Global Diastolic Strain Rate for the Assessment of Left Ventricular Relaxation and Filling Pressures

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Background—Diastolic strain rate (SR) measurements that comprise all left ventricular (LV) segments are advantageous over myocardial velocity for assessment of diastolic function. Mitral early diastolic velocity (E)/SR ratio during the isovolumetric relaxation (IVR) period can be used to estimate LV filling pressures.

Methods and Results—Simultaneous echocardiographic imaging and LV pressure measurements (7F catheters) were performed in 7 adult dogs. Loading conditions were altered by saline infusion and caval occlusion, and lusitropic state was changed by dobutamine and esmolol infusion. A curve depicting global SR was derived from each of the 3 apical views, and SR was measured during IVR (SR$_{IVR}$) and early LV filling (SR$_E$). SR$_{IVR}$ had a strong correlation with time constant of LV pressure decay during the IVR period (τ) ($r$=-0.83, $P<0.001$), whereas SR$_E$ was significantly related to LV end-diastolic pressure ($r=0.52, P=0.005$) in the experimental stages where τ was <40 ms. In 50 patients with simultaneous right heart catheterization and echocardiographic imaging, mitral E/SR$_{IVR}$ ratio had the best correlation with mean wedge pressure ($r=0.79, P<0.001$), as well as in 24 prospective patients ($r=0.84, P=0.001$). E/SR$_{IVR}$ was most useful in patients with ratio of E to mitral annulus early diastolic velocity (E/Ea ratio) 8 to 15 and was more accurate than E/Ea in patients with normal ejection fraction and regional dysfunction (both $P<0.01$).

Conclusions—Global SR$_{IVR}$ by 2-dimensional speckle tracking is strongly dependent on LV relaxation. E/SR$_{IVR}$ can predict LV filling pressures with reasonable accuracy, particularly in patients with normal ejection fraction and in those with regional dysfunction. (Circulation. 2007;115:1376-1383.)

Key Words: diastole ■ echocardiography ■ heart failure ■ hemodynamics

D oppler echocardiography, including tissue Doppler imaging, is applied to assess left ventricular (LV) relaxation and to predict filling pressures.\textsuperscript{1-5} Although the ratio of mitral early diastolic velocity to early diastolic velocity (E/Ea ratio) is clinically useful, it has a number of limitations that can limit its accuracy.

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First, the approach with mitral annulus velocities assumes that the measurement, at either a single site or multiple sites, is a representation of global LV relaxation. The difference between sites is most exaggerated in patients with regional wall motion abnormalities but exists even in subjects without segmental dysfunction.\textsuperscript{3,4} In that regard, the average of Ea velocity at multiple sites results in a better prediction of filling pressures,\textsuperscript{5} which nevertheless is still an approximation of global function. The potential effect of left atrial (LA) pressure is another limitation to Ea. Because Ea occurs during the early phase of LV filling, it is subject to the influence of not only LV relaxation but also LA pressure,\textsuperscript{6,7} which is most noticeable in the absence of cardiac disease.\textsuperscript{6,7} Furthermore, in some patients with cardiomyopathy, the Ea velocity can fall within the normal range. In these cases, when LV size is taken into consideration, for example, the ratio of Ea to the LV long-axis dimension, diastolic annular excursion is actually reduced, and the abnormal diastolic function can be readily identified.

Therefore, a measurement that represents the performance of all myocardial segments, that is load independent, and that accounts for the initial LV size would circumvent all of the aforementioned limitations. We hypothesized that diastolic strain rate (SR) measurements, which account for the initial segmental length when averaged from all LV segments at a time when the mitral valve is still closed, ie, during the isovolumetric relaxation (IVR) period, can circumvent the aforementioned problems with Ea. Furthermore, it is possible to estimate mean LA pressure with the use of the ratio (Figure 1) of mitral E to diastolic SR measured during the IVR period, in a manner analogous to that of the E/Ea ratio.

In that regard, deformation measurements derived by speckle tracking have been validated in animal and human studies\textsuperscript{8-11} and offer advantages over the Doppler-derived approach given their angle independence. With the use of this technique, it is possible to obtain a global curve of SR and
strain that encompasses all myocardial segments. From this curve, global measurements (an average of all segments) of IVR SR and early diastolic SR can be derived.

We undertook the present study to examine the hemodynamic determinants of these signals in animal studies and to explore their utility in identifying abnormal LV relaxation and predicting LV filling pressures in consecutive patients undergoing right heart catheterization.

**Methods**

**Animal Studies**

**Animal Preparation**

The animal study was approved by the Baylor College of Medicine Animal Protocol Review Committee, and animals were treated in compliance with the 1985 National Institutes of Health guidelines for the care and use of laboratory animals. Seven adult mongrel dogs weighing 19 to 28 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg body wt), intubated, and mechanically ventilated. Adjustment of tidal volume and oxygen concentration ensured maintenance of normal arterial blood gas and pH levels.

A high-fidelity pressure catheter (7F, Millar, calibrated relative to atmospheric pressure before introduction) was advanced into the LV (retrograde from the right femoral artery through the aortic valve) to record LV pressures continuously. A balloon catheter was advanced into the inferior vena cava through the right femoral vein. The balloon was inflated in sequential steps to reduce venous return and decrease LV filling. Throughout the procedure, surface ECG (lead II) and ventricular pressure signals were acquired simultaneously on a computer-based data acquisition system (Cardiodynamics BV, Leycom-CFL-512, Argonstraat, the Netherlands). LV pressure was digitized with a 5-ms sampling frequency, and recordings were taken at end expiration.

**Echocardiographic Studies**

Dogs were imaged in the standard parasternal and apical (apical 4-chamber, 2-chamber, and long-axis) views with the use of a GE Vivid 7 ultrasound system. Two-dimensional (2D) image acquisition was performed at a frame rate of 80 to 100 frames per second, and 3 cardiac cycles were stored in cineloop format. The studies were stored digitally for subsequent offline analysis.

**Experimental Protocols**

LV filling pressures were increased with intravenous infusion of isotonic saline and decreased with inflation of the balloon placed in the inferior vena cava. Both the infusions and occlusions were performed in a sequential manner with data acquired at stepwise increments and decrements of LV end-diastolic pressure (EDP). After a stable hemodynamic state at each LVEDP level was achieved, LV systolic and diastolic pressures, heart rate, and 2D strain data were acquired.

To evaluate the influence of LV relaxation on global diastolic SR, dobutamine was administered at a dose of 5 μg/kg per minute with reacquisition of echocardiographic and pressure data. Dobutamine infusion was then terminated, and after the animals returned to their baseline state, esmolol with its negative lusitropic properties was administered (0.5 mg/kg IV) with subsequent reacquisition of data. To assess the interaction between filling pressures and ventricular relaxation on global SR measurements, fluid administration and inferior vena cava occlusion were repeated during the dobutamine infusion and later with esmolol.

**Data Analysis: Hemodynamic Measurements**

The following LV pressures were monitored: minimal, LVEDP (determined by the peak of the R wave on the ECG), and end-systolic pressure (ESP). The maximum and minimum LV dp/dt and the time constant of LV pressure decay during the IVR period (τ) were also ascertained.

**Echocardiographic Analysis**

Longitudinal SR analysis was performed with the use of a commercially available speckle tracking system in an ECHOPAC workstation. In this speckle tracking system, the displacement of speckles of myocardium in each spot was analyzed and tracked from frame to frame. Adequate tracking was verified in real time and corrected, if needed. Specifically, every loop was divided into basal, mid, and apical segments, and tracking of every segment was displayed and approved. LV global strain and SR in each view were calculated with the use of the entire length of the LV myocardium (Figure 2). Peak global SR during the IVR period (SRIVR) and early diastole (SRE) were measured. The global SR values from the 3 apical views were also averaged and used for final analysis.

**Human Studies**

**Initial Group**

The institutional review board of the Patient Advocacy Council approved the protocol, and patients provided written informed consent. The group comprised 50 consecutive patients who were undergoing right heart catheterization in the cardiac catheterization laboratory (n = 24) or the intensive care unit (n = 26). Inclusion criteria were sinus rhythm and satisfactory echocardiographic and pressure recordings. Two postoperative patients were excluded for suboptimal apical views, resulting in an overall feasibility of 50 of 52.
TABLE 1. Hemodynamic Changes in the Different Experimental Stages

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Inferior Vena Cava Occlusion</th>
<th>Saline Infusion</th>
<th>Dobutamine</th>
<th>Esmolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>106±11*</td>
<td>101±9*</td>
<td>100±14*</td>
<td>116±7†</td>
<td>92±11</td>
</tr>
<tr>
<td>ESP, mm Hg</td>
<td>94±11†</td>
<td>63±7‡</td>
<td>100±35*</td>
<td>150±47†</td>
<td>83±37</td>
</tr>
<tr>
<td>Minimum pressure, mm Hg</td>
<td>2.9±2.8§</td>
<td>0.1±1.9§</td>
<td>7.8±4.2</td>
<td>2.9±2.5§</td>
<td>10±4.9</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>7±3.6§</td>
<td>2.4±1.8§</td>
<td>15.5±5.5</td>
<td>5±3.1§</td>
<td>21.3±8</td>
</tr>
<tr>
<td>τ, ms</td>
<td>27±7.6*</td>
<td>24±7†</td>
<td>33±7*</td>
<td>22±5†</td>
<td>44±15</td>
</tr>
<tr>
<td>dP/dt, mm Hg/s</td>
<td>1365±285*</td>
<td>1190±213*</td>
<td>1495±533*</td>
<td>5133±2500†</td>
<td>1019±133</td>
</tr>
<tr>
<td>−dP/dt, mm Hg/s</td>
<td>1746±697¶</td>
<td>1085±325$§</td>
<td>1771±763*</td>
<td>4285±677†</td>
<td>1000±683</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>63±15</td>
<td>38±5**</td>
<td>70±9</td>
<td>56±4</td>
<td>73±9</td>
</tr>
</tbody>
</table>

*p<0.05 vs dobutamine and esmolol stages.  †p<0.05 vs esmolol stage.  ‡p<0.05 vs dobutamine stage.  §p<0.05 vs saline infusion and esmolol stages.  ¶p<0.05 vs inferior vena cava occlusion, saline infusion and esmolol stages.  ‡p<0.05 vs inferior vena cava occlusion, dobutamine and esmolol stages.  *p<0.05 vs saline infusion, dobutamine and esmolol stages.  **p<0.05 vs baseline, saline infusion and esmolol stages.

or 96%. Patients had simultaneous echocardiographic and hemodynamic measurements.

**Echocardiographic Studies**

Patients were imaged in a supine position with the use of a GE Vivid 7 ultrasound system. Two-dimensional image acquisition was performed with the standard parasternal and apical (apical 4-chamber, apical 2-chamber, and apical long-axis) views at a frame rate of 80 to 100 frames per second, and 3 cardiac cycles were recorded. In the apical 4-chamber view, pulse-Doppler sample volume was placed at the mitral valve tips to record 3 to 5 cardiac cycles at end expiration. Mitral annulus velocities by pulse wave Doppler were recorded from the septal, lateral, anterior, and inferior sites.5 Gains and filters were adjusted carefully to eliminate background noise and allow for a clear tissue signal. The studies were stored digitally for subsequent offline analysis.

**Echocardiographic Analysis**

The analysis was performed offline without knowledge of hemodynamic data. LV end-diastolic volume (EDV), ejection fraction (EF), regional function (both motion and systolic thickening in multiple views), and LA maximum volume were measured according to the recommendations of the American Society of Echocardiography.14 All Doppler values represent the average of 3 beats. Mitral inflow was analyzed for peak E and mitral late diastolic velocity (A), E/A ratio, deceleration time of E velocity, and isovolumetric relaxation time (IVRT). From the pulmonary vein flow velocity curves (feasible in 20 patients), the systolic filling fraction was computed, and the difference between atrial velocity in pulmonary venous flow signal and mitral A velocity duration was calculated.1 Ea and late diastolic annular velocity (Aa) were measured, and the dimensionless ratio E/Ea1−3 was computed. In addition, similar to the canine experiments, SR⁎ and SR were obtained. An average of 5 minutes was needed to measure global SR⁎ and SR.

**Reproducibility**

Ten studies were randomly selected, and repeat analysis was performed by a second observer. Mean interobserver difference for SR⁎ was 0.016±0.04 (range, −0.04 to 0.07) s−1, whereas it was 0.03±0.08 (range, −0.16 to 0.1) s−1 for SR.

**Hemodynamic Measurements**

Hemodynamic data were collected by an investigator unaware of the echocardiographic measurements at end expiration and represent the average of 5 cycles. Cardiac output was derived by the thermodilution technique (average of 3 cardiac cycles with <10% variation). All pressures including pulmonary capillary wedge pressure (PCWP) (verified by fluoroscopy, phasic changes in pressure waveforms, and oxygen saturation) were determined with the use of balanced transducers (0 level at midaxillary line).

In the initial population, τ was computed with the use of the previously validated equation \( τ = IVRT/(\ln ESP - \ln PCWP) \),15 where IVRT was measured by Doppler, and ESP and PCWP were obtained by invasive measurements. In patients without LV pressure measurements, LVEF was derived by the following previously validated expression: \( ESP = 0.9 \times \text{systolic blood pressure} \).16

**Prospective Population**

The utility of the E/SR⁎ ratio to predict filling pressures was next examined in a prospective group of 24 consecutive patients (age, 56±17 years; 5 women) who had simultaneous Doppler and right heart catheterization. The diagnoses of these patients were as follows: coronary artery disease (n=12), idiopathic dilated cardiomyopathy (n=5), aortic stenosis (n=3), acute severe aortic regurgitation (n=1), and ascending aortic aneurysm (n=3).

**Statistical Analysis**

The hemodynamic and echocardiographic measurements were compared in the experimental stages by repeated-measures ANOVA with pairwise multiple comparison procedures performed by the Holm-Sidak method. Regression analysis was applied to examine the relation between hemodynamic and 2-dimensional–derived global SR measurements.

For the human studies, regression analysis was used to examine the relation between Doppler and hemodynamic variables. For all 50 patients, receiver operating characteristic (ROC) curves were used to examine the accuracy of the different echocardiographic measurements in identifying patients with mean PCWP >15 mm Hg. The sensitivity and specificity of the different echocardiographic measurements for prediction of elevated filling pressures were compared with the \( χ^2 \) test. Multiple regression analysis was performed to determine the independent predictors of PCWP in patients. Statistical significance was defined as \( P≤0.05 \).

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Animal Experiments**

A summary of the echocardiographic and hemodynamic measurements at the different experimental stages is shown in
Patients (20%) had diabetes mellitus. Ten of the 50 were imaged after aortic valve replacement, and one had severe acute aortic regurgitation. Five patients of mild severity in 9 cases and mild to moderate severity in 3 women. Twelve patients had mitral regurgitation, which was function was present.

Hemodynamic Determinants of Global SR During IVR
SR
\(_{\text{IVR}}\) did not show a significant change with the decrease and increase in LVEDV with changes in preload. On the other hand, SR
\(_{\text{VR}}\) had good significant correlations with \(\tau\) and \(-dP/dt\) (Figure 3) and weaker correlations with heart rate \((r=-0.42, P<0.01)\) and minimal pressure \((r=-0.52, P<0.001)\). On multiple regression analysis, \(\tau\) was the only independent predictor of SR
\(_{\text{VR}}\). The ratio of mitral E to SR
\(_{\text{IVR}}\) showed a significant correlation with LV pre-A pressure \((r=0.81, P<0.01)\) and EDP \((0.75, P<0.01)\).

Hemodynamic Determinants of Global SR During Early Diastolic Filling
As for SR
\(_{e}\), a significant positive correlation, albeit weak, was present with LVEDP in the experimental stages, where \(\tau<40\) ms \((r=0.52, P=0.005)\), whereas no significant correlation was noted in the stages where \(\tau>40\) ms \((r=0.29, P=0.48)\). With respect to \(\tau\), SR
\(_{e}\) had a significant inverse correlation \((r=-0.65, P=0.035)\) in the stages where myocardial dysfunction was present.

Human Studies
The mean age of the 50 patients was 59±16 years (14 women). Twelve patients had mitral regurgitation, which was of mild severity in 9 cases and mild to moderate severity in 3 patients. One patient had mild aortic regurgitation, and another had severe acute aortic regurgitation. Five patients were imaged after aortic valve replacement, and one had severe aortic stenosis. Coronary artery disease (by coronary angiography) was present in 29 patients (58%), and 23 (46%) had previous coronary artery bypass surgery. Ten of the 50 patients (20%) had diabetes mellitus.

\(E/SR_{\text{VR}}\) for the Prediction of Mean PCWP
Table 2 presents a summary of the hemodynamic and echocardiographic measurements of the 50 patients. A good correlation was observed between SR
\(_{\text{VR}}\) and \(\tau\) (Figure 4).

Several significant relations were noted between mean PCWP and LA volume \((r=0.31, P=0.027)\) and Doppler (mitral E: \(r=0.56, P=0.001\); E/A ratio: \(r=0.45, P<0.01\); Ar−A: \(r=0.61, P<0.01\); E/Ea: \(r=0.68, P<0.01\)) measurements. The ratio of mitral E to SR
\(_{\text{VR}}\) related well to mean PCWP. Interestingly, the correlation coefficient was highest \((r=0.79, P<0.001; \text{Figure 5A})\) when the average value of SR
\(_{\text{VR}}\) from the 4-chamber, 2-chamber, and apical long-axis views was used versus the average from 4- and 2-chamber views \((r=0.65, P<0.001)\) or the 4-chamber view only \((r=0.61, P<0.001)\). On multiple regression analysis, the only independent predictor of mean PCWP was the E/SR
\(_{\text{VR}}\) ratio.

The mean difference between predicted PCWP and that obtained by cardiac catheterization was 0.26 mm Hg (SEE=0.6; Figure 5B). ROC analysis (area under the curve=0.93, P<0.0001; Figure 6) showed that a cutoff value of E/SR
\(_{\text{VR}}\) of 236 cm had the best accuracy in identifying patients with a mean PCWP >15 mm Hg, with a sensitivity of 96% and a specificity of 82%. In comparison, E/Ea ratio had an area under the curve of 0.85 (P=0.002; Figure 6).

Impact of LVEF on Accuracy of E/SR
\(_{\text{VR}}\) Ratio
The accuracy of this ratio was examined in patients with depressed EF versus those with normal EF. Thirty patients

Table 2. Hemodynamic and Echocardiographic Findings in Human Studies

<table>
<thead>
<tr>
<th>Heart rate, bpm</th>
<th>84±16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic/diastolic blood pressure, mm Hg</td>
<td>116±21/62±14</td>
</tr>
<tr>
<td>Pulmonary artery systolic and diastolic pressure, mm Hg</td>
<td>43±17/22±10</td>
</tr>
<tr>
<td>Mean PCWP, mm Hg</td>
<td>17±9</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>12±8</td>
</tr>
<tr>
<td>(\tau), ms</td>
<td>39±16</td>
</tr>
<tr>
<td>Cardiac index, L/min·m(^{-2})</td>
<td>2.6±0.8</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>41±22</td>
</tr>
<tr>
<td>LA volume index, mL/m(^2)</td>
<td>81±35</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.6±1.1</td>
</tr>
<tr>
<td>Deceleration time of E velocity, ms</td>
<td>183±71</td>
</tr>
<tr>
<td>Systolic filling fraction</td>
<td>0.41±0.21</td>
</tr>
<tr>
<td>Ar−A duration, ms</td>
<td>23±13</td>
</tr>
<tr>
<td>E/Ea ratio</td>
<td>15±9</td>
</tr>
</tbody>
</table>
| Average SR
\(_{\text{VR}}\), s\(^{-1}\) | 0.34±0.16 |
| Average SR
\(_{e}\), s\(^{-1}\) | 0.75±0.35 |
| E/SR
\(_{e}\), cm | 311±177 |
had reduced EF (24±10%; range, 10% to 48%) and a mean PCWP of 19±8 mm Hg (range, 4 to 30 mm Hg). Twenty patients had normal EF (64±6%; range, 50% to 75%) and a mean PCWP of 14±9 mm Hg (range, 4 to 40 mm Hg). Overall, good correlations were noted in both groups (EF <50%; r =0.74; normal EF: r =0.91; both P <0.01; Figure 5A). On the other hand, similar to previous reports, E/Ea (average Ea used) had a better correlation with mean PCWP in patients with depressed EF (r =0.71, P <0.001) versus those with normal EF (r =0.65, P =0.03).

**Impact of Regional Function on Accuracy of Doppler Ratios**

Twenty patients had regional dysfunction. Ten patients had apical akinesis, 13 had inferior/posterior dysfunction, 6 had septal hypokinesis/akinesis, and 2 had anterior wall dysfunction. A good correlation was present between mean PCWP and the ratio of mitral E to SRIVR in patients with regional dysfunction (r =0.83, P <0.01). On the other hand, E/Ea ratio had a somewhat better correlation with mean PCWP in patients without regional wall motion abnormalities (regional dysfunction: r =0.63; no wall motion abnormality: r =0.73; both P <0.01).

**Global Early Diastolic Strain Rate and LV Diastolic Function**

SR in averaged 0.75±0.35 s⁻¹ with a range of 0.26 to 1.79 s⁻¹. A significant negative correlation was present between SR in and τ and mean PCWP (Figure 7). We next explored the relation between the peak value of SR in and its onset in relation to the onset of mitral E velocity. In patients with SR in ≥0.9 s⁻¹ (1.2±0.25 s⁻¹), onset of SR in occurred before the onset of mitral E by 3.5±46 ms, whereas in patients with SR in <0.9 s⁻¹ (0.58±0.19; P <0.001 versus patients with SR in ≥0.9 s⁻¹), its onset followed that of mitral E velocity by 19±30 ms (P =0.027).

Importantly, the correlation between mean PCWP and E/SR in ratio, although significant, was weak and with wide scatter (r =0.58, P <0.001, SEE =6.8 mm Hg).

**Prospective Group**

The prospective group had a mean heart rate of 84±15/min, with a blood pressure (systolic/diastolic) of 121±24/68±17 mm Hg, a pulmonary artery pressure (systolic/diastolic) of 39±13/18±7 mm Hg, and a mean PCWP of 19±9 (range, 4 to 37) mm Hg. Mean right atrial pressure was 14±9 mm Hg, and the cardiac index was 2.3±0.6 L/min per square meter. The group had an EF of 48±20% (range, 10% to 71%) and LA volume of 72±37 mL. A significant correlation was observed, as noted in Figure 8, with a sensitivity of 100% and a specificity of 78%.

**Incremental Value of E/SR in Ratio Over Existing Methods in Identifying Patients With Increased Filling Pressures**

In the 74 patients combined, 15 patients had an E/Ea ratio <8, 25 patients had a ratio >15, and 34 patients had a ratio 8 to 15. All patients with ratio <8 had mean PCWP <15 mm Hg, whereas those with a ratio >15 had a mean wedge pressure >15 mm Hg. In the intermediate group, 17 had a mean PCWP >15 mm Hg, and the other half did not. Pulmonary venous flow signals were feasible in only 10 of 34 patients,
and LA volume was increased in 10 of 17 patients with mean PCWP <15 mm Hg. On the other hand, all 17 of 34 with PCWP >15 mm Hg had a mitral E/SRIVR >236, and 15 of 17 patients with PCWP <15 had a ratio <236.

Thirty-five patients had EF ≥50%. E/Ea had a sensitivity of 75% in identifying patients with mean PCWP >15 mm Hg, whereas E/SRIVR had a 100% sensitivity (P<0.01). Likewise, E/SRIVR had a significantly higher specificity in this group (78% versus 52%; P<0.001).

Twenty-five patients had regional dysfunction. E/Ea had a sensitivity of 68% in identifying patients with mean PCWP >15 mm Hg, whereas E/SRIVR had a 93% sensitivity (P<0.01). Likewise, E/SRIVR had a significantly higher specificity in this group (80% versus 60%; P=0.003).

**Discussion**

This study shows that global SRIVR derived by 2D speckle tracking relates well to hemodynamic indices of LV relaxation both in an animal model and in patients. Furthermore, the ratio of mitral E to SRIVR can be used to predict LV filling pressures with reasonable accuracy, particularly in patients with an E/Ea ratio of 8 to 15, those with normal EF, and those with regional dysfunction. Although SR is also dependent on LV relaxation in humans, this association is weaker than that of SRIVR, and the ratio of mitral E to SR is weakly related to mean PCWP.

**Noninvasive Assessment of LV Relaxation and Filling Pressures Using SRIVR**

A number of Doppler measurements are currently available to assess LV relaxation. The limitations of mitral inflow are well known, but the pattern itself is still useful to identify abnormal relaxation and predict LV filling pressures in patients with depressed EF.1–5,17,18 Ea velocity has been applied as well. It has the advantage of being less affected by loading conditions2,3,6,7 and being more accurate than mitral velocities in patients with normal EF.5 Nevertheless, Ea is acquired at the level of the mitral annulus with the assumption that it reflects global LV relaxation. Therefore, in situations in which regional dysfunction is present, its accuracy can be compromised, as noted in this study and in previous reports by us.5 This limitation of Ea was noted despite averaging it at multiple sites, and, as seen here, it led to lower accuracy in comparison with SRIVR derived from all myocardial segments. Furthermore, Ea velocity is affected by preload in the presence of normal or enhanced LV relaxation,6,7 and mitral valve disease and annular calcification affect its accuracy.19

Unlike previous methodology, we explored in this study indices of LV relaxation acquired from the LV myocardium. We believe that this approach represents a new paradigm in evaluating LV diastolic function because it is based on measurements obtained directly from the ventricular myocardium.
dium during IVRT and not mitral recordings during early LV filling. Therefore, problems related to annular and valvular pathology can be circumvented. Second, we obtained an index that was derived from all myocardial segments and is therefore representative of global LV performance. Third, we used the rate of diastolic expansion as opposed to absolute velocity, which isolates SR\textsubscript{ivr} from the effects of tethering and translation. Fourth, we were able to measure LV diastolic expansion rate during the IVR period, at a time corresponding to the decay in LV pressure due to its relaxation but while the mitral valve is still closed. The animal experiments support these conceptual advantages, given the good correlation of mitral valve is still closed. The animal experiments support these conceptual advantages, given the good correlation of NDE\textsubscript{a} with \( \tau \) and the absence of significant changes in SR\textsubscript{ivr} with alterations in loading conditions. Interestingly, a recent study in sheep reported on the strong correlation of the peak acceleration rate of the mitral annulus diastolic velocity during the IVR period with the time constant of LV relaxation\textsuperscript{20} and its independence of LA pressure. These observations support the notion that myocardial signals acquired during this phase of the cardiac cycle not only track LV relaxation better but can also be preload independent. However, the peak acceleration rate of the mitral annulus diastolic velocity is still acquired at the level of the mitral annulus and shows variable accuracy depending on whether the septal or lateral side is used,\textsuperscript{20} highlighting its vulnerability to annular disease and underlying regional function, as well as the need for an index that is derived directly from LV myocardium that captures the performance of all LV segments.

The human studies confirm the animal observations and in addition show the clinical application of SR\textsubscript{ivr} to assess LV relaxation and, in conjunction with mitral E velocity, to predict mean PCWP. As expected, the E/SR\textsubscript{ivr} ratio was more accurate than the E/E\textsubscript{a} ratio in patients with regional dysfunc-

Noninvasive Assessment of LV Relaxation and Filling Pressures Using SR\textsubscript{e}

SR\textsubscript{e} occurs during the period of early diastolic filling. Therefore, it is affected by LA pressure, ongoing LV relaxation, and LV stiffness. Previous animal studies have shown the positive effect of preload on segmental SR\textsubscript{e}\textsuperscript{21,22} and the significant correlation between SR\textsubscript{e} and LV relaxation\textsuperscript{20} and regional stiffness.\textsuperscript{21,22} Our observations in the animal experiments with respect to global SR\textsubscript{e} are consistent with the aforementioned studies.

However, in patients, global SR\textsubscript{e} exhibits a significant inverse correlation with mean PCWP, albeit a weak one. This is not a reflection of a direct relationship between the 2 variables but is due to the fact that patients with impaired LV relaxation frequently have a compensatory increase in mean PCWP. Therefore, it is primarily the relation between LV relaxation and SR\textsubscript{e} that leads to the inverse correlation between mean PCWP and SR\textsubscript{e} in humans. Overall, the direction and strength of associations in our study between SR\textsubscript{e} and \( \tau \)/LV filling pressures are very similar to previous reports in patients, including those with hypertrophic cardiomyopathy.\textsuperscript{23}

SR\textsubscript{e} peak value is dependent on the final balance between LV relaxation and LA pressure. In patients in whom myocardial expansion is delayed such that it occurs after the LA-LV pressure crossover, SR\textsubscript{e} is influenced mainly by LV relaxation. However, when it occurs earlier than this time point, it is affected as well by LA pressure, accounting for the observations in which SR\textsubscript{e} was higher than expected for the impaired LV relaxation, as inferred from the analysis of the time difference between the onset of mitral E and that of SR\textsubscript{e}. In that regard, SR\textsubscript{e} appears to have determinants similar to those of E/E\textsubscript{a}.\textsuperscript{6,7}

Limitations

The measurement of global SR\textsubscript{ivr} requires more expertise and is contingent on the presence of adequate apical views, and therefore it is not feasible in patients with absent or suboptimal apical windows. However, in this study, which included supine patients on the cardiac catheterization table or in the intensive care unit, the feasibility was excellent at 96%. In addition, intravenous contrast can be used to achieve optimal visualization of LV myocardium in challenging cases. The average frame rate of 80 to 100 frames per second is lower than that used with the Doppler-based approach. This may have led to an underestimation of the peak SR value. However, a larger sector is essential to encompass all LV segments and not individual walls. Furthermore, we have noticed that this rate is associated with better tracking than higher frame rates.

There was a wide variation in the relation between PCWP and E/SR\textsubscript{ivr} ratio, which can be challenging for the prediction of a specific value. However, it is possible to work with certain partitions to achieve the highest accuracy. In particular, all patients, except 1, with a ratio <236 had a mean PCWP <15 mm Hg. Conversely, all patients, except 1, with a ratio >300 had PCWP >15 mm Hg. Likewise, most of the patients (75%) with a ratio ≥236 but <300 had increased PCWP. Five patients in the prospective group with severely depressed LVEF (<20%) had very low values of SR\textsubscript{ivr} (≤0.05 s\textsuperscript{−1}) and, accordingly, had markedly increased ratios (>1500). However, the latter 5 cases all had restrictive LV filling and a mean PCWP >25 mm Hg. These results in patients with advanced cardiomyopathy merit additional studies, and a different regression model may be needed in this group.

The application of E/SR\textsubscript{ivr} ratio in patients not in sinus rhythm has not been examined. However, the concept should still be valid, although its accuracy remains to be determined. The accuracy of the ratio depends in part on the relation between mitral E velocity and LA pressure and LV relaxation, and the accuracy of peak E velocity is affected by the presence of mitral valve disease.\textsuperscript{19}

Conclusions

Global SR\textsubscript{ivr} relates well to \( \tau \), both in an animal model and in patients. The ratio of E to SR\textsubscript{ivr} can be used to predict LV filling pressures with reasonable accuracy, particularly in patients with E/E\textsubscript{a} ratio 8 to 15, normal EF, and regional dysfunction.
Acknowledgment
We thank Daryl Schulz for his help with the animal experiments.

Disclosures
None.

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CLINICAL PERSPECTIVE
Diastolic dysfunction plays an important role in the pathophysiology of heart failure, particularly in patients with normal ejection fraction. Noninvasive indices of left ventricular relaxation and filling pressures correlate with exercise tolerance and are associated with cardiac morbidity and mortality. Accordingly, Doppler echocardiography, including tissue Doppler imaging, can play an important role in the evaluation of patients with heart failure and preserved ejection fraction. The ratio of mitral early diastolic velocity to mitral annulus early diastolic velocity (E/Ea ratio) is currently the most practical measurement to use for this objective. However, it has a number of limitations in patients with normal cardiac function, mitral valve disease, and regional dysfunction. A load-independent measurement that captures the performance of all myocardial segments would circumvent these limitations. We hypothesized that global diastolic strain rate during the isovolumetric relaxation period (SRivr) is such an index. Furthermore, it is possible to estimate LV filling pressures with the E/Srivr ratio in a manner analogous to that of the E/Ea ratio. We observed in animal studies that left ventricular relaxation is the main determinant of SRivr. In human studies with 50 patients, SRivr related well with the time constant of left ventricular pressure decay during the IVR period (τ). As hypothesized, the E/Srivr ratio had a good correlation with mean wedge pressure (r=0.79, P<0.001), as well as in 24 prospective patients (r=0.84, P=0.001). This novel approach appears most promising in subgroups in which annular Ea velocity has its limitations, namely, patients with an E/Ea ratio 8 to 15, patients with normal ejection fraction, and those with regional dysfunction.
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Circulation. 2007;115:1376-1383; originally published online March 5, 2007;
doi: 10.1161/CIRCULATIONAHA.106.662882
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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