Influence of Alterations in Loading on Mitral Annular Velocity by Tissue Doppler Echocardiography and Its Associated Ability To Predict Filling Pressures*

Didier C. Jacques, MD; Michael R. Pinsky, MD, FCCP; Donald Severyn, MS; and John Gorcsan III, MD

Study objectives: Early diastolic mitral annular velocity (E') by tissue Doppler echocardiography (TD) has been reported to be a load-independent index of left ventricular (LV) diastolic function, allowing the early diastolic mitral inflow velocity (E)/E’ ratio to be used clinically to predict LV filling pressures. However, preload independence of E’ has remained controversial, and E/E’ may not consistently be predictive of LV filling pressures. Our objectives were to test the hypotheses that E’ is affected by preload, and that alterations of preload, afterload, and contractility also affect E/E’.

Design, interventions, and measurements: An open-chest dog model was used (n = 8). High-fidelity pressure and conductance catheters were used for pressure-volume relations, and E’ was obtained by pulsed TD from the apical four-chamber view. Changes in preload and afterload were induced by vena caval and partial aortic occlusions, respectively. Data were collected during control phase and during infusions of dobutamine and esmolol to alter contractility.

Results: E’ was consistently and significantly associated with acute decreases in LV end-diastolic pressure in each dog (n = 200 beats; r = 0.93 ± 0.06 [mean ± SD]). Similar results occurred with dobutamine and esmolol infusions. This preload sensitivity was reflected in E/E’, which was inversely (rather than directly) correlated with LV diastolic pressure (r = 0.67). E/E’ was less affected by preload when diastolic dysfunction was induced by sustained partial aortic occlusion (time constant of isovolumic relaxation increased from 46 ± 19 to 53 ± 21 ms, p < 0.001).

Conclusions: E’ was significantly influenced by preload with preserved LV function and low filling pressures (< 12 mm Hg); accordingly, E/E’ was less predictive of LV filling pressures in this scenario. E/E’ was more predictive of LV filling pressures in the presence of diastolic dysfunction.

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Key words: diastole; Doppler echocardiography; ventricular function

Abbreviations: E’ = early diastolic mitral annular velocity; E = early diastolic mitral inflow velocity; EDP = end-diastolic pressure; Ees = end-systolic elastance; HR = heart rate; IVC = inferior vena cava; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; Pre-a = before atrial contraction; SV = stroke volume; τ = time constant of isovolumic relaxation; TD = tissue Doppler echocardiography

Tissue Doppler echocardiography (TD) has made significant contributions to the echocardiographic assessment of left ventricular (LV) diastolic function and LV filling pressures. The early diastolic mitral annular velocity (E’) measured by TD has been reported to be a relatively load independent index of LV relaxation.1–5 Furthermore, the ratio of early diastolic mitral inflow velocity (E) to E’ (E/E’) has been shown to be predictive of LV filling pressures in several studies6–11 and has begun to gain clinical acceptance. However, preload independence of E’ has remained controversial, and the effects of acute alterations in preload, afterload, and contractility on E’ and their related influence on E/E’ has not been established. Our
objective was to test the hypotheses that E' and E/E' are influenced by alterations in preload and afterload under control settings and changes in contractility induced by inotropic modulation.

**Materials and Methods**

**Preparation**

Eight mongrel male dogs weighing 22.8 ± 1.5 kg (mean ± SD) [range, 21 to 24 kg] were studied. The protocol was approved by the Institutional Animal Care and Use Committee, and conformed to the Position of the American Heart Association on Research Animal Use. All dogs were anesthetized with sodium pentobarbital (30 mg/kg induction, 1.0 mg/kg/h maintenance with intermittent boluses, if needed), underwent endotracheal intubation, and placed on mechanical ventilation. A 6-F 11-pole multielectrode conductance catheter (Webster Laboratories; Irvine, CA) was inserted via the right internal carotid artery with its tip positioned in the LV apex using fluoroscopic guidance. A LV micromanometer catheter (MPC-500; Millar; Houston, TX) was placed from the left common carotid artery. A second micromanometer-tipped catheter was introduced in a femoral artery and placed in the descending thoracic aorta. A 20-mm balloon catheter was inserted via the right femoral vein to the inferior vena cava (IVC). This balloon was partially filled with saline solution to intermittently occlude IVC flow and rapidly alter preload to determine sequential pressure-volume relations. A second 20-mm balloon catheter was inserted via the right femoral artery and placed in the descending thoracic aorta. A median sternotomy was performed, and the heart was suspended in a pericardial cradle. A 5-MHz multplane echocardiographic transducer was placed at the LV apex and adjusted to image the maximal longitudinal dimension, analogous to the apical four-chamber view used in transthoracic imaging (Fig 1). The transducer was interfaced with an echocardiographic system with TD echocardiography capabilities (PV 6000; Toshiba Medical Systems; Tochigi, Japan). The pulsed-Doppler sample volume was opened to 10 mm placed on the medial mitral annular sites as previously described. High-pass filtering was removed, and system settings were adjusted to optimize TD data. TD data were recorded on videotape for subsequent analog-to-digital conver-

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**Figure 1.** Echocardiographic image of the apical four-chamber view (right panel) from the open-chest dog model with corresponding pulsed TD display of mitral annular velocity (left panel). The sample volume is placed in medial mitral annulus. A' = late diastolic mitral annular velocity corresponding to atrial systole.
sion and quantitative analysis. An ECG was recorded continuously with limb electrodes. An epicardial pacing electrode was sewn on the right atrium to induce an electrical spike used to synchronize analysis of simultaneous Doppler echocardiography and hemodynamic data. For the conductance catheter, a 20-kHz constant amplitude current of 0.03-mA between proximal distal electrode pairs was used with a data processor as described previously (Sigma 5DF; Leycom; Leyden, Netherlands).12,13 Changes in volume were sensed as a change in resistance in the cross-sectional area of each electrode pair, with the sum of all segments reflecting total volume. Parallel conductance was calculated by the hypertonic saline solution method and subtracted to measure LV volume. All physiologic signals were digitized at 150 Hz (WINDAQ Software; DATAQ Instruments; Akron, OH) and recorded on a computer.

Protocol

Hemodynamic and echocardiographic data were obtained simultaneously during end-expiratory apnea. Preload and afterload alterations were repeated under three different contractile states: baseline (control period); dobutamine infusion (5 to 10 μg/kg/min) to increase contractility; and esmolol (bolus of 500 μg and continuous infusion of 100 to 400 μg/kg/min) to decrease contractility. Under each of these three contractile levels, the following hemodynamic alterations were induced: (1) transient IVC occlusions to decrease preload to minimum LV volume, (2) transient aortic occlusion to increase afterload by a 30 to 40 mm Hg pressure elevation, and (3) sustained aortic occlusion at the same level and new IVC occlusion, so that preload changes were produced under two different afterload levels. Each sequence was repeated to record E at the tips of the mitral leaflets using routine pulsed Doppler echocardiography and E’ using TD.15–18 Time for physiologic data to return to baseline was observed between each manipulation.

Data Analysis

The following hemodynamic parameters were analyzed: heart rate (HR), systolic BP, diastolic BP, stroke volume (SV), LV minimal diastolic pressure, LV diastolic pressure before atrial contraction (Pre-a), and LV end-diastolic pressure (LVEDP). The time constant of isovolumic relaxation (τ) was calculated according Weiss method.19 End-systolic elastance (Ees) was calculated as a relatively load independent measure of contractility as the slope of end systolic (maximum pressure/volume points) from each loop during IVC occlusions using an automated iterative linear regression technique. Peak E’ by TD and routine E were measured off-line using a digital Doppler analysis system. In conditions where the E’ and E waves merged with the atrial A waves, the diastolic peak velocity were called E’ and E, respectively, as has been previously described in human studies.7 Data from the identical corresponding LVEDP values were used for E/E’ calculations.

Statistical Analysis

A minimum of three consecutive beats before occlusion (baseline) and subsequent consecutive beat-to-beat measures during each change in loading were analyzed to the end of the occlusion. Analysis of variance for repeated measures with Newman-Keuls post hoc transformation was used, and a paired t test was used when variables existed as paired. Least squares linear regression was used to define relationships between TD and hemodynamic variables. All values are shown as mean ± SD. Significance was considered at p < 0.05.

RESULTS

Complete data sets on all eight dogs were available for control conditions. Two dogs had sustained ventricular arrhythmias with dobutamine infusion during IVC occlusion, and one dog during aortic occlusion. One dog was very sensitive to esmolol infusion for control conditions. Two dogs had sustained venous occlusions led to a significant decrease of LV filling pressures, SV, and E, with no HR change (Tables 1, 2), as expected. Consistent and significant

Table 1—Effects of Alterations in Preload*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 8)</th>
<th>Dobutamine (n = 6)</th>
<th>Esmolol (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>IVC Occlusion</td>
<td>Baseline</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>109 ± 14</td>
<td>110 ± 14</td>
<td>130 ± 19</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>150 ± 25</td>
<td>108 ± 19†</td>
<td>204 ± 38</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>124 ± 21</td>
<td>91 ± 18†</td>
<td>153 ± 33</td>
</tr>
<tr>
<td>LVMP, mm Hg</td>
<td>4.0 ± 3.8</td>
<td>0.1 ± 2.1†</td>
<td>3.3 ± 5.1</td>
</tr>
<tr>
<td>LV Pre-a, mm Hg</td>
<td>5.2 ± 3.7</td>
<td>1.4 ± 2.7†</td>
<td>5.6 ± 4.7</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>7.2 ± 4.9</td>
<td>2.0 ± 2.4†</td>
<td>7.3 ± 5.7</td>
</tr>
<tr>
<td>SV, mL</td>
<td>16 ± 6</td>
<td>13 ± 7†</td>
<td>21 ± 5</td>
</tr>
<tr>
<td>τ, ms</td>
<td>42 ± 7</td>
<td>42 ± 14</td>
<td>32 ± 11</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>45 ± 16</td>
<td>35 ± 12†</td>
<td>57 ± 24</td>
</tr>
<tr>
<td>E', cm/s</td>
<td>5.1 ± 2.1</td>
<td>3.2 ± 1.4†</td>
<td>7.8 ± 2.9</td>
</tr>
</tbody>
</table>

*p < 0.05 vs preceding baseline.

*Data are presented as mean ± SD. LVMP = LV minimal diastolic pressure.
decreases in E’ also occurred from 5.1 ± 2.1 to 3.2 ± 1.4 cm/s (p < 0.005) under control conditions (Fig 1, left). A’ also decreased, from 7.6 ± 4.2 to 5.9 ± 3.7 cm/s (p < 0.05). Consecutive beats during IVC occlusion demonstrated a close correlation between E’ and LVEDP for each dog (r = 0.92 ± 0.05, Fig 2). Dobutamine increased Ees from 4.4 ± 1.3 to 8.5 ± 1.0 mm Hg/mL (p < 0.05), and esmolol decreased Ees from 5.1 ± 2.7 to 2.3 ± 0.9 mm Hg/mL (p < 0.05), documenting intended alterations in contractility. Decreases in E’ with IVC occlusions also occurred during these alterations in contractility, and E’ remained significantly correlated with LVEDP (Fig 3, left panels).

### Table 2—Effects of Alterations in Afterload*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 8)</th>
<th>Dobutamine (n = 7)</th>
<th>Esmolol (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Aortic Occlusion</td>
<td>Baseline</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>103 ± 10</td>
<td>101 ± 13</td>
<td>138 ± 20</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130 ± 21</td>
<td>170 ± 25†</td>
<td>178 ± 43</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>107 ± 17</td>
<td>136 ± 18†</td>
<td>139 ± 34</td>
</tr>
<tr>
<td>LVMP, mm Hg</td>
<td>3.0 ± 3.5</td>
<td>5.2 ± 4.3†</td>
<td>3.0 ± 4.1</td>
</tr>
<tr>
<td>LV Pre-a, mm Hg</td>
<td>4.1 ± 3.6</td>
<td>6.2 ± 4.4†</td>
<td>4.8 ± 4.1</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>4.8 ± 3.6</td>
<td>7.6 ± 4.4†</td>
<td>8.3 ± 7.9</td>
</tr>
<tr>
<td>SV, mL</td>
<td>17 ± 4</td>
<td>17 ± 5</td>
<td>18 ± 6</td>
</tr>
<tr>
<td>τ, ms</td>
<td>41 ± 6</td>
<td>49 ± 7†</td>
<td>31 ± 11</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>40 ± 10</td>
<td>39 ± 15</td>
<td>65 ± 17</td>
</tr>
<tr>
<td>E’, cm/s</td>
<td>4.6 ± 1.0</td>
<td>4.1 ± 1.1</td>
<td>8.8 ± 5.7</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. See Table 1 for expansion of abbreviation.
†p < 0.05 vs preceding baseline.

**Influence of Afterload on E’**

Transient partial aortic occlusion resulted in increases in LV systolic pressure from 130 ± 21 to 170 ± 25 mm Hg (p < 0.05), consistent with significantly increased LV afterload. E’ was unaffected at 4.1 ± 1.1 from 4.6 ± 1.0 cm/s (Table 1, Fig 4). E’ was relatively insensitive to increases in afterload during alterations in contractility by dobutamine and esmolol infusion, respectively. There was no significant correlation of beat-to-beat changes in LV systolic pressures and E’ aortic occlusion (Fig 5). During periods of sustained increased afterload induced by partial aortic occlusion, an increase in τ was

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/22019/ on 04/28/2017)
observed from 46 ± 19 to 53 ± 21 ms (p < 0.001), consistent with a decrease in LV diastolic relaxation. E' was relatively unaffected by transient or sustained increases in afterload.

**Effects of Preload and Afterload on E/E’**

E/E’ was determined during baseline and IVC occlusions during control conditions and altered contractually induced by dobutamine and esmolol. Although E was also influenced by preload as expected, the influence of preload reduction on E’ was greater, resulting on a significant inverse relationship between E/E’ and LVEDP (range, –3 to 19 mm Hg) [Fig 6, top, A; r = −0.67, p < 0.005] or between E/E’ and LV Pre-a pressure (range, –4 to 17 mm Hg) [r = −0.63, p < 0.005]. During sustained increased afterload, where diastolic dysfunction was induced as evidenced by an increased τ, the influence of preload reduction on E/E’ was less pronounced, and there was no significant correlation between E/E’ and LVEDP (Fig 6, bottom, B) or between E/E’ and LV Pre-a pressure.

**Discussion**

This animal model confirms the significant and predictable influence of acute preload reduction on
E' under variable conditions, including changes in contractility by positive and negative inotropic modulation, as well as sustained increased afterload. In addition, E/E', which is used clinically to estimate LV filling pressures, was greatly affected by decreases in preload in the low range of LV filling pressures that were examined (<12 mm Hg). Transient and sustained increases in afterload did not affect E' under similar conditions of varied levels of contractile state. E/E' was less affected by changes in preload under conditions of sustained aortic occlusion, where an increase in \( \tau \) was induced, consistent with transient diastolic dysfunction.

Sohn et al.\(^{11} \) were among the first to suggest that E' by TD was a preload independent measure of LV diastolic function. They showed that E' was not significantly altered in patients by rapid infusion of normal saline solution to increase preload, nor IV nitroglycerin to decrease preload. They observed a relatively weak but significant inverse correlation of \( \tau \) with E' \( (r = -0.56, p < 0.01) \), and concluded that E' may be potentially used as a measure of LV diastolic function. Nagueh et al.\(^{10} \) extended these observations and proposed the novel mitral inflow to annular velocity ratio (E/E') using peak E from mitral inflow and E' from the lateral wall in the four-chamber view as a means to predict LV filling pressures. They observed an E/E' > 10 to be predictive of a mean pulmonary capillary wedge pressure > 15 mm Hg. They also reported E/E' was predictive of LV filling pressures in patients with sinus tachycardia, heart transplant recipients, and patients with hypertrophic cardiomyopathy.\(^7,9,10\) Other studies include Kim and Sohn,\(^{20} \) who showed a significant correlation of E/E' with LV diastolic Pre-a pressure, and Ommen et al.\(^{21} \) who correlated E/E' with mean LV diastolic pressures. They found E/E' to be most predictive of LV filling pressures in patients with LV dysfunction, defined as ejection fractions < 50%.

Despite these data supporting the preload independence of E' and E/E' as being directly related to LV filling pressures, these concepts may not apply to all hemodynamic states. The Frank-Starling relationship would predict longitudinal LV ejection and expansion, measured by E', to be directly related to LV filling.\(^{22} \) Early diastolic relaxation is known to be an active process that starts before the end of the LV ejection, and continues during early filling and accordingly is influenced by preload. Our present study supports this closely coupled relationship of E' with LV filling and demonstrates an inverse (rather than direct) relationship of E/E' with LV EDP. Firstenberg et al.\(^{23} \) similarly observed a consistent reduction in E' with acutely decreased preload and concluded E' to be preload dependent. Furthermore, they also suggested that E' was less influenced by preload in...
situations where \( \tau \) was prolonged, suggesting diastolic dysfunction, but did not report on findings related to E/E' as we do in the present study. This group also studied measures of E' in seven normal volunteers who underwent measures of pulmonary capillary wedge pressure during alterations in preload induced by lower body negative pressure and volume loading. They observed that E/E' was a relatively unreliable indicator of LV filling pressures in this group of subjects with normal LV function, and was only weakly correlated with LV filling pressures. Another condition that supports the concept that E/E' is not always predictive of LV filling pressure is constrictive pericardial disease, where E/E' was found to have an inverse relationship to LV filling pressure.

Limitations

This was a canine model in which the animals had normal LV function, and these findings may not translate to humans with cardiac disease. However, it is likely that these findings may exist in humans with normal LV function where similar acute hemodynamic and load alterations occur. Although tachycardia affects assessment of E' where E' and A waves were merged, the use of a merged peak diastolic
NS was significantly increased during sustained aortic occlusion.

Although E' and E velocity as E' has been shown to be clinically useful in patients with tachycardia. Although E' and E were not measured simultaneously, this limitation was minimized because E' was paired with measures of E where LVEDP and diastolic Pre-a pressures were not significant.

Conclusions and Clinical Implications

This study extends the use of E' as a measure of diastolic LV function by demonstrating its afterload independence. However, E' appears clearly dependent on preload, in particular in the setting of normal LV function and low filling pressures. E/E' is also affected by this preload dependence. Clinical situations of hypovolemia in patients with preserved LV function may be associated with E/E' that are disproportionately elevated, despite low filling pressures. This condition and constrictive pericarditis appear to be exceptions not to use E/E' to estimate LV filling pressures. The effects of preload on E' and E/E' appear less pronounced in models of diastolic dysfunction and in humans with myocardial disease.

References