect because most patients with this defect show passage of a few micro-bubbles from the right atrium to the left atrium, while many also show a "negative contrast" effect. Contrast studies probably are not positive in all these patients.

The study of valve anatomy is useful when atrial septal defect is suspected, and this is best accomplished using two dimensional echocardiography. The possibility of mitral stenosis, which can masquerade as atrial septal defect, or occasionally be associated with it (Lutembacher's syndrome), can be rapidly assessed. Similarly, the existence of mitral valve prolapse (frequently associated with a secundum atrial septal defect) or of clefts in the mitral or tricuspid valve (associated with a primum defect) can be shown.

Doppler echocardiography: Pulsed Doppler echocardiography may add additional information when M mode or two dimensional echocardiographic studies show features of right ventricular volume overload. Conventional Doppler recording detects only approximately two thirds of atrial septal defects with left to right shunting and is not useful when predominant right to left shunting is present. However, the pulsed Doppler technique is highly reliable in detecting pulmonic and
tricuspid valve insufficiency. Thus, if a patient with features of right ventricular volume overload has no pulmonary or tricuspid insufficiency by Doppler recording, an atrial septal defect is highly likely.

Summary: Both radionuclide and echocardiographic procedures are helpful in evaluating the patient with a suspected atrial septal defect. Either technique is quite sensitive to the presence of such a defect. Thus, a normal first pass radionuclide study or a normal-sized right ventricle by echocardiography makes an atrial septal defect extremely unlikely. An abnormal radionuclide or echocardiographic study would also be helpful, but each approach has some important (and largely complementary) limitations. The tracer study, although more specific for atrial septal and the degree of shunt, is less useful for defining the location of the defect or associated valve lesions. Echocardiography may be helpful in demonstrating the anatomy of the defect and is sensitive to valve lesions, but it is less specific than tracer studies for this defect and cannot reliably measure the size of the shunt. As a final point, it should be emphasized that definitive demonstration of an atrial septal defect, determination of the degree of left-to-right shunt, and measurement of intracardiac pressures would require only a right heart catheterization. The morbidity and mortality of such a procedure are extremely low. Thus, although noninvasive test results might help, some physicians might wish to move directly to right heart catheterization when clinical evidence suggests presence of an atrial septal defect.

Case 7
A middle-aged man had triple coronary bypass surgery in 1974 and patent grafts in 1975 with normal left ventricular function. At present, he has progressive angina and dyspnea on exertion.

Role of exercise isotope imaging in assessing graft patency: Bypass grafts can be studied in a fashion similar to native coronary arteries with either exercise thallium-201 imaging or exercise isotope ventriculography. Regional perfusion abnormalities or regional wall motion abnormalities would be expected with exercise isotope studies in the setting of graft stenoses or occlusion or nongrafted stenotic vessels. Exercise isotope imaging is probably most helpful in the early postoperative period. Here, the anatomy has been recently defined, and the geographically localizing value of isotope imaging may be useful. For example, if a patient had bypass grafting to the left anterior descending coronary artery and had nongraftable disease in the circumflex arterial distribution and experienced mild angina 4 months postoperatively, an exercise isotope study showing normal wall motion or perfusion, or both, in the left anterior descending coronary arterial distribution but abnormalities in the circumflex arterial system would point away from the graft as the source of pain and possibly eliminate the need for catheterization.

In the particular case presented, the long interval after initial surgery and the possible need for repeat surgery largely negate the utility of isotope studies. Because cardiac catheterization is required for surgery, one might reasonably go directly to it. Only if congestive heart failure were the major problem, and angiography a lesser problem, might one perform either radionuclide angiography or two dimensional echocardiography initially. If severe left ventricular dysfunction were found, this information might direct one away from cardiac catheterization and surgery. Although both Doppler echocardiogram and computed tomography have been used experimentally to assess graft patency, neither has been sufficiently studied for routine clinical application.

Case 8
A 50-year-old woman had mild hypertension, a family history of premature coronary disease, and a typical chest pain. Physical examination and testing electrocardiogram are normal.

Application of Bayes' theorem of probability of disease: This case illustrates the use of Bayes' theorem in applying exercise testing alone or exercise testing combined with thallium-201 imaging or radionuclide ventriculography to the diagnosis of coronary artery disease. The pretest probability of disease in this patient derived from clinical data (that is age, sex, character of pain and other risk factors) is in the range of 30 percent. Exercise radionuclide imaging or ventriculography would, if results were positive, increase the likelihood of disease to greater than 70 percent and, if negative, decrease the likelihood of disease to about 10 percent. This much greater degree of certainty about the probability of the presence or absence of disease could then direct one either toward or away from coronary arteriography. Exercise testing alone, with a generally lower sensitivity and specificity, would have less effect on the post-test probabilities of disease. Women, in particular, are a subset in which cost effectiveness is a major concern. In the Coronary Artery Surgery Study, for example, about 50 percent of women with typical angina were found to have normal coronary arteries. There is obviously ample opportunity to improve precateterization screening in this group. There is, however, less experience with exercise radionuclide imaging in women at present, and breast tissue attenuation can occasionally be a problem, particularly with thallium-201 imaging.

Mitral valve prolapse is also a possibility in this patient and could be best evaluated with echocardiography. The mitral valve prolapse syndrome may occasionally produce exercise perfusion defects or exercise regional wall motion abnormalities in patients with normal coronary arteries. In a man of this age with atypical chest pain, however, the likelihood of coronary disease is about 50 to 60 percent and a negative exercise radionuclide study would reduce it to only 20 to 25 percent, a range of probability that would be less useful in deciding whether to perform coronary arteriography.
Case 9

The patient is a 16 year old boy with a grade 3/6 systolic ejection murmur at the left sternal border, discovered on a school physical examination that was required before participation in competitive sports. An electrocardiogram shows hypervoltage without ST-T changes.

The main question is whether one should do any test at all. This depends on the full assessment of the physical findings and how worrisome the electrocardiogram is. If one is going to do a test, one should do a two-dimensional echocardiogram because one can tell if the patient has hypertrophic cardiomyopathy, pulmonary stenosis, a congenitally malformed aortic valve, discrete subaortic stenosis, an atrial septal defect or many other relevant possibilities.

Editor's note: After a brief discussion, there was full agreement with this approach. None of the participants wanted to do a nuclear scan.