Assessment of Left Ventricular Pressure-Volume Relations Using Gated Radionuclide Angiography, Echocardiography, and Micromanometer Pressure Recordings

A New Method for Serial Measurements of Systolic and Diastolic Function in Man

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SUMMARY This study was designed to validate the use of combined invasive and noninvasive methods in assessing serial pressure-volume relations in man. Ten patients undergoing cardiac catheterization were studied with simultaneous intracardiac micromanometer pressure recordings, gated radionuclide angiography, and echocardiography. Systolic and diastolic function were measured at rest, during right atrial pacing rates of 100 and 120 beats/min and after nitroglycerin administration. Right atrial pacing studies (rate of 100 beats/min) were performed in duplicate to determine the reproducibility of the method. At the conclusion of each study, the model was validated with contrast angiography.

Good reproducibility was evident when measuring the maximum and average filling and ejection rates, time to peak filling rate, ejection fraction, the modulus of chamber stiffness, the time course of left ventricular relaxation, global average stress and ventricular work indexes using the model described above. These data were not significantly different (p > 0.05) from comparable data obtained from contrast angiography. Right atrial pacing and nitroglycerin administration resulted in predictable alterations in the pressure-volume loop and in the systolic and diastolic measurements. The maximum and average filling rates, ejection rates and time to peak filling rate appeared to be heart rate-dependent variables.

By combining available invasive and noninvasive methods, accurate pressure-volume relationships can be determined. Because the method we tested provides accurate volumetric and timing measurements for cardiac events and does not alter hemodynamics, it may be useful for obtaining serial assessments of the pressure-volume relationship in man.

THE IMPORTANCE of understanding the left ventricular pressure-volume relationship in man has been well documented.1,2 Assessment of this relationship requires simultaneous ventricular volume and intraventricular pressure measurements; however, accurate measurement of change in left ventricular volume is technically difficult. Contrast angiographic volume determinations are hampered by alterations in the hemodynamics, arrhythmias and opacification of the ventricle for only a few beats. In addition, frame-by-frame volume determinations are extremely time-consuming, and contrast angiography can only be performed once, or possibly twice, because of the dye load involved. Recently, echocardiography has been used to determine left ventricular volume changes,3 but this technique may be inadequate for measuring volume, and segmental myocardial wall motion abnormalities can introduce significant error in the volume determinations. However, echocardiography does accurately measure wall thickness and timing of valvular opening and closure.

Radionuclide angiography uses a nongeometric, count-derived measurement of ventricular volume that is independent of geometric shape requirements and thus avoids the difficulties associated with echocardiography and contrast angiography. A radionuclide angiographic volume curve can be constructed without the laborious frame-by-frame planimetry required by contrast angiography. In addition, serial studies can be performed without altering hemodynamics. Gated radionuclide angiographic methods suffer from the need to average a large number of cardiac cycles in order to obtain accurate volume measurements. This problem may be partially circumvented by pacing at a constant heart rate.

Thus, each method has its own intrinsic attributes as well as problems. This study was designed to test whether the simultaneous use of the invasive and noninvasive techniques described can provide accurate pressure-volume data so that serial studies can be performed without utilizing contrast angiography.

The specific objectives were to validate the combined use of radionuclide angiography, echocardiography and micromanometer pressure recordings by comparing it to standard contrast angiography, to assess the reproducibility of data derived during serial studies and to assess whether the interventions of heart rate variation and nitroglycerin predictably alter the systolic and diastolic functional values so obtained.

Methods

The study was conducted in the cardiac catheterization laboratory.
Patients

Institutional review committees concerning the protection of human subjects approved all aspects of the study, and all patients gave informed consent. Five males and five females, mean age 49 years (range 42–64 years), were studied. Five patients had multivessel occlusive coronary artery disease, three primary myocardial disease and two chest pain with normal coronary arteries.

Procedures and Measurements

All patients were studied in the postabsorptive state. All medications were discontinued 24 hours before cardiac catheterization. A #8F Millar micrometer-tipped pigtail angiographic catheter was introduced percutaneously into the right femoral artery and advanced into the left ventricle. This catheter was used to record simultaneous left ventricular pressures and dP/dt at a paper speed of 250 mm/sec. The micrometer pressures were balanced to zero, calibrated with the fluid-filled system and recorded at low (0–40 mm Hg) and high (0–200 mm Hg) pressure ranges. The dP/dt was calibrated in a standard fashion using an Electronics for Medicine V 2203 pressure amplifier. All pressures were recorded on an Electronics for Medicine VR-12 recorder. A #6 bipolar pacing catheter was advanced to the high right atrium through the right femoral vein.

Single-plane left ventricular contrast angiography was performed in the 30° right anterior oblique projection. Forty-two milliliters of Renografin-76 (meglumine diatrizoate) were injected at a rate of 12 ml/sec, and the heart was paced at a rate of 100 beats/min throughout the angiogram. Contrast cineangiography was performed at 60 frames/sec using a Siemens Cardio Scope-U. The system was adapted to an Electronics for Medicine cine trace unit, which simultaneously labeled the film frame number and left ventricular pressure recording. This technique permitted accurate alignment of the pressure and volume recordings.

Left ventricular volumes were calculated at a framing interval of 16.7 msec by planimetrizing the individual frames and using the Kennedy modification of the Dodge and Sandler formula for single-plane angiography.4

Red blood cells were tagged with stannous pyrophosphate and, after a 20-minute delay, were labeled in vitro with 25 mCi of technetium-99m pertechnetate.4 Imaging was performed with a General Electric Med III mobile gamma camera. The camera was positioned in a left anterior oblique position with a caudal tilt so as to isolate the left ventricle. Images were acquired in frame mode at 32 frames per RR interval by summing the radioactivity in the ventricle over 3 minutes using a high-sensitivity, parallel-hole collimator. The acquisition of images was gated to the ECG using an American Optical (AO) gate. A Hewlett-Packard oscilloscope was used to determine the exact time data acquisition commenced in relation to the ECG. The AO gate was triggered at the midpoint of the downslope of the R wave of the ECG. Thus, accurate synchronization of the radionuclide-derived volume measurements with intracardiac micromanometer pressure recordings was obtained. The mobile gamma camera was directly linked to a Medical Data System (MDS) A2 40,000 multiterminal computer system. The data were both spatially and temporally filtered using Fourier filtering techniques to produce images with a high signal-to-noise ratio and good anatomic resolution. Background subtraction and construction of time-activity curves were performed in a standard fashion. The data collected were corrected for number of cycles, time per frame and radionuclide decay using the formula

\[
\text{left ventricular counts} = \frac{\text{(number of cardiac cycles imaged)}}{\text{(time/frame)}} \times e^{-0.009(\Delta T)}
\]

where \(\Delta T\) = interval in minutes between the time of data acquisition and the time of contrast angiography.

Available MDS A2 computer software allowed construction of a derivative curve from the time-activity curve (fig. 1). Peak ejection and filling rates were computed in left ventricular counts per second. These values were normalized for the number of left ventricular end-diastolic counts and the derivative curve directly displayed peak filling and peak ejection rates in terms of end-diastolic volumes per second (EDV/sec). The average filling rate was obtained by integrating the area under the diastolic portion of the derivative curve and dividing this area by the length of diastole in seconds. The average ejection rate was obtained making similar calculations using the systolic portion of the derivative curve. The time to peak filling rate (TTPFR) was measured as the difference between the time to end-systole and the time to peak positive EDV/sec.

The MDS A2 computer was also used to construct volume and derivative curves from the contrast angiography data. This was achieved by editing in the volumes derived from contrast angiography at 16.7-msec intervals using the midportion of the downslope of the R wave from the ECG as the reference point for the end-diastolic volume. Using this technique, volume and derivative curves were displayed in a fashion similar to the radionuclide angiographic (RNA) data. The curves generated from RNA and contrast angiography were then compared.

An Electronics for Medicine ECHO IV was used to record the onset of mitral valve opening. Simultaneous dP/dt and echocardiography of the mitral valve allowed accurate determination of the interval between peak negative dP/dt and mitral opening. Left ventricular wall thickness was obtained when feasible, but often was not well defined.

Experimental Protocol

The protocol is outlined in table 1. Simultaneous baseline radionuclide angiography, echocardiography, and left ventricular pressures were recorded. Duplicate studies were obtained at an atrial pacing rate of 100 beats/min to assess the reproducibility of the model. The study was repeated at an atrial pacing rate of 120 beats/min to determine the effect of heart rate on the
variables measured. After reequilibration, the effect of nitroglycerin on the pressure-volume relationship was examined. A dose of sublingual nitroglycerin adequate to precipitate a fall in the systolic blood pressure of at least 20 mm Hg was administered. The measurements were then repeated during atrial pacing at 100 beats/min. The final step in the protocol was designed to validate the radionuclide angiographic model described above. With reestablishment of the baseline blood pressure, contrast angiography was performed during right atrial pacing at 100 beats/min.

The left ventricular end-diastolic counts, obtained from the second 100-beats/min pacing study (table 1), was assumed equal to the left ventricular end-diastolic volume determined from the contrast angiographic study. Based on this calculation, a correction factor relating radioactive counts per second per cycle to volume was made and used to convert counts to volume for the remaining RNA studies.

**Data Calculation**

Left ventricular pressures were recorded for five to 10 beats during acquisition of the radionuclide data and during contrast angiography. Because respiration affects transmural cardiac pressures, all pressures were obtained at end-expiration and care was taken to ensure that the patient did not perform either a Valsalva or Mueller maneuver. The radionuclide-derived volume measurements acquired over 3 minutes were aligned with the pressure recording of a single end-expiratory representative beat and from these data pressure-volume loops were constructed. Pressure-volume loops were likewise constructed from the contrast angiographic data. All extrasystoles and postextrasystolic beats were excluded from the study and only atrial paced beats were used.

Ventricular work indexes can be determined by calculating the area defined by the pressure-volume relationship using planimetry. Stroke work and diastolic work indexes were calculated for all studies and were used as a crude means of comparing the areas defined by the pressure-volume loops. Work index units are g·m²/m² BSA/beat.

The end-diastolic, end-systolic and peak systolic pressure-volume points were obtained from the pressure-volume loop. The end-diastolic point coincided with the midportion of the downslope of the R wave from the ECG. The end-systolic point was taken as the point of minimum volume, while the peak systolic point was taken as the point of maximum pressure. The pressure was then divided by the appropriate volume at each of the points.

The time course of left ventricular relaxation (T time), was calculated from a simultaneous echocardiogram displaying mitral valve opening, left ventricular dP/dt and left ventricular pressure recorded at a paper speed of 250 mm/sec. The T time was used as the best available reflection of active relaxation.

The modulus of chamber stiffness (Kp) is the rate of change of chamber stiffness with increasing pressure. The Kp was calculated by measuring the slope of the graph of dP/dV vs the pressure from the peak of the rapid filling wave to end-diastole. Kp was used as the best available measurement of the passive diastolic filling characteristics of the left ventricle.

End-diastolic and end-systolic global average stress measurements and wall mass were obtained in five patients. The stress parameters were calculated using the formula

\[
S = \frac{P \times D}{4h (1 + h/D)}
\]

where S = global average wall stress, P = pressure, D = left ventricular diameter and h = wall thickness. Wall thickness was obtained from the echocardiogram and the contrast angiogram. The assumption was made that the left ventricle is a sphere and, using the formula \[ V = \frac{4}{3} \pi r^3 \], the radius and diameter of the ventricle were calculated. Volume measurements were obtained from the radionuclide and contrast angiograms. Left

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**TABLE 1. Experimental Protocol**

<table>
<thead>
<tr>
<th>Pres-</th>
<th>Echo</th>
<th>RNA</th>
<th>Contrast angio</th>
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<tbody>
<tr>
<td>1. Baseline</td>
<td>X</td>
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<td>2. Atrial pacing at 100 beats/min</td>
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<td>3. Atrial pacing at 100 beats/min</td>
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<td>4. Atrial pacing at 120 beats/min</td>
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<tr>
<td>5. Atrial pacing at 100 beats/min + TNG</td>
<td>X</td>
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<td>6. Atrial pacing at 100 beats/min</td>
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</table>

**Abbreviations:** X = procedure performed; RNA = radionuclide angiography; TNG = trinitrolycerin.
ventricular wall mass was calculated using the formula 
\[ M = \frac{[4/3 \pi (r + h)^3]}{r} - V \times (1.050), \]
where \( M \) = wall mass, \( r \) = left ventricular radius, \( h \) = wall thickness, and \( V \) = ventricular volume.

**Statistical Analysis**

A univariate test for normality was performed on each variable of interest. Studies that had a Gaussian distribution were compared with the paired \( t \) test, while those with a non-Gaussian distribution were analyzed with the Wilcoxon signed-rank test. When comparing studies, a \( p \) value > 0.05 was used to imply no significant difference between the studies.

The percent change from baseline was calculated for each intervention. Based on the test for normality, an appropriate paired-measures test was calculated. A \( p \) value < 0.05 was used to indicate a significant difference between the intervention and the baseline study.

**Results**

**Determination of Reproducibility and Validity**

For each patient, the pressure and volume curves were plotted as represented by the results of a single patient shown in figures 2 and 3. On visual inspection, there is remarkable similarity in the data and this was a consistent finding throughout the study. When the diastolic portion of the pressure-volume curve was expanded (fig. 4), there was again good reproducibility and the data were similar to those obtained from contrast angiography. Further verification of the reproducibility and validity of the pressure-volume relationship obtained using combined radionuclide angiography,
echocardiography and micromanometer pressure recordings is shown in figure 5. The end-systolic, peak systolic and end-diastolic pressure-volume points and the stroke and diastolic work indexes were reproducible when obtained using this technique and did not significantly differ from the contrast angiographic data.

The reproducibility of multiple indexes derived from the volume curve, derivative curve and the pressure-volume relationship, at an atrial pacing rate of 100 beats/min, is presented in table 2.

The radionuclide angiographic data (atrial pacing rate 100 beats/min) and the contrast angiographic data are listed in table 3. In no instance were statistical differences observed. To further clarify whether individual variation existed, peak and average filling and ejection rates, and the interval between end-systole and the peak filling rate are displayed in figure 6. Some individual variation appeared evident and might be especially significant for the calculation of TTPFR and peak ejection and filling rates. Statistically, however, no significant differences were evident.

**Interventions**

Simultaneous radionuclide angiography, echocardiography and intracardiac micromanometer pressure recordings were used to evaluate the effect of nitroglycerin and various pacing rates on the left ventricular pressure-volume relationship (fig. 7).

The configuration of the pressure-volume loop was altered in a predictable fashion after each intervention. With an increase in the atrial pacing rate to 120 beats/min, the pressure-volume loop was shifted to the left primarily because of a reduction in the left ventricular end-diastolic filling pressure and an increase in the inotropic state. After nitroglycerin, the pressure-volume loop was shifted further to the left and inferiorly because a reduction in the peak systolic pressure and a further decrease in the ventricular end-diastolic pressure.

The effect of nitroglycerin and pacing on maximum negative dP/dt, Kp, T time, TTPFR and peak and average filling rates is displayed in figure 8. The maximum negative dP/dt remained essentially unchanged at atrial pacing rates of 100 and 120 beats/min. The Kp was not significantly altered by atrial pacing or nitroglycerin. After nitroglycerin administration, the maximum negative dP/dt decreased; however, this decrease did not reach statistical significance compared with the baseline studies and atrial pacing at 100 beats/min. The T time decreased in a predictable fashion with atrial pacing and was not altered by nitroglycerin. The average and peak filling rates were significantly increased by atrial pacing at 100 beats/min when compared to the

**Figure 4.** Comparison of the catheterization angiographic diastolic pressure-volume data with the radionuclide angiographic data. Expansion of the diastolic portion of the pressure-volume curve from the opening of the mitral valve to end-diastole reveals the similarity in the curves obtained using the two different techniques. Cath Angio = catheterization angiography, CAD = coronary artery disease.

**Figure 5.** Comparative analysis of pressure-volume (P/V) loops — the end-systolic, peak systolic and end-diastolic pressure-volume points and stroke and diastolic work indexes. The reproducibility of the repeat radionuclide angiographic (RNA) studies is evident. No significant differences existed between the RNA and catheterization angiographic (Cath Angio) studies.
baseline study and a further augmentation was noted at a pacing rate of 120 beats/min. Nitroglycerin did not significantly alter the filling rates. The TTPFR decreased with atrial pacing, but the change only reached statistical significance when the baseline study was compared to that recorded at an atrial pacing rate of 120 beats/min. After nitroglycerin, the TTPFR was not significantly altered.

The effects of atrial pacing and nitroglycerin on diastolic measurements of left ventricular function are displayed in figure 9 as percent change from baseline. The increase in filling rates associated with atrial pacing paralleled the decrease in T time more closely than any other hemodynamic measurement.

The effect of atrial pacing and nitroglycerin on systolic function is shown in figure 10. The ejection fraction was not altered by atrial pacing at 100 and 120 beats/min but was significantly augmented after nitroglycerin. Peak and average ejection rates and maximum positive dP/dt increased significantly with atrial pacing at 100 and 120 beats/min. A significant decrease in maximum positive dP/dt was observed after nitroglycerin administration compared with atrial pacing at 100 beats/min, but the average and peak ejection rates were not significantly altered by nitroglycerin when equivalent pacing rates were assessed.

Discussion

The results of the reproducibility analysis suggest that virtually all of the measurements of left ventricular function determined from contrast angiographic pressure-volume calculations could be reliably obtained in the population studied using radionuclide angiography, echocardiography and left ventricular micromanometer pressure recordings. The excellent reproducibility of data obtained using this model was applicable to patients with coronary artery disease, congestive heart failure and to patients without apparent cardiac disease.

Because of the marked limitations of the methods used for comparative analysis of pressure-volume loops, visual inspection was initially used in all cases. Figure 2 is an example. Excellent reproducibility was evident. The shape of the gated radionuclide angiographically derived pressure-volume loop is strikingly similar to the contrast angiographic study (fig. 3). Other investigators have assessed the reproducibility of the left ventricular pressure-volume relationship derived

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<tr>
<th>Table 2. Reproducibility of the Radionuclide Angiographic Measurements</th>
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<td>Peak filling rate (EDV/sec)</td>
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<td>Peak ejection rate (EDV/sec)</td>
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<td>Ejection fraction (%)</td>
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<td>Modulus of chamber stiffness</td>
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<td>End-systolic stress (dyn · 10³/cm²)</td>
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<td>End-diastolic stress (dyn · 10³/cm²)</td>
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<td>Wall mass (g)</td>
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Values are mean ± SEM.
Abbreviations: NP = nonparametric (Wilcoxon signed-rank) test used because of non-Gaussian distribution of data; P = parametric (paired t) test used because of Gaussian distribution of data.

<table>
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<th>Table 3. Comparison of Radionuclide Angiographic and Contrast Angiographic Data</th>
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from contrast angiography and have noted that in subjects studied with contrast ventriculograms 30 minutes apart, volume measurements were quite similar in the repeat studies, but the ventricular diastolic pres-
sures in these patients were higher in the second study. This augmentation in pressure is probably the result of residual effects of the contrast used during the preceding ventriculogram. More elaborate means of assessing reproducibility were not conducted in that study. By holding the heart rate steady with pacing, this study demonstrates that accurate volumetric data can be obtained by use of gated radionuclide angiography and the resultant pressure-volume loop is similar to that obtained with single-beat contrast angiographic data. No alterations in diastolic pressure or any other hemo-
dynamic variable was observed between duplicate radionuclide angiographic studies. Further comparison of the pressure-volume loops involved comparative analysis of end-systolic, peak systolic and end-diastol-
ric pressure-volume points and stroke and diastolic work indexes (fig. 5). No significant differences were demonstrated between duplicate radionuclide angio-

**Figure 6.** Comparison of individual filling rates, ejection rates and time to peak filling rate obtained from catheterization angiography (Cath Angio) and radionuclide angiography (RNA). When individual patients were graphically analyzed, little variation was seen between repeat RNA studies, but occasional discrepancies are noted when these studies were compared to the catheterization angiographic data. Despite this, no significant differences were demonstrable.

**Figure 7.** Effect of variable pacing rates and nitroglycerin on the pressure-volume relationship derived from radionuclide angiography. (A) The radionuclide pressure-volume loop was altered in a predictable fashion by both atrial pacing and nitro-
glycerin. These data strongly suggest that the radionuclide angiographic pressure-volume derivation can appropriately identify interventional changes in the pressure-volume relation-
ship in man. (B) This expansion of figure 7A dramatizes the effects of heart rate and nitroglycerin on the diastolic portion of the pressure-volume loop from the opening of the mitral valve to end-diastole. CAD = coronary artery disease.
Figure 8. Effects of variable pacing rates and nitroglycerin (Nitro) on diastolic function. The maximum negative dP/dt and modulus of chamber stiffness (Kp) were not significantly altered by the various interventions. With atrial pacing, time course of left ventricular relaxation (T time) and time to peak filling rate decreased while the peak and average filling rates increased. These timing intervals and filling rates were not significantly changed by nitroglycerin.

Figure 9. Percent change in diastolic measurements after variable pacing rates and nitroglycerin (Nitro). The diastolic timing intervals and filling rates appear to be heart rate–dependent. The increase in the filling rates associated with atrial pacing closely paralleled the decrease in time course of left ventricular relaxation (T time). Kp = the modulus of chamber stiffness; MAX − dP/dt = maximum negative dP/dt; TTPFR = time to peak filling rate.
graphic studies or between the radionuclide and contrast angiographic data.

The reproducibility and excellent correlation with contrast angiography extended to the calculation of $K_p$, the modulus of chamber stiffness, and to the measurement of end-diastolic wall stress. In addition, because the opening of the mitral valve is precisely known from the echocardiogram, accurate measurement of $T$, the time course of left ventricular relaxation, can be determined from the simultaneous left ventricular $dP/dt$ and the mitral valve echocardiogram. Assuming end-diastolic wall stress is an accurate measurement of preload and $K_p$ reflects passive ventricular filling characteristics and $T$ time reflects active relaxation, then use of this combined invasive and noninvasive approach allows for an accurate assessment of these diastolic variables. This study was not designed to assess the clinical relevance of these variables, but it does suggest that the data obtained from the radionuclide model are as accurate as those from contrast angiography.

Further validation of the radionuclide angiographically derived pressure-volume loops is supported by observations after variable pacing rates and the administration of nitroglycerin. Increasing heart rates shifted the pressure-volume curve to the left because of the combined effect of reduction in preload and an increase in the inotropic state (fig. 7). Nitroglycerin shifted the curve downward and to the left because of a reduction in preload and afterload. Although these data certainly are not novel, they suggest the radionuclide angiographically derived pressure-volume relationship responds in a predictable fashion to the interventions.

Although this study confirms that both peak and average ejection and filling rates are reproducible and similar to contrast angiographic values, it also suggests that considerable intra-individual variation exists (fig. 6). As might be expected, the use of the average ejection...
tion and filling rates, rather than the respective peak values, results in less intra-individual variability.

Recent interest has focused on the use of left ventricular ejection and filling rates as expressions of systolic and diastolic left ventricular function. Impaired left ventricular diastolic filling and prolongation of the TTPFR have been observed in patients with coronary artery disease. Caution must be taken in evaluating diastolic function or predicting the presence of coronary artery disease based on the diastolic filling rates and the TTPFR because these measurements appear to be heart rate-dependent. This study was not designed to investigate this further, but we are examining this issue in a larger population with a variety of underlying cardiac diseases.

It was of considerable interest that with increasing heart rate, the T time, derived from the exponential portion of isovolumic relaxation, decreased while the filling rates increased. If this relationship can be confirmed with a larger series, it might suggest that ventricular filling rates from the radionuclide angiographic volume curve more closely reflect active rather than passive filling characteristics of the left ventricle. With increasing heart rates a similar relationship between Kp and the filling rates and times was not observed.

We have described a new means of assessing the left ventricular pressure-volume relationship. This method combines the accuracy and simplicity of radionuclide angiographically derived volume measurements with echocardiographic timing of mitral valvular motion and with intracardiac micromanometer pressure recordings. A composite picture of left ventricular systolic and diastolic function can be obtained using this method, which is both reproducible and similar to that obtained with single-beat contrast angiography. Interventions such as higher pacing rates and nitroglycerin predictably alter these data. Because hemodynamics are unaltered by the method, serial studies can be performed in a wide variety of heart diseases.

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References
Assessment of left ventricular pressure-volume relations using gated radionuclide angiography, echocardiography, and micromanometer pressure recordings. A new method for serial measurements of systolic and diastolic function in man.

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