Determinants of diastolic myocardial tissue Doppler velocities: influences of relaxation and preload

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Firstenberg, Michael S., Neil L. Greenberg, Michael L. Main, Jeanne K. Drinko, Jill A. Odabashian, James D. Thomas, and Mario J. Garcia. Determinants of diastolic myocardial tissue Doppler velocities: influences of relaxation and preload. J Appl Physiol 90: 299–307, 2001.—Myocardial tissue Doppler echocardiography (TDE) has been proposed as a tool for the assessment of diastolic function. Controversy exists regarding whether TDE measurements are influenced by preload. In this study, left ventricular volume and high-fidelity pressures were obtained in eight closed-chest dogs during intermittent caval occlusion. The time constant of isovolumic ventricular relaxation (τ) was altered with varying doses of dobutamine and esmolol. Peak early diastolic myocardial (Em) and transmitral (E) velocities were measured before and after preload reduction. The relative effects of changes in preload and relaxation were determined for Em and compared with their effects on E. The following results were observed: caval occlusion significantly decreased E (ΔE = 16.4 ± 3.3 cm/s, 36.6 ± 13.7%, P < 0.01) and Em (ΔEm = 1.3 ± 0.4 cm/s, 32.5 ± 26.1%, P < 0.01) under baseline conditions. However, preload reduction was similar for Em and E under all lusitropic conditions (P = not significant), but these effects on Em decreased with worsening relaxation. At τ < 50 ms, changes in Em with preload reduction were significantly greater (ΔEm = 2.8 ± 0.6 cm/s) than at τ = 50–65 ms (ΔEm = 1.2 ± 0.2 cm/s) and at τ > 65 ms (ΔEm = 0.5 ± 0.1 cm/s, P < 0.05). We concluded that TDE Em may be less preload dependent (16, 26); however, this hypothesis has not been rigorously tested in a well-controlled animal model.

The aims of this study are 1) to investigate the effects of acute changes in preload on Em, 2) to determine whether these effects are modulated by ventricular relaxation, and 3) to compare the relative effects of preload and relaxation on Em with the changes observed in mitral inflow early filling velocity (E).

METHODS

Animal protocol. Eight healthy mongrel dogs weighing 27.5 ± 0.4 kg (range = 26.5–29 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv for induction, 1.0 mg·kg⁻¹·h⁻¹ for maintenance) and ventilated with room air by a Harvard respirator. The right femoral and carotid arteries and the right internal jugular vein were isolated and cannulated with valved sheaths (USCI, Hemaquen 8F). A 6-Fr, 11-pole combination conductance catheter with dual high-fidelity pressure sensors (Millar Instruments, Houston, TX) was advanced after adequate calibration from the right carotid artery to the LV apex using echocardiographic guidance. The electrical impedance measured by five pairs of conductance electrodes was analyzed by a conductance data processor (Leycom Sigma 5DF, Leyden, Netherlands) as pre-

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viously described (3). The end-diastolic and end-systolic impedances were calibrated at baseline with the LV volumes obtained by two-dimensional (2D) echocardiography, using the biplane Simpson’s rule. The pressure transducers were positioned in the LV cavity and the proximal ascending aorta.

A 23-mm Mansfield balloon catheter was introduced through the femoral vein and advanced to the upper limit of the inferior vena cava under fluoroscopic guidance. The balloon catheter was inflated intermittently for ~15–30 s throughout the experiment to occlude caval flow. Arterial blood pressure and central venous pressure were monitored via fluid-filled catheters together with a single electrocardiogram (ECG) lead coupled to an oscilloscopic multichannel recorder (EM models M1101C and M2101B).

A total of five different isotropic-lusitropic conditions were attempted in each animal, including 1) baseline, 2) dobutamine at 5 μg·kg⁻¹·min⁻¹ (low dose), 3) dobutamine at 10 μg·kg⁻¹·min⁻¹ (high dose), 4) esmolol at 50 μg·kg⁻¹·min⁻¹ (low dose), and 5) esmolol at 100 μg·kg⁻¹·min⁻¹ (high dose). A period of stabilization was allowed between each stage (range = 5–20 min). All animals received 1,000 ml of Ringer lactate before the initiation of the experiment and a continuous 20–30 ml/h infusion. Four runs were not performed due to hemodynamic instability (2 high-dose esmolol and 2 high-dose dobutamine runs). Two runs were excluded because of equipment failure.

This protocol was approved by our Institutional Animal Care and Research Committee and conforms to the position of the American Heart Association on research animal use.

Echocardiographic study. Complete 2D echocardiographic studies, including pulsed and color standard and tissue Doppler, were obtained at baseline and during each condition using an Acuson Sequoia 512 (Mountain View, CA) echocardiograph. To obtain longitudinal myocardial tissue velocities, color M-mode tissue Doppler recordings of the interventricular septum were acquired from the apical four-chamber view with the best alignment of the M-mode cursor placed in the basal portion of the interventricular septum (11). The color M-mode Doppler method was chosen over spectral pulsed Doppler to obtain simultaneous velocity and anatomic information. This permitted us to locate the sample volume at exactly the same myocardial region during each condition. Doppler scales, temporal resolution (sweep speed = 100–200 mm/s), gains, and filters were adjusted to optimize the spectral display. 2D gains and the color scales were reduced overall until aliasing velocities were visualized. During each caval occlusion run, between 6 and 20 complete cardiac cycles were recorded. Full-screen images (2–3 cardiac cycles per screen) were captured into digital memory and stored onto the hard drive of the echocardiograph. After the experiment, all images were transferred to a Windows 95 Pentium-based workstation. Before analysis, each image, originally stored in a DICOM RLE-compressed format, was converted to a BMP format using MedArchive (Secure Archive, Indianapolis, IN), a DICOM image-review system.

Standard transmural pulsed Doppler signals were then serially recorded during repeat caval occlusion. The sample volume was placed at the level of the tips of the mitral valve leaflets, and the audio signals were acquired and digitized simultaneously with the intracardiac pressure measurements by connecting the audio output of the echocardiograph to the data-acquisition apparatus. Pulsed Doppler audio signals underwent short-time Fourier transformation (20-kHz sampling frequency with 256 sample width, 128 sample shift per analysis, using a Hamming window) to reconstruct the spectral Doppler images and extract the mitral inflow velocity profiles (13).

A timing signal marker was coupled to the echocardiographic system and to the data acquisition board to match pressure, volume, and Doppler signals for each corresponding heart beat. LV pressure, ECG, and timing marker signals were digitized and acquired with 1-ms resolution with the use of a multifunction I/O board (AT-MIO-16, National Instruments, Austin, TX) interfaced with a computer workstation (Pentium 200-MHz PC) using customized software developed with LabVIEW v.5.0 (National Instruments).

Data analysis. The time constant of isovolumic relaxation (τ) was determined using the monoexponential equation from the LV pressure waveform of Weiss et al. (32) after curve fitting by use of the Levenberg-Marquardt nonlinear least-squares parameter estimation technique (24). Consistent with previous work by Yellin et al. (33), a zero asymptote (b = 0) was used. During each caval occlusion run, τ was determined for each heartbeat.

Offline analysis of the digital TDE and pulsed Doppler images was performed using custom-developed LabVIEW software. Color TDE images underwent filtering and smoothing, and the temporal velocities were extracted in the region of the base of the intraventricular septum. A 2.0-cm range of velocities was abstracted and averaged in a method similar to that previously described and validated for abstracting mitral inflow velocities from transmitial color M-mode images (9, 30). E₀ was defined as the peak velocity waveform identified between the isovolumic relaxation waveform and the atrial contraction waveform as defined by the onset of the ECG P wave (Fig. 1). To validate the application of color TDE for determining E₀, pulsed tissue Doppler velocities were obtained in 20 animal × conditions before caval occlusion. Color TDE velocities correlated well with pulsed-wave TDE (r = 0.89, y = 1.03x + 1.5, P < 0.001, standard error of estimate = 0.71 cm/s). The intra- and interobserver variabilities for the method were 9.1% (r = 0.97, y = 0.92x + 0.07, P < 0.001) and 4.5% (r = 0.97, y = 0.88x + 0.29, P < 0.001), respectively.

In all cardiac cycles, a discrete E₀ wave could be identified from the color TDE images, which is consistent with clinical experience with pulsed Doppler TDE (6). With the use of the timing marker, each E₀ value was subsequently matched with its corresponding values for end-diastolic volume (EDV), end-diastolic pressure (EDP), and τ. Similar customized software was used to determine the peak mitral inflow E-wave.
DETERMINANTS OF EARLY DIASTOLIC TISSUE VELOCITIES

A

B

C

D

Em (cm/sec) 4.80
EDV (ml) 65.33
EDP (mmHg) 8.61
Tau (msec) 44.90
velocity for each cardiac cycle during caval occlusion from the digitally reconstructed pulsed Doppler signals. Peak E-wave velocities were also matched with their corresponding EDV, EDP, and τ.

**Statistical analysis.** All statistical analyses were performed with Systat 7.0 (SPSS, Chicago, IL). Continuous variables were compared using Student’s t-tests for paired and unpaired data when appropriate. One-way repeated-measures ANOVA was used for grouped data obtained under multiple conditions. Simple least-square linear regression analysis was used to test the association between continuous variables. For all statistics, a P value of <0.05 was considered statistically significant.

To test the hypothesis that $E_m$ is influenced by acute changes in preload before and after inferi

To test the hypothesis that the effect of preload on $E_m$ is decreased with impairment of ventricular relaxation, we compared the effects of caval occlusion on $E_m$ under varying inotropic-lusiotropic conditions (baseline and high- and low-dose dobutamine and esmolol infusions) and according to different values of τ (group 1: τ was <50 ms; group 2: τ = 50–65 ms; and group 3: τ was >65 ms) by ANOVA.

To test the hypothesis that the effect of acute changes in preload in E is less dependent on relaxation than is $E_m$, changes in E and $E_m$ induced by preload reduction were compared under different conditions of ventricular relaxation by ANOVA, analysis of covariance where appropriate (to control for inotropic-lusiotropic state), and paired Student's t-tests. Paired Student's t-tests were also performed to compare the relative percent change in E and $E_m$ with changes in preload for each group. Linear regression analysis was performed to evaluate the relationship between τ and the changes in $E_m$ and E with caval occlusion.

**RESULTS**

**Effects of acute changes in preload on $E_m$ and E (hypothesis 1).** Thirty-four different inotropic-lusiotropic conditions were analyzed. Each dog (n = 8) underwent caval occlusion under baseline conditions (Table 1). Caval occlusion resulted in an average decrease in EDP of 5.6 ± 2.1 mmHg and a corresponding decrease in EDV of 26.1 ± 12.4 ml. The changes in preload were accompanied by an average decrease in both $E_m$ (1.3 ± 0.4 cm/s, 32.5 ± 26.1%, P < 0.01) and E (16.4 ± 3.3 cm/s, 36.6 ± 13.7%, P < 0.01). Although caval occlusion resulted in slight decreases in heart rate (Δheart rate = −0.9 ± 2.0 beats/min, 1.1 ± 2.4%) and τ (Δτ = −3.9 ± 5.5 ms, 7.0 ± 9.5%), these changes were neither statistically nor physiologically significant. Furthermore, baseline heart rate, preload EDV and EDP, and the changes in these variables were similar for runs during which tissue Doppler was obtained vs. similar runs during which pulsed Doppler was obtained. Overall, for each milliliter decrease in EDV, $E_m$ decreased 0.08 ± 0.03 cm/s (1.8 ± 0.6%) and for each mmHg decrease in EDP, $E_m$ decreased 0.22 ± 0.09 cm/s (5.4 ± 1.1%).

**Influence of LV relaxation on the effects of caval occlusion on $E_m$ (hypothesis 2).** Mean values for $E_m$, E, and various hemodynamic variables before and after caval occlusion and under varying lusiotropic-inotropic conditions are also summarized in Table 1. Baseline τ (56.1 ± 12.1 ms) increased, as expected, during esmolol infusion (low dose: 66.0 ± 10.9 ms, P < 0.01; high dose: 69.0 ± 14.6 ms, P < 0.01) and decreased with dobut-
Table 2. Summary of physiological measurements and $E_m$ when caval occlusion results were classified by preocclusion $\tau$

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 11)</td>
<td>(n = 13)</td>
<td>$P$</td>
</tr>
<tr>
<td>$\tau$, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 50$ ms</td>
<td>$39.5 \pm 6.4$</td>
<td>$59.7 \pm 7.7$</td>
<td>$76.6 \pm 9.7$</td>
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<td>$50–65$ ms</td>
<td>$9.0 \pm 2.6$</td>
<td>$13.2 \pm 2.9$</td>
<td>$7.2 \pm 2.5$</td>
<td>NS</td>
</tr>
<tr>
<td>$&gt; 65$ ms</td>
<td>$2.0 \pm 0.01$</td>
<td>$3.0 \pm 0.01$</td>
<td>$10.3 \pm 0.01$</td>
<td>NS</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>$8.4 \pm 3.4$</td>
<td>$9.6 \pm 2.0$</td>
<td>$12.3 \pm 2.9$</td>
<td>NS</td>
</tr>
<tr>
<td>Post</td>
<td>$3.9 \pm 2.7$</td>
<td>$5.4 \pm 2.3$</td>
<td>$7.2 \pm 2.5$</td>
<td>NS</td>
</tr>
<tr>
<td>$P$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td></td>
</tr>
<tr>
<td>EDV, ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>$57.0 \pm 17.0$</td>
<td>$56.3 \pm 19.4$</td>
<td>$49.7 \pm 12.3$</td>
<td>NS</td>
</tr>
<tr>
<td>Post</td>
<td>$34.0 \pm 8.6$</td>
<td>$35.5 \pm 17.0$</td>
<td>$30.3 \pm 10.7$</td>
<td>NS</td>
</tr>
<tr>
<td>$P$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td></td>
</tr>
<tr>
<td>$E_m$, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>$5.6 \pm 2.2$</td>
<td>$3.4 \pm 1.2$</td>
<td>$2.4 \pm 0.9$</td>
<td>0.01</td>
</tr>
<tr>
<td>Post</td>
<td>$3.0 \pm 0.9$</td>
<td>$2.2 \pm 0.7$</td>
<td>$1.7 \pm 1.0$</td>
<td>0.02</td>
</tr>
<tr>
<td>$P$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td>$0.04$</td>
<td></td>
</tr>
</tbody>
</table>

Values are averages $\pm$ SD.

Effects of preload and relaxation on transmitral $E$ vs. $E_m$ (hypothesis 3). Changes in inotropic-lusitropic conditions, before caval occlusion, resulted in significant changes in $E$ ($P < 0.05$ by ANOVA). Unlike the effects of alterations on relaxation on $E_m$ (see above), no significant independent relationship was observed between $\tau$ and $E$ [$\tau = -0.42(E) + 76.5, r = 0.23, P = NS$]. For all runs, caval occlusion resulted in a significant decrease in $E$ ($P < 0.05$, Table 1). For baseline conditions, for each milliliter decrease in EDV preload reduction, $E$ decreased $0.6 \pm 0.1$ cm/s (1.8 $\pm 0.5\%$, $P = NS$ vs. change in $E_m$), and, for each mmHg decrease in EDP, $E$ decreased $3.0 \pm 0.7$ cm/s (6.9 $\pm 0.8\%$, $P = NS$ vs. change in $E_m$). When all runs were classified according to $\tau$, the effects of preload reduction were similar for each group (Table 3, Fig. 3B). For group 1, preload reduction caused a decrease in $E$ by $12.3 \pm 2.3$ cm/s. Groups 2 and 3 showed similar decreases in $E$ with caval occlusion (14.3 $\pm 2.7$ and 9.5 $\pm 2.0$ cm/s, respectively, $P = NS$ by ANOVA). Furthermore, no

Fig. 2. Regression analysis of the relationship between $E_m$ and $\tau$ for all runs before preload reduction.

Fig. 3. Effects of preload reduction on $E_m$ and transmitral velocity ($E$) for runs when classified by $\tau$. Numbers inside columns represent average change in $E_m$ (A) and $E$ (B) with preload reduction. Group 1, $\tau < 50$ ms; group 2, $50–65$ ms; group 3, $> 65$ ms. Error bars represent $\pm$ SE.
relationship was observed between the effects of caval occlusion on $E$ and $\tau$ ($\Delta E/\Delta$EDP = $-0.05(\tau) + 60.7$, $r = 0.02$, $P = \text{NS}$).

Significant differences were observed between the relative effects of preload reduction on $E_m$ and $E$ for the different groups. As demonstrated in Fig. 4, preload reduction resulted in a statistically significant greater relative percent decrease in $E_m$ than in $E$ ($P < 0.05$); however, for group 2, the relative decreases in $E_m$ and $E$ were similar ($P = \text{NS}$). In contrast, for group 3, the relative decrease was less for $E_m$ than for $E$ ($P < 0.05$).

**DISCUSSION**

The results of this present study, conducted in a well-controlled animal experimental setting, indicate that early diastolic tissue Doppler $E_m$ are affected by acute changes in preload. However, in contrast to that shown for early $E$, the effect of preload on $E_m$ is modulated by the rate of LV relaxation. This observation carries important clinical implications and helps to explain why $E_m$ has been shown to be decreased in those patients with diastolic dysfunction, abnormal LV relaxation, even in the presence of elevated LV filling pressures, and pseudonormalized mitral inflow patterns.

Doppler echocardiography over the last two decades has emerged as the most important clinical tool for the assessment of diastolic dysfunction (20). The presence of specific LV filling and pulmonary venous flow patterns has been shown to be related to different stages of hemodynamic impairment and has been shown to have important prognostic implications in patients with restrictive and dilated cardiomyopathies (7, 25). Early clinical studies demonstrated that the normal Doppler LV filling patterns [elevated $E$, normal or short deceleration time, low atrial contraction velocity ($A$), and an $E$-to-$A$ ratio of >1] change to a pattern of reduced $E$, prolonged deceleration time, and increased $A$ with an $E$-to-$A$ ratio of <1 in patients with impaired LV relaxation (28). However, it was later recognized that, with more advanced diastolic dysfunction, the compensatory elevation of LV filling pressure resulted in pseudonormalization of the mitral filling pattern (29). To evaluate these clinical observations further, Choong et al. (5) conducted hemodynamic studies in instrumented dogs undergoing acute changes in preload. They demonstrated that mitral inflow patterns

![Fig. 4. Relative changes in $E_m$ and $E$ with preload reduction for different groups of $\tau$. The relative changes in $E_m$ and $E$ for each ml change in EDV (A) and for each mmHg change in EDP (B) are shown. P values compare relative changes in $E_m$ vs $E$ for each group. Numbers inside columns represent average changes, with error bars indicating $\pm$ SE.](http://jap.physiology.org/)

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**Table 3. Summary of physiological measurements and $E$ when caval occlusion results were classified by preocclusion $\tau$**

<table>
<thead>
<tr>
<th>Group 1 ($n = 10$): $\tau &lt; 50$</th>
<th>Group 2 ($n = 11$): $\tau = 50–65$</th>
<th>Group 3 ($n = 13$): $\tau &gt; 65$</th>
<th>ANOVA $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau$, ms</td>
<td>39.8 ± 7.6</td>
<td>64.9 ± 9.2</td>
<td>79.2 ± 11.0</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>7.5 ± 1.7</td>
<td>9.3 ± 2.5</td>
<td>10.8 ± 3.7</td>
</tr>
<tr>
<td>Post</td>
<td>4.3 ± 1.7</td>
<td>4.4 ± 1.9</td>
<td>7.1 ± 2.6</td>
</tr>
<tr>
<td>$P$</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>EDV, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>51.1 ± 11.7</td>
<td>50.3 ± 17.8</td>
<td>54.9 ± 13.2</td>
</tr>
<tr>
<td>Post</td>
<td>32.8 ± 14.6</td>
<td>32.8 ± 14.6</td>
<td>35.7 ± 9.7</td>
</tr>
<tr>
<td>$P$</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>$E$, cm/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>39.7 ± 10.1</td>
<td>39.6 ± 7.9</td>
<td>33.0 ± 8.3</td>
</tr>
<tr>
<td>Post</td>
<td>27.46 ± 6.92</td>
<td>25.5 ± 5.5</td>
<td>23.4 ± 4.0</td>
</tr>
<tr>
<td>$P$</td>
<td>0.01</td>
<td>0.01</td>
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</table>

Values are averages ± SD.
were influenced by a complex interaction between atrial and ventricular relaxation and loading conditions. Using univariate and multivariate analysis, they demonstrated through changes in left atrial pressures (actual ranges of pressure were not reported) and relaxation that $E$ was directly related to left atrial V-wave pressure ($r = 0.58, P < 0.0001$) and LV EDP ($r = 0.50, P < 0.0001$) and inversely related to $\tau$ ($r = -0.32, P < 0.004$). Their observed correlation between $E$ and $\tau$ was modest, whereas in our experiments it was similar but not statistically significant. The dual effect of preload and relaxation on $E$ often makes interpretation of transmitral filling patterns difficult and significantly limits the clinical utility of this index in isolation. For instance, an increase in the $E$-to-$A$ ratio in response to cardiovascular drugs may indicate either an improvement in relaxation or paradoxically a deterioration of LV diastolic function with increased preload (19).

Although assessment of pulmonary venous flow is often helpful for distinguishing normal from pseudonormal filling, in many cases, pulmonary venous flow recordings, unlike tissue Doppler images, are difficult to obtain by transthoracic echocardiography (6). Furthermore, the interpretations of these patterns may be equivocal due to the complex effects of left atrial contractility, relaxation, pulmonary venous compliance, heart rate, and atroventricular conduction (1).

Doppler tissue echocardiography, a modified application of Doppler that selectively detects the motion of the myocardium, has been more recently applied to the study of diastolic function. Garcia et al. (8) demonstrated that this technique was useful to differentiate patients with constriction from those with restrictive cardiomyopathy. Despite similar transmitral inflow patterns, patients with restrictive cardiomyopathy had reduced early diastolic $E_m$, presumably reflecting the impairment of LV relaxation in these patients. Oki et al. (21) later demonstrated a strong negative linear correlation between $\tau$ and $E_m$ in humans undergoing cardiac catheterization. This correlation was stronger than that observed for $E$ when Oki et al. included different groups of patients with normal and elevated LV filling pressures, suggesting that $E_m$ was less preload dependent than transmitral filling indices. The clinical utility of tissue Doppler has also been demonstrated in differentiating hypertrophic cardiomyopathy from athlete’s hearts (23) and detecting regional LV dysfunction during acute ischemia (4). Sohn et al. (26) studied the effects of preload on tissue Doppler velocities in patients with normal and abnormal diastolic function. They demonstrated no statistically significant change in $E_m$ in 20 patients with known relaxation abnormalities (average baseline transmitral deceleration time $= 311 \pm 84$ ms) after a 500- to 700-ml saline infusion (preinfusion $E_m = 5.3 \pm 1.2$ cm/s, postinfusion $E_m = 5.7 \pm 1.7$ cm/s; $P = NS$) and in 11 normal patients (preinfusion $E_m = 9.5 \pm 2.2$ cm/s, postinfusion $E_m = 9.2 \pm 1.7$ cm/s; $P = NS$). However, the normal patients did not undergo simultaneous invasive pressure monitoring and the changes in LV volumes were not reported; therefore, the actual changes in preload are unknown. Other studies, on the other hand, showed a strong association between tissue velocities and preload dependent indices of LV function such as ejection fraction, suggesting that tissue Doppler velocities also had to be influenced by preload (12).

Our results help to reconcile these apparently discrepant observations, confirming that tissue Doppler relaxation velocities are influenced by acute changes in preload. However, this effect is less pronounced in ventricles with impaired relaxation, which explains why $E_m$ would remain reduced even in the presence of high ventricular filling pressure in patients with advanced diastolic dysfunction. The lack of a significant change in $E_m$ with alterations in preload in patients with impaired relaxation demonstrated in previous clinical studies is consistent with our results. The decreased preload dependency with prolonged $\tau$ may reflect a relative inability of ventricles with impaired relaxation to further “improve” their function in response to increases in preload.

The clinical significance of our observations is that, with impaired or worsening ventricular relaxation, changes in early diastolic $E_m$ become less preload dependent. Therefore, $E_m$ may be a more reliable index of diastolic function in patients with established heart disease. In subjects with normal relaxation, preload may significantly influence tissue Doppler velocities. These effects, however, are also reflected in mitral inflow $E$. Therefore, it is important to analyze the specific mitral inflow velocity in addition to tissue Doppler velocity patterns to differentiate the relative effects of preload and relaxation when interpreting these patterns in normal subjects.

**Limitations.** Our results are derived from pharmacologically induced changes in preload in an animal model with normal underlying ventricular mechanics. Validation of our results in humans with normal and/or impaired ventricular function and altered LV geometry is required. Furthermore, TDE derives longitudinal velocities from a single point or region within the myocardium, thereby limiting the global assessment of diastolic function in patients with known wall-motion abnormalities. In addition, TDE-derived velocities are theoretically inherently limited by the rotational and tethering (i.e., normal or hyperdynamic myocardium “pulling” akinetic myocardium, potentially resulting in erroneous assessment of the abnormal regions) effects of an actively contracting and relaxing heart. A relatively new TDE method, strain-rate analysis, which measures segmental tissue deformation, may overcome this limitation in the future.

In these experiments, we chose to apply color TDE with the intent of averaging the velocities over a greater region of the base of the intraventricular septum (region of interest of $\pm 1$ cm) than what would be typically obtained from the limited sample size of pulsed Doppler techniques. Although this technique is not typically used clinically and requires customized software for analysis, the low intra- and interobserver variability, the correlation with conventional pulsed...
Doppler, and previous validation of this velocity determination technique (9) nevertheless support its application.

In our animal protocol, we did not address the potential effects of changes in afterload or atrioventricular conduction, each of which could also affect tissue Doppler velocities.

In conclusion, longitudinal $E_p$, as measured using TDE, are affected by changes in preload. However, in contrast to conventional transmural E-wave velocities, this effect is less significant in ventricles with impaired relaxation ($\gamma$). Understanding the combined effects of preload and relaxation on both tissue and transmural Doppler indices is critical to their application in evaluating diastolic function.

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