Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography

ROXANN ROKEY, M.D., LAWRENCE C. KUO, M.D., WILLIAM A. ZOGHBI, M.D., MARIAN C. LIMACHER, M.D., and MIGUEL A. QUINONES, M.D.

ABSTRACT To determine the relationship between Doppler-derived flow velocity through the mitral anulus and angiographic parameters of left ventricular filling, 30 patients were studied by two-dimensional echocardiography combined with pulsed Doppler echocardiography followed within 1 hr by left ventricular angiography. The average heart rate for each test was 69 beats/min. Doppler-derived parameters included: early peak diastolic velocity (E) and peak atrial velocity, peak filling rate computed as E x cross-sectional area of the mitral anulus derived from the anular diameter, normalized peak filling rate computed as peak filling rate divided by the left ventricular end-diastolic volume determined by two-dimensional echocardiography, and half filling fraction derived from the time-velocity integral of the Doppler-determined velocity curve. Frame-by-frame left ventricular volumes were obtained throughout diastole from single-plane cineangiograms. A volume-time curve with its derivative was generated by computer processing from which peak filling rate, normalized peak filling rate, and half filling fraction were measured. Morphologically, the Doppler-derived velocity profile resembled the derivative of the angiographic volume curve. In patients with reduced angiographic peak filling rates, early peak diastolic velocity was often decreased less than 45 cm/sec with a relative increase in peak atrial velocity resulting in an early peak diastolic velocity to peak atrial velocity ratio less than 1.0. There were no significant differences in mean values for peak filling rate, normalized peak filling rate, and half filling fraction by Doppler echocardiography vs angiography (296 vs 283 ml/sec, 1.9 vs 2.0 sec^{-1} and 0.55 vs 0.55, respectively). A significant correlation was observed between Doppler echocardiographic and angiographic peak filling rate (r = .87, SEE = 91.5 ml/sec) and between Doppler and angiographic normalized peak filling rate (r = .83, SEE = 0.52 sec^{-1}). The correlation between early peak diastolic velocity and angiographic peak filling rate was significant but with a lower r value (.64). Doppler measurements of half filling fraction or early peak diastolic velocity to peak atrial velocity ratio correlated with angiographic parameters but this was predominantly true for a subgroup of 15 patients with similar diastolic filling periods during both tests (range of r values .71 to .85). These findings validate the use of Doppler measurements of mitral inflow velocities in the noninvasive assessment of left ventricular filling dynamics.


PARAMETERS of left ventricular diastolic filling such as peak filling rate and filling fractions are useful indicators of diastolic left ventricular function and are frequently reduced in patients with coronary artery disease, hypertension, or cardiomyopathy.\textsuperscript{1–5} Left ventricular cineangiography and radionuclide angiography have been the primary methods for determining these indexes. Both techniques, however, are time consuming and unsuitable for serial beat-to-beat evaluation. A simpler and more easily repeatable noninvasive method of deriving these measurements would therefore be desirable and is potentially available in the form of pulsed Doppler echocardiography.

Doppler-determined velocity of blood flow through the mitral anulus is related to left ventricular diastolic flow. We have shown that, in the absence of mitral regurgitation, the product of the area under the velocity curve or time velocity integral (TVI) determined by Doppler echocardiography and the cross-sectional area of the mitral anulus accurately determine stroke volume.\textsuperscript{6} Theoretically, the product of instantaneous blood velocity and cross-sectional area should provide
a measure of instantaneous flow. Furthermore, in the absence of other sources of left ventricular filling such as aortic regurgitation, early peak transmural flow determined by Doppler echocardiography should reflect the peak rate of filling.

The purpose of this investigation was therefore two-fold: (1) to determine the relationship between Doppler-derived early peak flow through the mitral anulus and angiographically derived left ventricular peak filling rate and (2) to evaluate other simplified measurements of mitral inflow velocity as possible indexes of diastolic function.

Methods

Clinical population. Forty-nine patients in normal sinus rhythm undergoing diagnostic cardiac catheterization were initially evaluated. Each patient underwent a two-dimensional and pulsed Doppler echocardiographic study within 1 hr of cardiac catheterization. A left ventricular angiogram was obtained from each patient before coronary angiography. Patients were excluded for any of the following reasons: (1) use of an intravenous medication and/or sublingual nitroglycerin before left ventriculography (n = 4), (2) a heart rate for either test greater than 110 beats/min (n = 4), and (3) ventriculograms with poor opacification or frequent premature ventricular contractions (n = 11). Of the remaining 30 patients (24 men and six women, mean age 54 years, range 27 to 72) five had normal coronary angiograms, normal left ventricular ejection fractions (those greater than 50%), and normal wall motion; 10 had coronary artery disease, defined as 50% or greater luminal diameter narrowing in at least one major coronary artery, with normal ejection fractions and wall motion; five had coronary artery disease with normal ejection fractions but with regional wall motion abnormalities; seven had ischemic or primary cardiomyopathy with reduced ejection fraction; and three had moderate-to-severe mitral regurgitation with normal coronary arteries. None of the patients had auscultatory or Doppler echocardiographic evidence of mitral stenosis or aortic regurgitation.

Doppler and two-dimensional echocardiographic examinations. Two-dimensional images and Doppler echocardiograms were obtained with either an Advanced Technology Laboratory Mark V sector scanner equipped with a 3.0 MHz mechanical transducer or an Electronics for Medicine/Honeywell sector scanner equipped with 2.25 and 3.5 MHz mechanical transducers. Both systems have pulsed Doppler capability with a moveable Doppler cursor and an adjustable sample volume depth. The sample volume depth of the Electronics for Medicine transducer is adjustable to 16 cm and the sample volume length is adjustable from 2 to 20 mm (set at 5 mm for this study). The Advanced Technology Laboratory sample volume depth is adjustable to 17 cm and the sample volume size is fixed at 2 mm. Fast-Fourier transform analysis of the returning sound wave frequencies is used by both systems for graphic representation of the Doppler shifts.

Blood velocity (V) was calculated from the Doppler equation as

\[ V = \frac{(C)(\Delta F)}{2(fo)(\cos \theta)} \]

where \( C \) = sound velocity in tissue or 1540 m/sec; \( \Delta F \) = Doppler shift; \( fo \) = emitting frequency of the transducer; \( \theta \) = angle of incidence between the sound waves and flow. Because of the parallel orientation between sound waves and flow used in this investigation, \( \theta \) was assumed to be zero for all studies (cos \( \theta \) = 1.0). The Advanced Technology Laboratory system displays the Doppler shifts in kilohertz and conversion to velocity (in cm/sec) can be done by multiplying the Doppler shift by a factor of 25.7. The Electronics for Medicine system solves the Doppler equation automatically and displays the data as velocity (in cm/sec).

Patients were examined while in the left lateral recumbent position with the use of standard views from the parasternal and apical windows. Recordings of mitral inflow velocity were made as previously described\(^6\) from an apical four-chamber view that provided good visualization of the left ventricular cavity and mitral valve leaflets. The sample volume was placed at the level of the mitral anulus with the cursor oriented parallel to an imaginary line bisecting the left ventricle from apex to mitral valve and the Doppler signals were recorded at a paper speed of 100 mm/sec (figure 1).

Doppler and two-dimensional echocardiographic measurements and calculations. All measurements were made in at least five cardiac cycles and averaged with a computer-interfaced graphic analyzer (Digisonic EC-200) equipped with a tablet digitizer, internal calipers, and a videocassette system capable of frame-by-frame bidirectional playback. The diastolic filling period was defined as the interval from the upstroke to the downstroke of the Doppler signal. Early peak diastolic velocity and peak atrial velocity were measured as shown in figure 1. The TVI or area under the velocity curve for the entire diastolic filling period and for one-half of the filling period were derived by digitizing the contour of the darkest portion of the curve.

The diameter of the mitral anulus was measured from the four-chamber view two to three frames after initial maximal opening of the mitral valve in the same manner as described in our previous study of measurement of cardiac output.\(^6\) Measurements were taken from the inner edge of the lateral bright corner of the anulus to the inner edge of the medial corner just below the insertion of the mitral leaflets (figure 1). The cross-sectional area of the mitral anulus was derived from the anular diameter assuming a circular geometry such as \( \pi r^2 \), where \( r \) represents half of the diameter. The long-axis of the left ventricle was measured in the four-chamber view from the outer margin of the apex to the lateral corner of the mitral anulus, and the largest minor axis (D\(_{max}\)) was obtained as the largest internal diameter measured from either the parasternal long-axis or the apical view, as previously described.\(^7\)

Three indexes of diastolic function were calculated with the two-dimensional Doppler and Doppler echocardiographic measurements: (1) Peak filling rate (in ml/sec) was determined as the peak early diastolic velocity times the cross-sectional area of the mitral anulus. (2) Normalized peak filling rate (in sec\(^{-1}\)) was determined as peak filling rate divided by the left ventricular end-diastolic volume. End-diastolic volume (EDV) was derived with a method previously validated in our laboratory as EDV = \( (3.42 L \times D_{max}) - 6.44 \),\(^7\) where \( L \) = the long axis of the left ventricle. (3) Half filling fraction was determined as the TVI at one-half diastolic filling period divided by the total diastolic TVI.

Angiographic method. All of the angiographic studies were performed in one of three laboratories with the use of a brachial cutdown or percutaneous femoral technique. Single-plane left ventricular angiograms were obtained with patients in the 30 degree right anterior oblique position after the injection of 40 to 50 ml of contrast medium (meglumine diatrizoate) and at held midinspiration with use of frame rates of 30, 45, or 60 frames/sec (frame rates varied from laboratory to laboratory). A 1 cm grid was filmed to correct for magnification. Frame-by-frame left ventricular silhouettes were traced from one cardiac cycle during sinus rhythm that was not preceded by premature con-
tractions starting two frames before end-systole (smallest ventricular size) and ending two frames after end-diastole (largest ventricular size). Left ventricular volumes and ejection fractions were calculated with the single-plane modification of the area-length method and corrected for overestimation with the Kennedy regression equation. All measurements were made by an observer unaware of the results of the Doppler study.

A volume-time curve was computer generated from the individual data points and smoothed with a five-point least square quadratic estimation. The instantaneous slope or dV/dt of the volume curve was computed and plotted against time (figure 2). The diastolic filling period was determined as the duration of time between end-systole and end-diastole based on the cineangiographic frame rate.

Three indexes of diastolic function were obtained angiographically: (1) Peak filling rate was determined as the largest derivative constrained to the first one half of diastole (figure 2). (2) Normalized peak filling rate was defined as peak filling rate divided by end-diastolic volume. (3) First one half filling fraction was defined as the volume at one half diastolic filling period minus the end-systolic volume divided by stroke volume.

Statistical analysis. Correlations between Doppler and angiographic measurements were by linear regression analysis. Comparison between mean values was done by paired t test. Fisher’s exact test was used to assess the association between Doppler-determined and angiographic parameters.

Mean heart rate for the group was 69 beats/min during Doppler echocardiographic as well as during ventriculographic examination. However, individual variations did occur. Thus, to assess the influence of variation in diastolic filling period between the two tests on the different correlations, a subgroup of 15 patients for whom Doppler echocardiographic and angiographic diastolic filling periods were only ±18% different was analyzed separately.

Results

The angiographic and two-dimensional and Doppler echocardiographic data from all patients are listed in

FIGURE 1. Apical four-chamber view of the heart including the Doppler-determined sample volume (SV) at the mitral anulus plane (arrow). The Doppler-derived mitral inflow velocity shows early peak diastolic velocity (E) and peak atrial velocity (A). The diastolic filling period begins with the upstroke of the diastolic Doppler signal and ends with termination of the diastolic Doppler signal. LV = left ventricle; LA = left atrium; RA = right atrium; RV = right ventricle.

FIGURE 2. Top, Computer-generated graphic display of an angiographic frame-by-frame left ventricular volume curve during diastole. The diastolic filling period (DFP) is determined as the time between the end-systolic volume (ESV) and end-diastolic volume (EDV). V ½ is the absolute volume of the left ventricle at one half DFP. Bottom, Instantaneous slope or derivative of the volume curve. Peak filling rate (PFR) represents the largest derivative within the first half of diastole.
Table 1. Table 2 lists the correlation coefficients and p values for the linear regression analysis comparing the angiographic parameters and the Doppler measurements.

Morphologically the derivative of the angiographic diastolic left ventricular volume curve resembled the Doppler-determined velocity profile (figure 3). Patients with reduced peak filling rates angiographically frequently showed a relative increase in the Doppler velocity during atrial contraction, with an early peak diastolic to peak atrial velocity (E/A) ratio of less than 1.0.

There were no significant differences in the mean values for peak filling rate or normalized peak filling rate determined by Doppler echocardiography and those by angiography (peak filling rate, 296 ± 180 vs 283 ± 189 ml/sec; normalized peak filling rate, 1.9 ± 0.8 vs 2.0 ± 0.93 sec⁻¹, respectively). Likewise, the mean values for first one half filling fraction by either method were the same (0.55 ± 0.10 vs 0.55 ± 0.16).

A significant correlation was observed between angiographic and Doppler-derived peak filling rates, with an r value of .87 and an SEE of 91.5 ml/sec (figure 4, A). A similar correlation was observed between angiographic and Doppler-derived normalized peak filling rate, with an r value of .83 and an SEE of 0.52 sec⁻¹ (figure 4, B). The correlation between angiographically and Doppler-determined one half filling fraction was significant (p = .001), but the r value was low (.57) compared with those for peak filling rate and normalized peak filling rate (table 2). The correlation coefficient increased to .76 when the comparison was limited to the subgroup of 15 patients with similar diastolic filling period results by the two tests.
TABLE 2
Angiography vs Doppler linear regression analysis

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DFP = diastolic filling period; Angio = angiography; others as in table 1.

Patients with mitral regurgitation had higher values for peak filling rate and normalized peak filling rate (>600 ml/sec and >3.0 sec⁻¹, respectively) by both techniques than the other patients. In contrast, low values for peak filling rate and normalized peak filling rate (<200 ml/sec and <2.3 sec⁻¹) were observed in the majority of the patients with ischemic or primary cardiomyopathy. A wider range of values was seen among the other groups of patients.

A modest but significant correlation was observed between peak early diastolic velocity and angiographic peak filling rate (r = .64). The correlations between the E/A ratio and the angiographic measurements were poor, with only the comparison with one half filling

**FIGURE 3.** Examples of angiographic volume curves and their derivatives with Doppler recordings of mitral anulus velocity in four different patients; one with a normal left ventricle (A), one with mitral regurgitation in (B), one with coronary artery disease and abnormal regional wall motion (C), and one with cardiomyopathy (D). Note the similarity between the derivative and the Doppler-determined velocity curves.
fraction achieving statistical significance. However, in the subgroup of 15 patients with similar results for diastolic filling period by the two tests, the comparison between E/A ratio and the angiographic parameters became highly significant, with \( r \) values ranging from .72 to .85.

A significant association (\( p < .01 \)) was found by Fisher’s exact test between measurements of early peak diastolic velocity and the E/A ratio by Doppler echocardiography and the angiographic measurement of normalized peak filling rate and one half filling fraction, with 2.3 sec\(^{-1}\) and 0.60 as cutoffs between normal and depressed values for the two parameters, respectively. These values were selected from the literature recognizing that insufficient data exist to define a normal range in large populations. Normal values for normalized peak filling rate and one half filling fraction were associated with an early peak diastolic velocity of 45 cm/sec or more in 100% and 94% of instances, respectively, and with an E/A ratio of 1.0 or more in 89% and 100% of instances, respectively. Lower values for normalized peak filling rate and one half filling fraction were associated with an early peak diastolic velocity of less than 45 cm/sec in 38% of instances, and with an E/A ratio less than 1.0 in 71% and 89% of instances, respectively.

**Discussion**

This study demonstrates the similarity between measurements of transannular mitral inflow determined with Doppler echocardiographic and angiographic measurements of left ventricular filling parameters. In addition to the similarity between the derivative of the diastolic left ventricular volume curve and the Doppler-derived mitral inflow velocity, measurements of peak filling rate and normalized peak filling rate by the two techniques correlated well with each other. Importantly, patients with extremely high and low filling rates were recognized by both. Interestingly, patients with reduced early filling rates frequently had a relative increase in atrial inflow velocity on their Doppler echocardiograms, resulting in a reversal of the early peak diastolic to peak atrial velocity ratio.

The major advantage of the Doppler technique is that it provides a noninvasive evaluation of diastolic function on a beat-by-beat basis, which should make it ideal for serial measurements. Except for the determination of end-diastolic volume, the other measurements needed are independent of ventricular geometry and are readily accessible in a majority of patients from the apical window. Of the initial 49 patients evaluated, none were excluded because of inadequate Doppler or two-dimensional echocardiographic studies. In our experience, the failure rate for recording Doppler flow velocities at the mitral anulus is on the order of 2%. In contrast, 11 of the 49 patients were excluded after the ventriculographic examination because of poor ventricular opacification or frequent premature ventricular contractions. Furthermore, only one cardiac cycle was processed in the remaining patients because of the need for excellent frame-by-frame opacification of the left ventricular cavity in the earliest possible beat. This is in marked contrast with the ability of Doppler echocardiography to average several cardiac cycles.

Our experience illustrates some of the limitations of contrast angiography in the assessment of diastolic function. In addition, the accuracy of angiography is dependent on the geometric considerations used in calculating volumes, the frame rate of the photographic system, the method chosen for curve smoothing, and the potential effects of the contrast medium on the
parameters measured. Nevertheless, angiography still represents the standard of comparison for any new method. The results of this investigation are, therefore, quite encouraging considering the potential sources of error for both techniques.

The main limitations of assessing left ventricular filling by Doppler echocardiography appear to be related to the determination of the cross-sectional area of the mitral anulus and the end-diastolic volume by two-dimensional echocardiography. The Doppler-determined inflow velocities are similar to those used in the derivation of stroke volume and are highly reproducible. The primary source of error of the velocities in assessing diastolic left ventricular function is the presence of significant aortic regurgitation or any other form of dual left ventricular filling. In contrast, the morphologic part of the method can be affected by the quality of the two-dimensional images, the presence of significant mitral annular calcification, and by errors introduced in the conversion of echocardiographic measurements into cross-sectional areas and left ventricular volumes. These errors may limit the accuracy of the technique in comparing peak filling rate and normalized peak filling rate between patients. On the other hand, these errors may be of lesser importance in serial measurements within the same patient when changes over time in echocardiographic dimensions are minor. For these reasons, we also elected to assess the use of the mitral inflow velocities alone as indexes of diastolic function.

A significant correlation was observed between peak early diastolic velocity and the angiographic measurement of peak filling rate. However, the low correlation coefficient precluded a close estimation of filling rates. Nevertheless, an early peak diastolic velocity of less than 45 cm/sec was highly associated with low values for the angiographic parameter. Thus, except for the extremes, measurements of early peak diastolic velocity alone without some estimate of cross-sectional area do not provide accurate between-patient assessments of peak filling rate. Early peak diastolic velocity may be used, however, to follow the effect of an intervention on peak filling rate if the intervention does not alter the cross-sectioned area of the mitral anulus.

Half filling fraction is an index of left ventricular filling that may be depressed in patients with coronary artery disease and has been useful in distinguishing restrictive cardiac amyloidosis from constrictive pericarditis. It has the additional advantage that it can be computed by the Doppler method without the need for measuring cross-sectional areas or ventricular volumes. Furthermore, this index incorporates the relative contribution to filling of early vs late diastole (or atrial systole). The E/A ratio is an even simpler measurement that also reflects the interaction of early and late diastolic filling. Both E/A ratio and one half filling fraction as determined by Doppler echocardiography correlated with the angiographic parameters of left ventricular filling, but predominantly in the patients with similar results for diastolic filling period in the two studies. This is not a surprising finding since the length of diastolic filling has been known to alter the relative contribution of atrial contraction to ventricular filling. Nevertheless, the association of the E/A ratio with angiographic one half filling fraction was such that the use of a cutoff value of 1.0 for the ratio allowed separation of normal (≥0.60) from reduced one half filling fraction in 93% of all patients studied.

Our results, therefore, indicate that the velocity of blood flow through the mitral anulus as determined by the Doppler method is influenced directly by alterations in left ventricular filling and that the product of velocity and annular area provides a measurement of left ventricular filling rate. These findings validate the use of the Doppler technique to assess left ventricular filling dynamics noninvasively in the absence of inflow obstruction or aortic regurgitation. Application of this technique should facilitate the evaluation of diastolic function in normal populations of various ages, in disease groups, and after physiologic or therapeutic interventions.

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