Continuous Wave Doppler Echocardiography for Noninvasive Assessment of Left Ventricular dP/dt and Relaxation Time Constant From Mitral Regurgitant Spectra in Patients

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Objectives. We previously demonstrated experimentally that the mitral regurgitant velocity spectrum can be used to estimate left ventricular pressure throughout systole and may provide a new noninvasive method for estimating maximal dP/dt and the relaxation time constant. This study was designed to test this method in patients.

Background. The maximal first derivative of left ventricular pressure (dP/dt) and the time constant of left ventricular isovolumetric relaxation (r) are important variables of left ventricular function, but the need for invasive measurement with high fidelity catheters has limited their use in clinical cardiology.

Methods. Twelve patients with mitral regurgitation were studied. The Doppler mitral regurgitant velocity spectrum was recorded simultaneously with micromanometer left ventricular pressure tracings in all patients. The regurgitant velocity profiles were digitized and converted to ventricular-atrial (VA) pressure gradient curves using the simplified Bernoulli equation and differentiated into instantaneous dP/dt. The relaxation time constant (r) was calculated assuming a zero pressure asymptote from catheter left ventricular pressure decay (τc) and from the Doppler-derived VA gradient curve with corrections. Two methods were used to correct the Doppler gradient curve to better approximate the left ventricular pressure decay before calculating the relaxation time constant: 1) adding an arbitrary 10 mm Hg (τ0), and 2) adding the actual mean pulmonary capillary pressure (τLA).

Results. The Doppler-derived maximal positive dP/dt (1,394 ± 302 mm Hg/s [mean ± SD]) correlated well (r = 0.91) with the catheter-derived maximal dP/dt (1,449 ± 307 mm Hg/s). Although the Doppler-derived negative maximal dP/dt differed slightly from catheter measurement (1,014 ± 289 vs. 1,195 ± 354 mm Hg/s, p < 0.01), the correlation between Doppler and catheter measurements was similarly good (r = 0.95, p < 0.0001). The correlation between τc and τ was excellent (r = 0.93, p < 0.01), but the Doppler-derived τ (50.0 ± 11.0 ms) slightly underestimated the catheter-derived τc (55.5 ± 12.8 ms, p < 0.01). This slight underestimation could be corrected by adding the actual pulmonary capillary wedge pressure to the Doppler gradient curve.

Conclusions. Doppler echocardiography provides an accurate and reliable method for estimating left ventricular maximal positive dP/dt, maximal negative dP/dt and the relaxation time constant (r) in patients with mitral regurgitation.

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The noninvasive evaluation of left ventricular systolic and diastolic function remains an important goal in cardiology (1-9). According to the Bernoulli equation, analysis of the Doppler mitral regurgitant velocity profile allows accurate calculation of the left ventricular pressure difference throughout systole and early diastole before mitral valve opening (2,3). Differentiation of this pressure difference then yields the rate of change in the left ventricular pressure (dP/dt)—in particular, peak positive dP/dt during isovolumetric contraction and peak negative dP/dt during ventricular relaxation (3). Furthermore, analysis of this pressure difference during isovolumetric relaxation can yield the relaxation time constant (4). We previously hypothesized that if changes in left atrial pressure during isovolumetric systole and diastole are negligible in relation to changes in left ventricular pressure, 1) the mitral regurgitant velocity up-slope should predict the left ventricular pressure increase during isovolumetric systole, and, thus, peak dP/dt, and 2) the mitral regurgitant velocity down-slope should predict the decay in left ventricular pressure during isovolumetric relaxation and thus yield peak negative dP/dt and the relaxation time constant. This hypothesis was examined in a canine model, and the results have been published elsewhere (3,4). However, such a detailed analysis has not been performed in humans. Therefore, the purpose of this study was to test the accuracy of Doppler-derived dP/dt and the reliability of the...
Doppler-derived relaxation time constant in patients with mitral regurgitation.

Methods

This study was conducted in 12 patients with mitral regurgitation who underwent routine cardiac catheterization at Massachusetts General Hospital (9 patients) or Hamburg University Hospital (3 patients). There were eight men and four women, with a mean age of 47 ± 18 years (range 21 to 72). Semiquantitative severity of mitral regurgitation was 1 to 2+ in 10 of 12 patients; 1 patient had 3+; and 1 had 4+ regurgitation by angiography (9). The etiology of mitral regurgitation was coronary artery disease in seven patients, cardiomyopathy in three and rheumatic mitral regurgitation in two. Ten patients were in sinus rhythm, and two had atrial fibrillation. In all patients, high fidelity left ventricular pressures were obtained during cardiac catheterization with micromanometer catheters and recorded simultaneously with continuous wave Doppler mitral regurgitant spectra.

Data acquisition. Doppler echocardiography. Two-dimensional echocardiographic images and continuous wave and color Doppler data were acquired using a Hewlett-Packard 72020 ultrasound imaging system. The presence of mitral regurgitation was defined by color Doppler flow mapping. The mitral regurgitant velocity curves were obtained from an apical approach by using either a nonimaging Doppler transducer or a combined imaging and Doppler transducer. In each case, the continuous wave Doppler ultrasound beam was aligned as parallel as possible to the color Doppler mitral regurgitant jets. If a blind continuous wave Doppler transducer was used, then the maximal and most clearly delineated velocity envelopes were recorded (3,4). All Doppler spectral velocity profiles and two-dimensional images were recorded at a speed of 100 mm/s on 0.5 in. (1.27 cm) videotape for further analysis.

Cardiac catheterization. Left heart catheterization was performed by way of the right femoral artery. A micromanometer-tipped catheter (Millar Mikro-tip, Millar Instruments) was inserted over a guide wire into the left ventricle to record ventricular pressure. Pulmonary capillary wedge pressures were recorded by using a Swan-Ganz flow-directed catheter. Great care was taken to ensure the accuracy of the pressure measurements. Fluid-filled transducers were balanced at atmospheric pressure and calibrated. All pressure measurements and a single electrocardiographic lead were continuously recorded on an eight-channel strip chart recorder. Paper speed was increased to 100 mm/s when recording was simultaneous with Doppler recording.

Data analysis. Doppler-derived dP/dt. The data were processed in the following manner: The continuous wave Doppler mitral regurgitant profile was traced manually—beginning at the initial part of the QRS wave and ending at the zero crossover point—and digitized at 5-ms intervals by using a Bitpad (Summagraphics, Inc.) interfaced with a customized program written in the Asyst programming environment (Macmillan, Inc.) (3,4). The instantaneous pressure decrease between the ventricle and atrium was calculated from the modified Bernoulli equation: ΔP = 4v², where ΔP is the pressure gradient (mm Hg), and v is the instantaneous regurgitant jet velocity (m/s). The pressure gradient curve was then reconstructed for each traced heartbeat (Fig. 1A). The instantaneous left ventricular dP/dt throughout systole and early diastole (isovolumetric relaxation period) was determined from this reconstructed pressure curve by differentiating the data at 5-ms intervals (Fig. 1A). The maximal dP/dt during the early systolic phase and the negative maximal dP/dt at the early diastolic phase were obtained from the instantaneous dP/dt curve (3). For each patient, three cardiac cycles were analyzed and the values averaged for further comparison.

Doppler-derived relaxation time constant. The left ventricular relaxation time constant (τ) was calculated assuming a zero pressure asymptote (6): P(t) = P₀e⁻ᵗ⁻τ, where P₀ is left ventricular pressure at the time of maximal negative dP/dt, at which point time t = 0, and τ was calculated by exponential regression (Fig. 1B). The natural logarithm of P was fitted to the line Bt + A, and τ was defined as −1/B, the negative reciprocal of the regression slope. Because the logarithm of left ventricular pressure minus atrial pressure is not equal to the logarithm of left ventricular pressure, an estimated atrial pressure was added to adjust the Doppler-derived pressure gradient curve to approximate left ventricular pressure (P) from which to calculate the Doppler-derived τ (4). On the basis of our earlier animal investigations (4), a fixed 10 mm Hg was added to the Doppler-derived VA pressure gradient for calculation of the relaxation time constant (τLV). Alternatively, we also used the actual pulmonary capillary wedge pressure added to the atriovenous (AV) pressure gradient for calculation of the relaxation time constant (τLA). For each hemodynamic stage, three cardiac cycles were analyzed and the values averaged for further comparison.

Catheter measurements. Simultaneous Millar catheter-recorded left ventricular pressures were manually traced and digitized at 5-ms intervals beginning at the initial part of the QRS wave and ending when the ventricular pressure was equal to the end-diastolic pressure. Instantaneous left ventricular dP/dt was determined from the ventricular pressure curve by numeric differentiation at 5-ms intervals. Maximal dP/dt at the early systolic phase and the negative maximal dP/dt at the early diastolic phase were obtained from the instantaneous dP/dt curve. Likewise, the left ventricular relaxation time constant was calculated using the zero asymptote, as proposed by Weiss et al. (6). For each patient, three cardiac cycles were analyzed and the values averaged for further comparison.

Statistical analysis. Data are expressed as mean value ± SD. Comparisons of maximal positive dP/dt, maximal negative dP/dt, and the relaxation time constant between Doppler and catheterization measurements were performed using...
deviation of the difference between Doppler- and catheter-based measurements (10). A p value ≤ 0.05 was considered statistically significant.

Results

Peak left ventricular systolic pressure was 123 ± 22 mm Hg, with an end-diastolic left ventricular pressure of 18 ± 4 mm Hg. The pulmonary capillary wedge pressure recording was obtained in only eight patients, demonstrating a mean pulmonary capillary pressure of 19 ± 5 mm Hg and a systolic (v) wave of 23 ± 7 mm Hg. The left ventricular ejection fraction measured by echocardiography was 56 ± 7%.

Peak positive dp/dt. For the 12 patients analyzed, the peak positive dp/dt derived from the Doppler mitral regurgitant velocity profiles (1,394 ± 302 mm Hg/s) was slightly lower than that derived from the Millar catheter recordings (1,449 ± 307 mm Hg/s), but the difference was not statistically significant (ΔdP/dt = -55 ± 126 mm Hg/s, p = NS). Overall correlation was excellent (r = 0.91, standard deviation of regression 131 mm Hg/s), and the two data sets lay close to the line of identity (Fig. 2).

Peak negative dp/dt. Similarly, Doppler estimation of peak negative dp/dt correlated well with the hemodynamic assessment (Fig. 3) but with a somewhat more prominent underestimation than that seen with peak positive dp/dt. There was a significant difference (p < 0.05) between Doppler peak negative dp/dt (1,014 ± 289 mm Hg/s) and the peak negative dp/dt from catheterization data (1,195 ± 154 mm Hg/s), with Δ(-dP/dt) = -182 ± 145 mm Hg/s.

Left ventricular relaxation time constant (τ). Figure 4 compares measurements of the relaxation time constant (τ), with the hemodynamic assessment along the x axis (τC = 55.5 ± 12.8 ms) and Doppler measurement along the y axis (τD = 50.0 ± 11.0 ms). There was a slight underestimation of the relaxation time constant by the Doppler method (Δτ = -5.5 ± 4.9 ms, p < 0.01) when the VA gradient was adjusted by adding an assumed left atrial pressure of 10 mm Hg, but overall there was excellent correlation across the data range. When the VA gradient was corrected by the mean pulmonary capillary wedge pressure (n = 8), the correlation between the Doppler-derived (τD = 57.3 ± 14.5 ms) and catheter-derived (τC = 58.5 ± 14.7 ms) relaxation time constants improved (Fig. 5), and no significant difference was found between the Doppler and catheter measurements (Δτ = 1.9 ± 7.6 ms, n = 8, p = NS).

Discussion

Widespread use of isovolumetric variables of left ventricular systolic and diastolic function is limited in large part by the need for invasive, high fidelity pressure measurements at cardiac catheterization. The present study has demonstrated that these important indexes of ventricular function can be quantified noninvasively by using Doppler echocardiography in patients with mitral regurgitation. Peak left ventricular...
dP/dt can be accurately determined from the upslope of the mitral regurgitant velocity profile, whereas the velocity downslope closely correlates with the peak negative dP/dt. Furthermore, the time constant of left ventricular relaxation (τ) can be calculated from the Doppler VA gradient curve in isovolumetric diastole after correction for estimated left atrial pressure. Because some degree of mitral regurgitation is commonly observed in patients with heart disease, these results may prove widely applicable in the routine evaluation of ventricular systolic and diastolic function by Doppler echocardiography if left atrial pressure is estimated by using Doppler echocardiography or pulmonary capillary wedge pressure simultaneously.

**Accuracy of ventricular dP/dt.** Accurate estimation of left ventricular dP/dt from the Doppler-derived VA gradient curve depends on several factors. First, the pressure gradient must be accurately calculated using the simplified Bernoulli equation. For the peak pressure difference across restrictive orifices typical of valvular regurgitation, this accuracy has been demonstrated both in experimental and clinical studies (2,3,7). However, when considering the instantaneous pressure difference, one cannot neglect a priori the inertial term in the complete Bernoulli equation, which has its largest magnitude at times of rapid velocity changes. Furthermore, there is concern that the finite temporal resolution of contemporary continuous wave Doppler equipment, which gathers data for 5 to 10 ms between Fourier transform velocity estimates, may limit the accuracy of tracking rapidly changing velocity (8). Fortunately, it has previously been shown in a canine model of mitral regurgitation that the instantaneous pressure gradient and its first derivative can be accurately measured throughout systole and isovolumetric diastole by applying the simplified Bernoulli equation to the Doppler mitral regurgitant velocity profile (3), supporting its use in human mitral regurgitation.

Second, one must consider the impact of atrial pressure on these calculations because we measure the VA pressure difference ∆P but use it as a surrogate for ventricular pressure itself. For dP/dt calculations, the rate of change of atrial pressure is of critical concern. If atrial pressure were constant, regardless of its absolute magnitude, then d ∆P/dt would precisely equal ventricular dP/dt. We have shown directly in the previous canine study (3) and by inference in the current study that at the time of peak positive ventricular...

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**Figure 2.** Top, Correlation between the maximal positive first derivative of left ventricular (LV) pressure (dP/dt) determined by the Doppler method and by Millar catheter-recorded left ventricular pressure. Bottom, Agreement plot of the difference between Doppler and catheter measurements of the maximal dP/dt. Note that there was no significant systematic underestimation or overestimation. SDR = standard deviation of regression.

**Figure 3.** Top, Correlation between the maximal negative dP/dt determined by the Doppler method and by Millar catheter-recorded left ventricular pressure. Bottom, Agreement plot of the difference between Doppler and catheter measurements of the maximal negative dP/dt. Note that there was a systematic underestimation by Doppler method. Abbreviations as in Figure 2.
dP/dt, the change in atrial pressure is negligible, leading to the accurate results shown in Figure 2.

For the maximal negative dP/dt, the decrease in atrial pressure associated with the downslope of the v wave during isovolumetric ventricular relaxation has a more adverse impact on the Doppler estimation. Both the previous canine investigation (3) and the current study show that the Doppler method tended to underestimate the catheter-derived peak negative dP/dt. Nevertheless, despite an average 15% underestimation, a very strong correlation was noted between these measurements (Fig. 3).

Doppler estimation of relaxation time constant (τ). Whereas Doppler-derived dP/dt is affected only by changes in atrial pressure, prediction of the exponential time constant of ventricular relaxation must also consider the absolute level of atrial pressure. This is due to fixed shifts in ventricular pressure that profoundly affect the results of exponential regression because of the nonlinear nature of the logarithmic transformation. Therefore, to obtain an accurate measurement of relaxation time constant, some estimate of atrial pressure must be added to the VA gradient. Ideally, this should be based on actual measured atrial pressure. An estimate of left atrial pressure from a pulmonary artery balloon catheter or from the difference between the systolic arterial pressure and the peak Doppler VA gradient should be available in most patients with mitral regurgitation (7). Alternatively, from our animal experiments, it appears that adding a fixed 10 mm Hg to the Doppler gradient yields an accurate estimation of relaxation time constant across a wide range of actual left atrial pressures (4). In the current human study, the Doppler-derived relaxation time constant calculated using a 10-mm Hg correction for mean atrial pressure also correlated well with the hemodynamic relaxation time constant. However, relaxation time constant was slightly (5.5 ms, 10% of the mean value) but significantly underestimated (Fig. 4), perhaps reflecting the higher pulmonary capillary pressure actually observed in these patients, which averaged 19 mm Hg. Correction using actual pulmonary capillary wedge pressure yielded better agreement (Fig. 5). Significant overestimation of relaxation time constant could result if a large atrial v wave (e.g., from acute severe mitral regurgitation) decreased rapidly during isovolumetric relax-
ation, leading to a flattening of the reconstructed ventricular pressure curve. Therefore, accuracy of relaxation time constant measurement based on the Doppler mitral velocity profile is adversely affected by an extremely elevated left atrial pressure and v wave, and correction by adding an estimated left atrial pressure to the Doppler data should be sought under these situations. Fortunately, in many patients an estimate of left atrial pressure may be available from pulmonary artery monitoring or from noninvasive measurement either by Doppler mitral inflow velocity profile or by subtracting the peak Doppler VA pressure gradient from systolic arterial blood pressure. Such estimates need not be precise because we have shown that adding an arbitrary value of 10 mm Hg to VA gradient data yielded accurate estimates of relaxation time constant in a wide range of actual left atrial pressures (4).

Several approaches have been proposed for calculating the exponential time constant of ventricular relaxation (9-14), assuming decay to a zero or nonzero pressure asymptote. Previous animal studies have shown relaxation time constant calculated using a zero asymptote to be an accurate approach in most cases (6,15,16,17), with less sensitivity to random noise in the data. Yellin et al. (13) have evaluated the accuracy of relaxation time constant calculated using a zero asymptote compared with the true relaxation time constant calculated using the actual asymptote in a nonfilling dog ventricle model by totally occluding the mitral annulus during one cardiac cycle, which allowed the ventricle to relax to its minimal pressure \( P_0 \) of \(-7.3 \pm 3.3 \) mm Hg (13). In that model, they demonstrated that relaxation time constant calculated using a zero asymptote is not different from the true relaxation time constant based on the nonfilling cycle. However, the zero asymptote may lead to significant error if the minimal pressure \( P_0 \) is extremely negative, as suggested by Ohtani et al. (16). There have been very limited data with regard to left ventricular minimal pressure in the human nonfilling ventricle. Paulus et al. (17) recorded a left ventricular minimal \( P_0 \) pressure ranging from \(-3 \) to \(-7 \) mm Hg during balloon occlusion of the mitral orifice in patients with mitral stenosis undergoing mitral balloon valvuloplasty. The zero asymptote was demonstrated to yield more accurate estimates of actual relaxation time constant than the nonzero asymptote approach in their study (17). In our previous animal study (3), we showed that the Doppler-derived relaxation time constant calculated using a zero asymptote accurately predicted the catheter-derived relaxation time constant using the same calculation (4). This, therefore, was the approach used in the current study.

An alternative method for calculating relaxation time constant \( \tau \) is to allow the pressure to decay to an arbitrary asymptote \( P_B \); \( P(t) = P_0 e^{-\frac{t}{\tau}} + P_B \). The variables \( P_B \) and \( P_0 \) and \( \tau \) can be estimated by either linear regression of \(-dP/dt\) against \( P \) or by nonlinear least-squares techniques (11,14-16). A potential advantage of this approach is that relaxation time constant defined in this way is independent of left atrial pressure, which is subsumed in the adjustable \( P_B \). Unfortunately, relaxation time constant defined with an arbitrary asymptote has been shown to have much greater beat to beat variability than the zero asymptote relaxation time constant and to deviate significantly from the zero asymptote relaxation time constant (13,17). This is probably due to the fact that allowing the nonzero asymptote involves a third degree of freedom in the variable estimation, resulting in increasing the correlation of the fit but only at the expense of widened variable confidence intervals.

Study limitations. The major limitation of this Doppler method is the requirement that patients have mitral regurgitation detectable by continuous wave Doppler echocardiography. Fortunately, mitral regurgitation is commonly observed in normal patients and is usually present in congestive, ischemic and hypertrophic cardiomyopathies (18-23). A further difficulty is to obtain a complete, well delineated regurgitant spectral envelope in patients with trace mitral regurgitation and eccentrically directed mitral regurgitant jets. In the current study we were able to record clear, complete velocity curves from eccentric regurgitant jets using apical views without significantly off-angle Doppler mitral velocity profile recording. As with any Doppler velocity measurement, the ultrasound beam must be aligned parallel to the velocity vectors at the regurgitant orifice to prevent underestimation of the pressure gradients. Underestimation of the VA gradient by a significantly off-angle recorded Doppler velocity profile could lead to underestimation of relaxation time constant. Thus, careful scanning is necessary to obtain maximal velocity spectra by blind Doppler transducer using auditory monitoring or by image-directed continuous wave Doppler transducers. However, a large scale prospective study is necessary to evaluate the feasibility and reproducibility of this method in unselected patients.

Current implementation of this instantaneous Doppler method demands careful hand digitization of the mitral regurgitant velocity profile. It is possible that if this method were integrated into the imaging software of an echocardiograph, an automated determination of isovolumetric variables might be easily accomplished.

Summary. In patients with mitral regurgitation, an isovolumetric variable of systolic left ventricular function, the maximal positive dP/dt, can be accurately estimated by using the upslope of the Doppler regurgitant velocity spectrum. The downslope of the Doppler spectrum allows calculation of indexes of left ventricular relaxation, such as maximal negative dP/dt and the relaxation time constant \( \tau \); however, the latter measurement requires an estimate of left atrial pressure. The Doppler-derived peak negative dP/dt and relaxation time constant are slightly underestimated, a problem anticipated to be more prominent in patients with high left atrial v wave pressure.
References


