Assessment of Left Ventricular Diastolic Function: Comparison of Doppler Echocardiography and Gated Blood Pool Scintigraphy

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Although left ventricular diastolic filling patterns can be examined by both Doppler velocity recordings and gated blood pool scintigraphy, few data exist regarding a comparison of these techniques. Therefore, Doppler echocardiography and scintigraphy were compared in 25 patients. Pulsed Doppler echocardiography was performed using an apical four chamber view with the sample volume at the level of the mitral anulus. Doppler measurements included peak velocity of the early diastolic filling wave, time to peak early diastolic velocity from both end-systole and end-diastole, diastolic time period and diastolic integrated velocity (early, atrial and total). The cross-sectional area of the mitral anulus and the left ventricular end-diastolic volume were estimated from measurements made on the apical four chamber view. Scintigraphic measurements included normalized peak filling rate, time to normalized filling rate from both end-diastole and end-systole, diastolic time period and relative diastolic filling during early and atrial filling.

Doppler echocardiography and scintigraphy compared favorably in assessment of fractional filling during early diastole (r = 0.84) and atrial systole (r = 0.85), ratio of early to atrial filling (r = 0.83), diastolic filling period (r = 0.94) and interval from end-diastole to peak early diastolic flow (r = 0.88). Normalized peak filling rate and time to normalized peak filling rate from end-systole did not correlate closely by these two techniques. The differences in normalized peak filling rate may be explained by difficulties in estimating mitral anulus cross-sectional area and left ventricular end-diastolic volume. The weak correlation for time from end–systole to peak flow was a result of the inclusion of isovolumic relaxation by scintigraphy, as opposed to its exclusion by Doppler echocardiography.

Thus, both Doppler echocardiography and gated blood pool scintigraphy provide comparable information regarding left ventricular filling when identical variables are measured, and both methods may be of value in assessing left ventricular diastolic properties.

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Recent studies (1,2) have reemphasized the importance of left ventricular diastolic dysfunction in the production of signs and symptoms of cardiac disease. Abnormal left ventricular diastolic performance without impaired systolic function has been observed in patients with ventricular hypertrophy (1,3) and in those with coronary artery disease (4,5). Accordingly, attention has been focused on the need for noninvasive methods to assess the diastolic properties of the left ventricle.

Previous attempts to evaluate diastolic function by noninvasive techniques have applied either Doppler velocity recordings (6) or radionuclide scintigraphy (2–4) to examine left ventricular filling patterns. Few data exist, however, regarding the validity of these techniques in the assessment of diastolic performance. Neither is it certain how the various measurements made by these techniques relate to each other. Therefore, the present study was undertaken to determine the relation between ultrasound and scintigraphic techniques as well as to help validate each method. To this end we compared various measurements of diastolic flow obtained by Doppler ultrasound and scintigraphy in a group of patients in whom both examinations were performed.

Methods

Study patients. Thirty-three patients who had combined two-dimensional Doppler echocardiography and gated blood pool scintigraphy within a 24 hour period were initially considered for this study. Three patients were excluded because of supraventricular or ventricular arrhythmia and five

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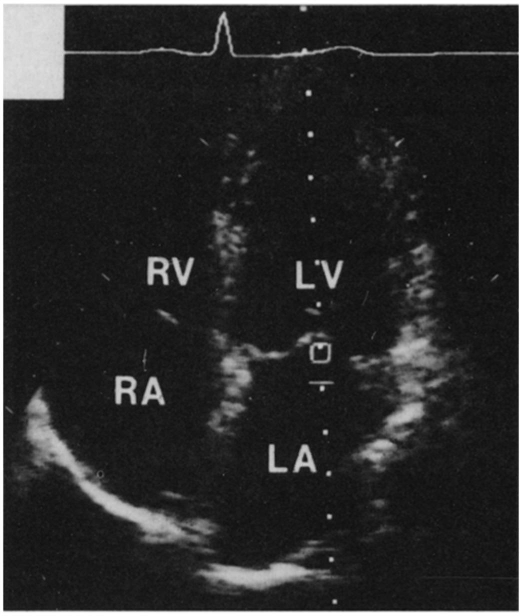


Figure 1. Apical four chamber view with the Doppler sample volume placed at the level of the mitral anulus (**white square**) and the **cursor** parallel to an imaginary line bisecting the left ventricle (LV) from apex to mitral valve. LA = left atrium; RA = right atrium; RV = right ventricle.

were excluded because the Doppler envelope could not be clearly displayed throughout diastole. The final study group comprised 23 men and 2 women aged 49 to 87 years (mean 64 ± 10). All had normal sinus rhythm without any demonstrated ectopic rhythm during a 30 second rhythm strip. Eighteen patients had cardiac disease due to coronary atherosclerosis or cardiomyopathy, including 12 patients with segmental wall motion abnormalities. Eight patients had a history of hypertension. No patient had evidence of mitral stenosis or aortic regurgitation by auscultation, Doppler study or echocardiography. Three patients did have mild mitral regurgitation by Doppler echocardiography. Nine patients were taking no cardioactive medications; 11 patients were being treated with nitrates, 8 with digoxin, 8 with a beta-adrenergic blocker and 5 with a calcium channel blocker.

Doppler and two-dimensional echocardiographic examination. Two-dimensional pulsed Doppler echocardiograms were obtained with a commercially available device (PASS, General Electric Inc.) equipped with a 2.5 MHz transducer. The Doppler signal was updated every 5 ms. Using the apical window, patients were examined while in the left lateral recumbent position. Mitral inflow velocity was recorded with the sample volume at the mitral anulus level and with the cursor parallel to an imaginary line bisecting the left ventricle from the apex to the mitral valve (Fig. 1). The mitral anulus was taken at the plane connecting the point of attachment of anterior and posterior mitral leaflets to the cardiac skeleton. With the sample volume positioned at the anulus level, the transducer was manipulated to obtain the maximal flow signal as assessed by examination of the auditory and spectral outputs. The diameter of the mitral valve anulus (D), the long axis of the left ventricle and the largest minor axis were measured at end-diastole using the apical four chamber view (7). The diameter of the mitral valve anulus was taken at the inner edge of the base of the mitral leaflets (6). The cross-sectional area of the mitral anulus was derived assuming a circular geometry such that the area equals $\pi \times D^2/4$. An estimate of left ventric-

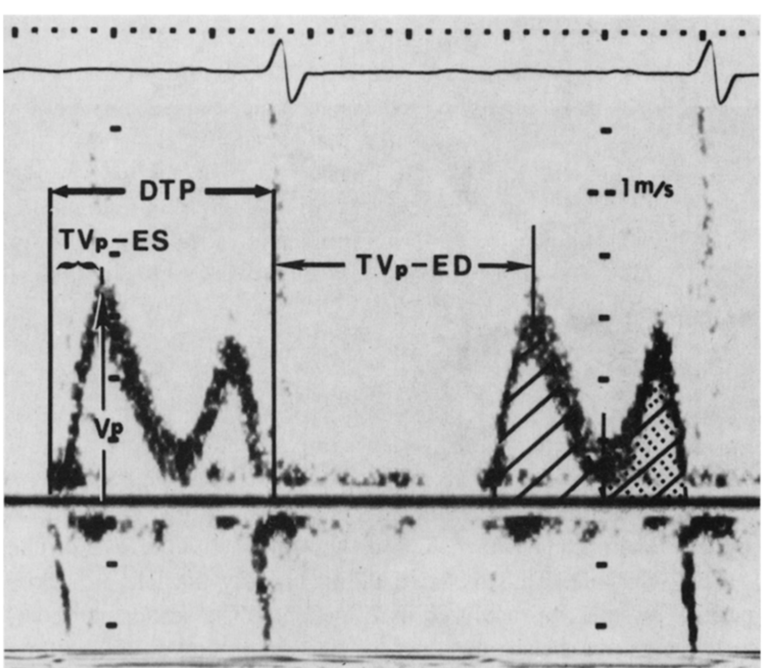


Figure 2. Representative Doppler tracing. The diastolic time period (DTP) was defined as the interval from mitral valve opening to closure. The time to peak early diastolic velocity (TVp) was measured from the onset of diastolic flow (TVp-ES) and from the end of diastolic flow (TVp-ED). Peak velocity (Vp) is identified as the maximal deflection in early diastole. The **dashed line** in the right diastolic filling curve demonstrates the contour of the velocity curve that was digitized. The **entire hatched area** was included as the total diastolic integrated velocity. The **hatched area without the dots** represents the integrated velocity for the early or rapid filling period. The **hatched area with the dots** represents the integrated velocity for atrial systole.

ular volume was calculated using the method of Tortoledo et al. (7).

Doppler measurements. Hard copy printout of the Doppler spectral signal was recorded at a paper speed of 100 mm/s. Doppler measurements were made from the darkest part of the spectral recording of at least five cardiac cycles and were averaged by a computer-interfaced graphic analyzer equipped with a digitizer (Fig. 2). Peak velocity of the early diastolic filling wave was identified as the maximal deflection during the first half of diastole. Time to peak early diastolic velocity was measured both from the onset of diastolic flow and the termination of diastolic flow of the previous cycle to the peak velocity of the early diastolic filling wave. The diastolic time period was defined as the interval from mitral valve opening to mitral valve closure as determined by valve clicks on the Doppler recording. The total diastolic integrated velocity or area under the velocity curve for the diastolic period was derived by digitizing the contour of the darkest portion of the curve. The early and atrial filling periods were empirically divided at the onset of atrial flow velocity (initial increase in velocity after the plateau phase of the early filling period) and the integrated velocity for each of these filling periods was measured (Fig. 2). The fraction of total filling during early and atrial filling was defined as the integrated velocity during early and atrial filling, respectively, divided by the total integrated velocity. The ratio of early to atrial filling was defined as the integrated velocity of early filling divided by the integrated velocity of atrial filling. The normalized peak filling rate was determined as the product of peak early diastolic velocity and the cross-sectional area of the mitral anulus divided by left ventricular end-diastolic volume. This normalization by end-diastolic volume was necessary for comparison with the scintigraphic measurement.

Radionuclide data acquisition. In vivo red blood cell labeling (8) was performed with 25 mCi of technetium-99m pertechnetate. A commercially available portable scintillation camera and digital computer were used. The patient was placed in the left anterior oblique position. The cardiac cycle was divided into 32 frames and counts were collected beginning on the upslope of the R wave. An RR interval exceeding ± 20% of the baseline RR interval resulted in rejection of the following cycles until the RR interval returned to the preselected range.

Completely automatic left ventricular analysis was performed with a standard program (9) that transforms these data to frequency domain, retaining the first three harmonics and the diastolic image. The left ventricular region of interest was used to create a 100 point volume curve (Fig. 3). From this curve and its first derivative the program determines the time of end-diastole (maximal counts), the time of end-systole (minimal counts), the normalized peak filling rate (maximal slope of the first derivative of the early filling portion), time of the normalized early peak filling

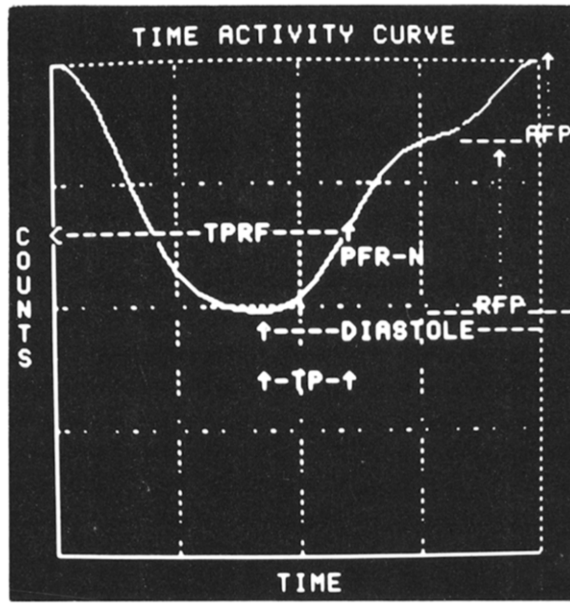


Figure 3. Representative time-activity curve derived from scintigraphic measurements. Identified are atrial filling period (AFP); normalized peak filling (PFR-N); rapid filling period (RFP) and time to normalized peak filling rate from end-diastole (TPRF) and from end-systole (TP).

rate and time to the peak filling rate from end-diastole and end-systole. The fraction of diastolic filling occurring during the early or rapid filling period and during atrial systole was also determined (Fig. 3). The early and atrial filling periods were empirically divided at the onset of atrial flow to correspond with the Doppler measurement. The ratio of early to atrial filling was defined as the fraction of filling during early diastole divided by the fraction of filling during atrial systole.

Statistical analysis. Correlations between Doppler echocardiographic and scintigraphic measurements were made by linear regression analysis. The mean value ± 1 SD for each variable was calculated separately for Doppler ultrasound and scintigraphic imaging. Paired *t* tests were used to compare the Doppler echocardiographic and scintigraphic measurements. The Bonferroni adjustment was made for multiple comparisons. A probability value of less than 0.05 was considered significant.

Results

Relative filling in early and late diastole. Early and atrial filling periods could not be clearly identified with scintigraphy in three patients because of the absence of a sharp change of counts on the time-activity curve in late diastole. Thus, relative filling in early diastole and atrial systole was analyzed in 22 patients. The scatter plot comparing measurements of the fraction of total diastolic filling occurring during the early or rapid filling phase for Doppler ultrasound and scintigraphy is shown in Figure 4A. The fraction of diastolic filling during the rapid filling phase recorded by Doppler ultrasound ranged from 0.29 to 0.80 and by scintigraphy from 0.36 to 0.80. A good correlation was observed between scintigraphic and Doppler measurements of this portion of diastolic filling with an r value of 0.84 ($p < 0.01$). Figure 4B shows a comparison of Doppler and scintigraphic values of the fraction of diastolic filling during atrial systole, which ranged from 0.20 to 0.71 by Doppler echocardiography and from 0.20 to 0.64 by scintigraphy. Good correlation also existed between the fraction of diastolic filling during atrial systole as determined by these methods ($r = 0.85$, $p < 0.01$). The scatter plot of the calculated ratio of early to atrial filling by Doppler ultrasound and scintigraphy is shown in Figure 4C; a good correlation was observed ($r = 0.83$, $p < 0.01$).

Peak filling rate. The results of linear regression analysis for measurements of the normalized peak filling rate as determined by scintigraphy and Doppler echocardiography are exhibited in Figure 4D and Table 1. The range of the normalized peak filling rate was 0.7 to 4.3 liters/s by Doppler study and 0.5 to 3.4 liters/s by scintigraphy. The correlation between scintigraphy and Doppler ultrasound observed for this variable was poor ($r = 0.46$, $p < 0.05$). Comparing the normalized peak filling rate by gated blood pool scintigraphy and the product of the peak velocity and mitral anulus area as determined by Doppler study without attempting to normalize the Doppler measurements for end-diastolic volume did not improve the correlation ($r = 0.46$, $p < 0.05$). Likewise, linear regression analysis of the scintigraphic normalized peak filling rate with peak velocity of the early diastolic filling wave yielded a similar correlation ($r = 0.49$, $p < 0.05$).

Diastolic time intervals. In the interval between the Doppler and scintigraphic studies some patients exhibited a change in heart rate. Therefore, 14 patients with less than a 5% difference in heart rate between the two studies were

Figure 4. Scatter diagrams for Doppler and scintigraphic measurements in 22 patients. **A,** Fraction of total diastolic filling occurring during the rapid filling phase. **B,** Fraction of total diastolic filling occurring during atrial systole. **C,** Ratio of early to atrial filling. **D,** Normalized peak filling rate. **Dashed** lines in **A** to **C** indicate 95% confidence limits.

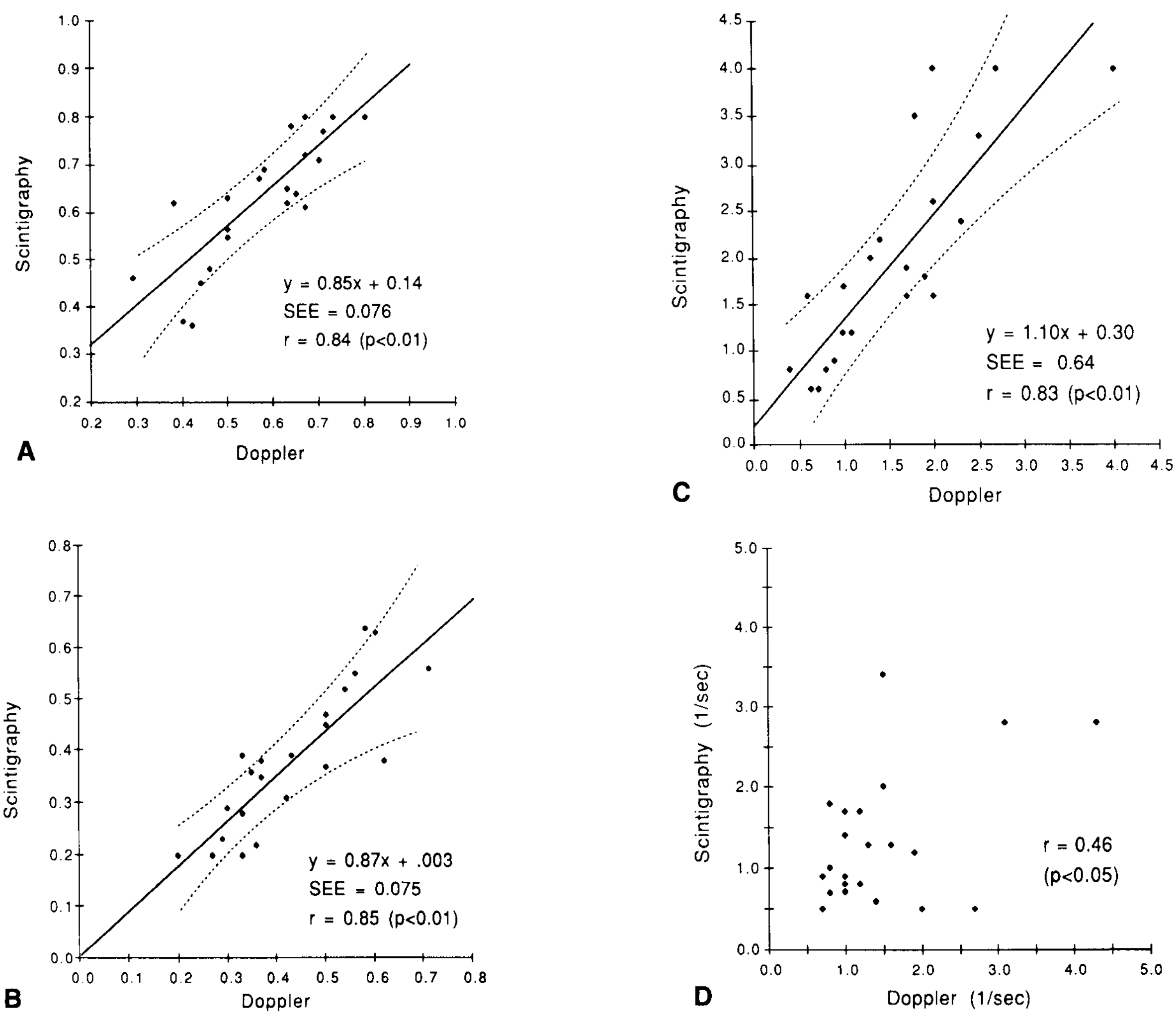


Table 1. Normalized Peak Filling Rates (liters/s) by Doppler Echocardiography and Scintigraphy for Individual Patients

Doppler	Scintigraphy
1.2	0.8
0.8	1.0
0.7	0.9
4.3	2.8
1.0	1.4
1.9	1.2
2.7	0.5
1.2	1.7
0.7	0.9
1.5	3.4
3.1	2.8
1.0	1.7
1.0	0.7
1.3	1.3
1.0	0.9
0.7	0.5
1.0	1.4
1.5	2.0
1.9	1.2
2.0	0.5
1.6	1.3
0.9	1.8
0.8	0.7
1.4	0.6
1.0	0.8

selected for regression analysis of measurements of various diastolic time intervals. Scintigraphic measurements of the diastolic time period ranged from 300 to 720 ms by Doppler ultrasound and from 360 to 780 ms by scintigraphy. Excellent correlation existed between these two techniques ($r = 0.94$, $p < 0.01$).

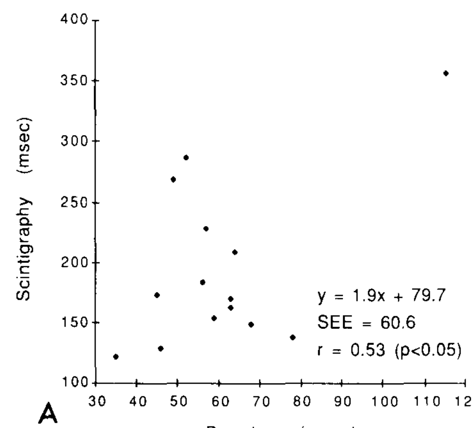
Comparison of measurements of the time from onset to peak of early diastolic flow velocity by Doppler ultrasound with those of time from end–systole (minimal counts) to peak early filling rate by scintigraphy (a frequently used radionuclide descriptor of diastolic function) revealed only a weak correlation of $r = 0.53$ ($p < 0.05$) (Fig. 5A). The range of values for this variable by Doppler echocardiography was 35 to 118 ms (61 ± 19, mean ± SD), while that for scintigraphy was 120 to 360 ms (196 ± 69) ($p < 0.01$). This difference was due to the isovolumic relaxation period, which was excluded by Doppler ultrasound but included by scintigraphy in the measurement of time from end-systole to peak filling. Therefore, we also measured the time to peak early diastolic velocity (by Doppler echocardiography) and peak early diastolic filling rate (by scintigraphy) from the point of end-diastole, which showed good correlation ($r = 0.88$, $p < 0.01$) (Fig. 5B). The range for this variable by Doppler ultrasound was 380 to 730 ms and by scintigraphy was 370 to 700 ms.

Table 2 summarizes the results of comparison of variables of diastolic function by scintigraphy and Doppler echocardiography. Note there were no significant differences between mean and standard deviation values for both techniques except for time from end-systole to peak early velocity and filling.

Discussion

Although both ultrasound (10–12) and radionuclide (3,4,13,14) techniques have been clinically applied to the assessment of diastolic function, few data exist comparing these two techniques. This study documents that Doppler echocardiography and gated blood pool scintigraphy provide comparable information about left ventricular diastolic flow when identical variables are measured. Thus, Doppler and scintigraphic assessment of percent filling during early diastole and atrial systole compared favorably, but absolute volumetric changes did not. Doppler measurements of the diastolic filling period and the time from end-diastole to peak early diastolic velocity also correlated closely with similar scintigraphic determinations. These correlations pro-

Figure 5. Scatter diagrams of the measurement in 14 patients of the time to peak early diastolic velocity by Doppler ultrasound versus time to peak early filling rate by scintigraphy. **A,** Measured from end-systole. **B,** Measured from end-diastole. **Dashed lines** in **B** indicate 95% confidence limits.



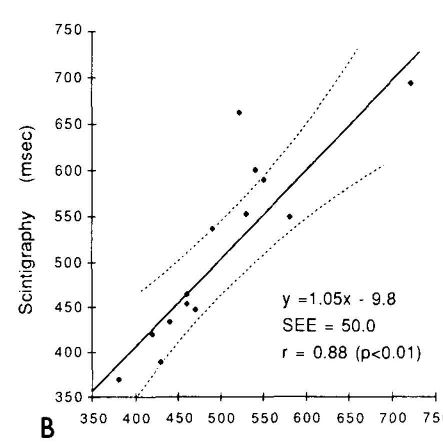


Table 2. Summary of Doppler and Scintigraphic Measurements of Diastolic Function

	Doppler	Scintigraphy	p Value
Fraction of flow in rapid filling phase	0.56 ± 0.14	0.62 ± 0.14	NS
Fraction of flow during atrial systole	0.44 ± 0.14	0.38 ± 0.14	NS
Normalized peak filling rate (liters/s)	1.4 ± 0.9	1.3 ± 0.8	NS
Diastolic time period (ms)	456 ± 133	497 ± 141	NS
Time from end-systole to peak filling (ms)	61 ± 19	196 ± 69	<0.01
Time from end-diastole to peak filling (ms)	499 ± 85	513 ± 101	NS

All values reported as mean ± SD. NS = not significant.

vide evidence that both methods provide reliable assessment of diastolic flow phenomena. A recent study by Spirito et al. (12) also showed that the diastolic flow velocity profile obtained with these two techniques compared favorably. Using phonocardiography in addition to Doppler ultrasound, they were able to determine aortic closure and correlate time intervals measured from end-systole. Using the ratio between the instantaneous peaks of Doppler flow velocity rather than the total or integrated area during each of these diastolic phases, they also correlated percent filling during early and late diastole as was done in this study.

Previous Doppler studies (10–12) have focused on the relative filling of the ventricle in early versus late diastole as a measure of diastolic dysfunction. Miyatake et al. (10) showed that the ratio of the atrial contraction phase to the rapid filling phase increased significantly with aging, presumably secondary to impairment of left ventricular distensibility in early diastole. Thus, it is of particular interest that measurements of the ratio of early to atrial filling by both techniques correlated well ($r = 0.83$). These findings suggest that both Doppler echocardiography and scintigraphy may be useful in evaluating and following diastolic function.

Evaluation of time to peak filling. A scintigraphic variable frequently used to assess diastolic function is the time from end-systole to the normalized peak filling rate (3,4,13,14). Although scintigraphic values for this interval in the present study agree with other radionuclide reports (3,4,13,14), they did not correlate with the analogous Doppler measurements. However, values for the time to peak filling measured from the previous end-diastolic point by each technique did correlate.

The primary explanation for the poor correlation when assessing time from end-systole to peak filling is the inclusion of isovolumic relaxation in the scintigraphic, but not the Doppler, measurements. Scintigraphy measures end-systole at the point of minimal counts (volume), so that the interval from end-systole to peak filling rate includes isovolumic relaxation and the rapid filling period up to the time of peak filling (15). In contrast, the Doppler measurement, which is made from the onset of diastolic flow, excludes isovolumic relaxation. This exclusion likely accounts for almost the entire 135 ms difference between Doppler (mean 61 ms) and scintigraphic (mean 196 ms) values for the interval from end-systole to peak filling rate.

Normalized peak filling rate. Doppler and radionuclide values also did not correlate closely in regard to another scintigraphic measurement often used to assess diastolic function, the normalized peak filling rate. Both Doppler echocardiography and scintigraphy identified the same interval in the cardiac cycle for the peak velocity of the early filling wave and the peak filling rate, respectively, because measurements to these points were identical when taken from end-diastole. This suggests that the poor correlation between Doppler ultrasound and scintigraphy for normalized peak filling rate may have been related either to difficulty in obtaining accurate estimates of end-diastolic volume with both techniques (16,17) or to difficulties in quantifying the mitral anulus cross-sectional area by ultrasound (18–21), or both.

In addition to the inherent errors in measuring peak velocity, longitudinal axis, largest minor axis and mitral valve anulus, several assumptions concerning left ventricular geometry must be made for volume (7,16) and area determinations. To convert Doppler velocity determinations to volumetric measurements for comparison with scintigraphy it is assumed that the anular cross-sectional area is circular as suggested by several (6,20,21) but not all (18,19) studies. It is also necessary to assume that the anular cross-sectional area remains relatively constant (6,20,21). A slight increase in the cross-sectional area of the mitral valve anulus from early to end-diastole (20) represents a potential source of error in the Doppler assessment of normalized peak filling rate. Scintigraphic measurements consist of the number of counts that are directly proportional to volume (22). Although the scintigraphic data are easily processed so that a constant linear proportion between counts and volume is maintained, it remains difficult to directly convert counts to absolute volume (17).

Scintigraphic evaluation of diastolic function. Despite limitations, radionuclide scintigraphy has become an accepted technique for clinical evaluation of diastolic function (3,4,11). Although the temporal resolution of scintigraphy was limited (32 frames per RR interval in this study), this rate has been adequate for evaluation of diastolic events in previous studies (23). In addition, the scintigraphic evaluation of diastole depends on a constant RR interval, unless data can be collected in list mode and reformatted. The inability to empirically separate early from atrial filling in some patients and to repeat measurements after several hours without administering more radioisotope are also potential disadvantages of the scintigraphic technique. The major advantage of radionuclide methods is the direct measurement of counts, which are proportional to volume (22). Changes in counts may then be directly related to changes in volume or flow. Previous studies have shown that left ventricular systolic and diastolic measurements obtained from gated blood pool scans, including peak filling rate and time to peak filling rate, adequately reflect the true averages of such values measured by an ultrahigh efficiency nonimaging detector (24).

Doppler echocardiographic evaluation of diastolic function. Compared with scintigraphy, Doppler echocardiography has both advantages and limitations. The advantages of the Doppler technique are the ability to evaluate diastolic flow on a beat by beat basis and the excellent 5 ms temporal resolution. In addition, Doppler ultrasound more readily enables one to discern the relative left ventricular velocity and inflow during early and atrial filling, providing another potential criterion for the evaluation of diastolic function. The width of the Doppler spectral tracing causes some error in measuring time intervals because of uncertainty in selecting the exact onset and termination of diastolic flow. The Doppler technique was limited in some patients by the absence of an adequate window to assess transmitral flow, a problem that may be compounded by difficulties in demonstrating endocardium for accurate left ventricular volume determinations or in visualizing the mitral anulus. Patients with inadequate Doppler recordings, aortic regurgitation or any other form of dual left ventricular filling must be eliminated from study.

Conclusions. This study helps demonstrate the ability of both Doppler ultrasound and scintigraphy to noninvasively assess left ventricular inflow patterns in the absence of mitral stenosis or aortic regurgitation. Additional studies comparing both methods with angiographic (6) or direct measurements of diastolic flow and pressure-volume derived variables of diastolic function are needed. However, the present data provide evidence that both Doppler and scintigraphic recordings reflect diastolic flow and may facilitate clinical evaluation of diastolic function.

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