Noninvasive Measurement of the Time Constant of Left Ventricular Relaxation Using the Continuous-Wave Doppler Velocity Profile of Mitral Regurgitation

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Background. The time constant of isovolumic relaxation (τ) is an important parameter of ventricular diastolic function, but the need for invasive measurement with high-fidelity catheters has limited its use in general clinical cardiology. The Doppler mitral regurgitant velocity spectrum can be used to estimate left ventricular (LV) pressure throughout systole and may provide a new noninvasive method for estimating τ.

Methods and Results. Mitral regurgitation was produced in nine dogs, and ventricular relaxation was adjusted pharmacologically and with hypothermia. High-fidelity ventricular pressures were recorded, and τ was calculated from these hemodynamic data (τ₀) assuming a zero-pressure asymptote. Continuous-wave mitral regurgitant velocity profiles were obtained, and the ventriculo-atrial (VA) pressure gradient was calculated by the simplified Bernoulli equation; τ was calculated from the Doppler data from the time of maximal negative dP/dt until LV-LA pressure crossovers. Three methods were used to correct the Doppler VA gradient to better approximate the LV pressure before calculating τ: 1) adding actual LA V wave pressure (to yield τ₁); 2) adding 10 mm Hg (τ₂); and 3) no adjustment at all (actual VA gradient used to calculate τ₃). The agreement between τ₀ and the three Doppler estimates of τ was assessed by linear regression and by the mean and standard deviation of the error between the measurements (Δτ).

Conclusions. This study demonstrates that the Doppler mitral regurgitant velocity profile can be used to provide a direct and noninvasive measurement of τ. Because mitral regurgitation is very common in cardiac patients, this method may allow more routine assessment of τ in clinical and research settings, leading to a better understanding of the role of impaired ventricular relaxation in diastolic dysfunction and the effect of therapeutic interventions. (Circulation 1992;86:272–278)

Key Words • diastolic function • Doppler echocardiography • τ
sured by using a combination of phonocardiography and M-mode or Doppler echocardiography alone, has been demonstrated to be related to $\tau$\textsuperscript{17}. Unfortunately, isovolumic relaxation time is also affected by both aortic and LA pressure.$\textsuperscript{18}$

We have previously demonstrated that the left ventriculoatrial (VA) pressure difference during systole and isovolumic diastole can be reliably and accurately determined by using continuous-wave Doppler mitral regurgitant velocity profiles.$\textsuperscript{19}$ In this study, we sought to extend these observations to derive LV $\tau$ from the isovolumic diastolic period of the Doppler mitral regurgitant velocity decay. We hypothesized that the VA pressure decay curve should reflect LV pressure decay if the LA pressure fluctuation were relatively minor during the isovolumic relaxation period. We tested this hypothesis in a canine model of mitral regurgitation in which continuous-wave Doppler mitral regurgitant velocity profiles could be obtained under various hemodynamic conditions representing a wide range of LV $\tau$. The Doppler-derived $\tau$ values were compared with those calculated from simultaneously recorded LV pressure.

**Methods**

**Animal Preparation**

This study conformed to the guiding principles of the American Heart Association guidelines for animal research. The experimental protocol has been previously described.$\textsuperscript{19}$ Briefly, nine adult dogs (weight, 25–34 kg) were anaesthetized with 30 mg/kg i.v. sodium pentobarbital, intubated, and ventilated with a Harvard respirator. A left thoracotomy was performed with the animal in supine position. The pericardium was opened, and a micromanometer-tipped catheter (Millar Mikro-tip, Millar Instruments, Houston, Tex.) and a short, narrow-bore fluid-filled catheter connected to a pressure transducer (Statham P23DB, Statham Instruments, Oxnard, Calif.) were inserted through the LV apex to record ventricular pressure. A second micromanometer-tipped catheter was inserted through a pulmonary vein into the LA to record LA pressure, and a third passed from the internal mammary artery into the aortic root to record aortic pressure.

Great care was taken to ensure the accuracy of the pressure measurements. Fluid-filled transducers were balanced at atmospheric pressure and calibrated against a mercury column. Micromanometer-tipped catheters were calibrated against the zero and mean pressures recorded by the fluid-filled transducers. All pressure measurements and a single ECG lead were continuously recorded on an eight-channel strip chart recorder (Hewlett-Packard model 7700, Hewlett-Packard, Waltham, Mass.). Paper speed was increased to 100 mm/sec when data for each experimental stage were formally recorded.

To control cardiac output, all venous return was drained from the superior and inferior venae cavae and coronary sinus and returned to the right atrium by calibrated roller pump. A second roller pump added or removed blood from the femoral arteries, thus allowing LV afterload to be varied independently of preload.$\textsuperscript{11}$

To create mitral regurgitation, short plastic tubes with diameters ranging from 2.8 to 4.5 mm were inserted into the anterior mitral leaflet, resulting in peak regurgitant flow rate ranging from 21 cm$^3$/sec to 88 cm$^3$/sec. In six dogs, the LA was enlarged by attaching a skin graft or prosthesis to the posterior wall of the atrium.

**Experimental Protocol**

In the first phase of the experiment, arterial pressure was altered by manipulating roller pump flow into or out of the femoral artery. Using this maneuver, systolic arterial pressure ranged from 65 to 145 mm Hg. In the second stage of the experiment, intravenous calcium (1 g) or propranolol (5 mg) was used to alter systolic and diastolic function. Finally, hypothermia was induced by cooling the blood during bypass, thereby allowing more dramatic alterations of $\tau$.$\textsuperscript{20}$ In total, 36 hemodynamic stages were obtained in nine dogs. In each experimental stage, the Doppler velocity profile, ECG, and LA, LV, and aortic pressures were recorded simultaneously.

**Doppler echocardiography.** For echocardiographic examination, the heart was stabilized in a pericardial cradle. Two-dimensional, continuous-wave, and color Doppler echocardiographic data were acquired by using a Hewlett-Packard 72020 ultrasound imaging system. The mitral regurgitant velocity curves were obtained by using an apical approach (four dogs) or an LA site (five dogs). In each case, the continuous-wave Doppler ultrasound beam was aligned as parallel as possible to the color Doppler mitral regurgitant jets. When a blind continuous-wave Doppler transducer was used, it was initially positioned based on the color Doppler images, and the maximal and most clearly delineated velocity envelopes were recorded. All echocardiographic data were recorded on half-inch videotape, and Doppler spectral velocity profiles were recorded at a speed of 100 mm/sec on strip chart paper for further analysis.

**Data Analysis**

The continuous-wave Doppler mitral regurgitant profile was traced manually from the onset of the QRS wave until the zero crossover point of the velocity and digitized at 5-msec intervals with customized computer software (ASYST, Macmillan, Inc., New York). The instantaneous pressure drop between LV and LA was calculated throughout systole from the modified Bernoulli equation $\Delta p = 4v^2$, where $\Delta p$ equals the pressure difference (mm Hg) and $v$ equals the instantaneous regurgitant jet velocity (meters per second) (Figure 1). The instantaneous LV $dp/dt$ throughout systole and isovolumic diastole was determined by differentiating this reconstructed pressure curve.$\textsuperscript{19}$ LA and LV pressure curves, recorded simultaneously with the Doppler data, were manually traced and digitized at 5-msec intervals beginning at the onset of the QRS wave and ending at the LA and LV pressure crossover. From these curves, instantaneous VA pressure gradient and LV $dp/dt$ were calculated.

The LV relaxation time constant ($\tau$) was calculated from both Doppler and catheter data, assuming a zero-pressure asymptote$\textsuperscript{6,21}$: $p(t) = p_0 e^{-t/\tau}$, where $p_0$ is LV pressure at the time of maximal negative $dp/dt$, at which point time $t$ is assigned to be 0. $\tau$ was calculated by exponential regression: the natural logarithm of $p$ was fitted to the line $A + Bt$, and $\tau$ was defined as $-1/B$. This method was initially applied to the uncorrected Doppler gradient data to yield $\tau_0$. Because the Doppler-derived
pressure data reflected the difference in LV and LA pressures (rather than actual LV pressures), we anticipated a systematic error in τ estimation. To overcome this, we tested two different adjustments to the Doppler data to better approximate true LV pressure before calculating τ: 1) addition of the actual LA pressure (measured hemodynamically at the time of LV–LA pressure crossover) to Δp to calculate τLA and 2) addition of a fixed LA pressure of 10 mm Hg to Δp to calculate τlob. For each hemodynamic stage, three cardiac cycles were analyzed, and the values were averaged for further comparison. LV pressure and pressure difference data were analyzed from the time of maximal negative dp/dt until LV–LA pressure crossover.

Variability study. To determine intraobserver variability, Doppler- and Millar catheter-derived τ from 10 hemodynamic stages were determined by one examiner (C.C.) on two separate days and paired for statistical comparison. The correlation coefficient of linear regression analysis between the two measurements was 0.96 (p<0.0001) for Doppler-derived τ and 0.95 (p<0.0001) for Millar-derived τ.

Statistical analysis. Data are expressed as mean±SD. Linear regression was used to compare Doppler- and catheter-derived VA pressure gradients. The hemodynamically determined τ (τH) and the variously adjusted Doppler-determined τ (τb, τLA, and τlob, symbolized generally by τb) were compared by linear regression. In addition, the error in the estimation (Δτ=τb−τH) was studied for bias and scatter by analysis of agreement.22 The proportional error between Doppler- and catheter-derived τ (Δτ/τH) was correlated with the mean LA pressure and LA V wave pressure by using linear regression. A value of p<0.05 was considered statistically significant.

Results
For all stages analyzed, the peak LV pressure averaged 99±23 (56–142) mm Hg, mean LA pressure was 13±6 (4–30) mm Hg, and peak LA pressure (V wave) was 16±9 (5–35) mm Hg. The heart rate varied from 60 to 150 beats per minute.

Accuracy of Doppler-derived pressure gradients during isovolumic relaxation. The Doppler-derived instantaneous VA pressure gradients correlated well with Millar catheter–derived VA pressure gradients for each case (r=0.96–0.99); on average, the mean Doppler-derived
gradients during isovolumic relaxation (19.6±8.1 mm Hg) were slightly but significantly (p<0.01) lower than Millar-derived pressure gradients (21.5±9.3 mm Hg).

Comparison of Hemodynamic and Doppler-Derived \( \tau \)

For the 36 stages analyzed, hemodynamically derived \( \tau \) ranged from 29 to 135 msec (63.4±25.7 msec).

Without any adjustment to the Doppler-derived VA pressure gradient, the Doppler-derived \( \tau \) (27.6±9.4 msec) was significantly smaller than Millar-derived \( \tau \)h but with strong linear correlation (\( \tau \)H=0.30\( \tau \)r+9.4; \( r=0.79, p<0.001; \) Figure 2, left panel). The proportional magnitude of this error (\( \Delta \tau /\tau \)r) correlated with both mean LA pressure (\( r=-0.54, p<0.001 \)) and V wave pressure (\( r=-0.50, p<0.001; \) Figure 2, right panel).

Doppler-derived \( \tau \) using adjusted Doppler-derived VA gradient curve. Adding the actual LA V wave pressure to the Doppler-derived VA data yielded a highly accurate estimate of the relaxation time constant (\( \tau \)L=66.3±24.4 msec, \( \tau \)L=0.92\( \tau \)r+7.6; \( r=0.95, p<0.001; \) Figure 3, left panel) without systematic underestimation or overestimation at any LA pressure (Figure 3, right panel).

When the Doppler-derived VA pressure gradient was adjusted by the addition of 10 mm Hg, the Doppler-derived \( \tau \)H (61.8±25.5 msec) was not significantly different from \( \tau \)H (\( \tau \)H=0.89\( \tau \)r+4.9; \( r=0.88, p<0.001; \) Figure 4, left panel). There was a tendency toward underestimation of \( \tau \) when the mean LA pressure was more than 20 mm Hg, as shown in the right panel of Figure 4.

Discussion

The present study demonstrates that the continuous-wave Doppler mitral regurgitant velocity profile reliably reflects LV pressure decay during isovolumic relaxation. Furthermore, we have shown that the relaxation time constant \( \tau \) can be estimated from this velocity spectrum. This is potentially very useful for clinical evaluation of diastolic dysfunction, as it provides for the first time a noninvasive method that directly measures \( \tau \), one of the fundamental parameters of ventricular diastolic performance. To date, clinical studies of ventricular relaxation have required catheterization with high-fidelity pressure manometers, limiting study to cross-sectional evaluations of various disease entities and assessing the immediate effect of pharmacological or mechanical interventions. Certainly, the ability to measure \( \tau \) longitudinally in large numbers of patients would improve our understanding of diastolic dysfunction and perhaps aid in its clinical management.

Doppler Measurement of Left VA Pressure Gradient During Isovolumic Relaxation

We have previously demonstrated that Doppler-determined instantaneous VA pressure gradients throughout systole correlated well with catheter-determined pressure gradients. Evidently, the simplified Bernoulli relation accurately converts mitral regurgitant velocity into VA pressure difference, indicating that viscous and inertial factors are negligible in this circumstance. In the current study, there was similarly an excellent correlation (\( r=0.96–0.99 \) for all cases) between Doppler- and catheter-determined VA pressure gradients during the isovolumic relaxation.

In the absence of changes in LA pressure, the rate of change of the VA pressure gradient should equal that of LV pressure during isovolumic diastole. However, small LA pressure fluctuations have been observed in humans as well as in the current canine study. We observed that the LA pressure usually peaked around aortic valve closure with a slight decrease at the end of isovolumic relaxation. Such a fall in LA pressure would blunt the decrease in VA pressure gradient in compar-
ision with the true LV pressure decay. In general, however, the fall in LV pressure far outweighs the fluctuation in LA pressure during isovolumic relaxation; in the current study, neglecting LA pressure fluctuation did not significantly affect our ability to extract τ from the data.

**Derivation of LV Relaxation Time Constant From Doppler Mitral Regurgitant Velocity Profile**

To calculate τ in this study, we applied the logarithmic method, assuming a zero ventricular pressure asymptote. However, τ derived directly from the Doppler VA gradient seriously underestimated catheter-derived τ, because log(pLV−pLA) is numerically smaller than log(pLV), especially near the VA crossover point. Therefore, it was necessary to raise the Doppler-derived VA gradient curve by approximately the LA pressure to better estimate the true LV pressure decay. The ideal correction method is to add the actual LA V wave pressure to the observed VA gradient. When this was done, a very accurate estimate of τ was obtained (Figure 3). It should be recognized that in many clinical situations, an estimate of LA pressure is actually available either via pulmonary artery monitoring or by calculating the difference between peak systolic blood pressure and the peak VA pressure from the mitral regurgitant spectrum. When such an estimate of LA pressure is obtainable, it should be added directly to the isovolumic VA gradient before calculating τ.

To explore the situation in which LA pressure is unknown, we tested an approach in which a fixed offset of 10 mm Hg was added to the VA gradient data. τ derived by using either of these adjustments correlated well with those derived from catheter data (Figure 4). Not surprisingly, however, there were systematic errors introduced when the actual LA pressure differed from the assumed LA pressure by a significant amount; τ was overestimated when the LA pressure was underestimated, and vice versa. Figure 5 shows a mathematical simulation of this error constructed in the following manner. First, LV pressure decay was approximated as a monoeponential decay to a zero asymptote. Second, a fixed LA pressure from 0 to 30 mm Hg was imposed, and the time course of the VA gradient was calculated. Finally, a user-specified, assumed LA pressure was added to the VA gradient, and from this reconstructed curve, exponential regression was performed to calculate the observed τ. Figure 5 shows the percent error in τ estimation as a function of actual LA pressure for assumed LA pressure correction factors of 0, 10, and 20 mm Hg. These theoretical errors closely mirror the observed discrepancies in Figure 4. It suggests that assuming an LA pressure of 10 mm Hg should yield estimates of τ with an accuracy of ±15% when true LA pressure ranges between ≈5 and 20 mm Hg. This compares favorably to the sixfold variation in τ observed with maximal sympathetic and parasympathetic stimulation.

**Alternative Calculation of τ**

There is methodological controversy regarding the optimal definition and calculation of τ. In this study, we calculated τ by using exponential regression, assuming that LV pressure decays to an asymptote of 0 mm Hg, an approach shown to be accurate in most cases and to have very little beat-to-beat variability. An alternative definition allows the pressure to decay to an arbitrary asymptote pₐ: p(t)=p₀e⁻ᵗ/τₐ+pₐ. The parameters p₀, pₐ, and τ can be estimated either by linear regression of −dp/dt against p or by nonlinear least-squares techniques. A potential advantage of this latter approach in the analysis of mitral regurgitant velocity might be that τ defined in this way is independent of LA pressure, which is subsumed in the adjustable constant pₐ. Indeed, if p(t) truly decayed to a zero asymptote, then the pₐ derived from the VA gradient would equal −LA pressure, providing an approach to obtain τ and LA pressure at once. Unfortunately, τ defined with an arbitrary asymptote has been shown to...
have much greater beat-to-beat variability than the zero-asymptote \( \tau \) and true \( p_h \) usually is negative, making LA pressure difficult to estimate.

**Limitations**

Clearly, a major limitation of this method is the requirement for mitral regurgitation to be present. However, mitral regurgitation is commonly observed in normal patients\(^{41-43} \) and is usually present in patients with congestive, ischemic, and hypertrophic cardiomyopathies.\(^{44-49} \) In patients in whom the characterization of ventricular relaxation is especially pertinent. Unfortunately, it is further required that this mitral regurgitation produce a signal of sufficient amplitude to be quantifiable throughout isovolumetric relaxation. This may be difficult in patients with only trace mitral regurgitation and may make it difficult to establish a reliable normal range for \( \tau \) estimated in this way. Clearly, a prospective clinical study is needed to establish the feasibility of this method in unselected patients.

The need of estimated LA pressure to correct the VA gradient data is another difficulty. Figure 2 emphasizes the feasibility of this method in unselected patients.

**Summary**

The relaxation time constant is a widely accepted parameter for assessing ventricular diastolic function. Until now, invasive measurement of LV pressure by high-fidelity catheters has been required to calculate \( \tau \), preventing its routine clinical application. In this study, we have demonstrated that the Doppler mitral regurgitant velocity profile can be used to provide a direct and noninvasive measurement of \( \tau \). Because mitral regurgitation is very common in cardiac patients, this method may allow more routine assessment of \( \tau \) in clinical and research settings, leading to a better understanding of the role of impaired ventricular relaxation in diastolic dysfunction and the effect of therapeutic interventions.

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