Determinants of Left Ventricular Early-Diastolic Lengthening Velocity
Independent Contributions From Left Ventricular Relaxation, Restoring Forces, and Lengthening Load

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Background—Peak early-diastolic mitral annulus velocity (e') by tissue Doppler imaging has been introduced as a clinical marker of diastolic function. This study investigates whether lengthening load (early-diastolic load) and restoring forces are determinants of e' in addition to rate of left ventricular (LV) relaxation.

Methods and Results—In 10 anesthetized dogs, we measured e' by sonomicrometry and tissue Doppler imaging during baseline, volume loading, caval constriction, dobutamine infusion, and occlusion of the left anterior descending coronary artery. Relaxation was measured as the time constant (τ) of LV pressure decay by micromanometer. Lengthening load was measured as LV transmural pressure at mitral valve opening (LVP \text{MVO}). Restoring forces were quantified by 2 different indices: (1) As the difference between minimum and unstressed LV diameter (L_{\text{min}}-L_0) and (2) as the estimated fully relaxed LV transmural pressure (FRP_{\text{est}}) at minimum diameter. In the overall analysis, a strong association was observed between e' and LVP \text{MVO} (β=0.49; P<0.001), which indicates an independent effect of lengthening load, as well as between e' and L_{\text{min}}-L_0 (β=−0.38; P<0.002) and between e' and FRP_{\text{est}} (β=−0.31; P<0.002), consistent with an independent contribution of restoring forces. A direct effect of rate of relaxation on e' was observed in a separate analysis of baseline, dobutamine, and ischemia when postextrasystolic beats were included (β=−0.06, P<0.01).

Conclusions—The present study indicates that in the nonfailing ventricle, in addition to LV relaxation, restoring forces and lengthening load are important determinants of early-diastolic lengthening velocity. (Circulation. 2009;119:2578-2586.)

Key Words: diastole ■ echocardiography ■ heart failure ■ hemodynamics ■ mechanics

A

ssessment of left ventricular (LV) lengthening velocities by tissue Doppler imaging (TDI) plays an important role in the evaluation of patients with suspected diastolic dysfunction. Lengthening velocities are recorded at the mitral annulus from apical views, and there are 2 main velocity waves that represent early-diastolic (e') and atrial-induced (a') myocardial lengthening. Most of the clinical focus has been on e', which has demonstrated a close correlation with global LV relaxation rate, quantified invasively as the time constant of LV isovolumic pressure fall (τ).1−4 Accordingly, e' has been proposed as a marker of diastolic dysfunction. Furthermore, the ratio of peak early transmitral flow velocity (E) over e' correlates with LV end-diastolic pressure, and an elevated E/e' ratio has been introduced as a clinical marker of elevated LV diastolic pressure.5 In patients with heart failure and normal ejection fraction, an elevated E/e' ratio may serve as evidence of diastolic heart failure.5 Therefore, e' could become a key measure in the echocardiographic evaluation of LV function; however, insight into the mechanisms that regulate the magnitude of e' is limited.

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The observed correlation between e' and τ does not imply that e' is determined exclusively by LV relaxation, and both loading conditions and diastolic recoil have been suggested as determinants of e'.3,6,7 Previous studies of isolated cardiac muscle preparations8,9 and of in situ dog hearts10 have shown that myocardial lengthening rate is determined by end-systolic length and loading conditions. Furthermore, the relationship between load and myocardial lengthening rate was dependent on both the timing and the magnitude of the applied load; ie, elevation of peak systolic load reduced LV lengthening rate, whereas load applied during myocardial relaxation (late load) increased lengthening rate.9,10 Therefore, late load has also been termed “lengthening load.”11

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The aim of the present study was to determine how mechanisms other than the rate of LV relaxation may contribute to \( e' \) in the nonfailing LV. Therefore, we investigated the roles of LV lengthening load and restoring forces in addition to the rate of myocardial relaxation as determinants of \( e' \). As a measure of LV lengthening load, we used LV transmural pressure at the time of mitral valve opening (LVP_{MVO}). The rationale for using LVP_{MVO} as a measure of lengthening load is that it reflects the external distending load during early filling and is a function of the force that pushes blood into the ventricle at the onset of filling. The other mechanism that may contribute to early-diastolic filling is the restoring forces that have been generated during previous systole. This is analogous to a spring that has been compressed below its slack length and lengths when the compression is released. Restoring forces were quantified by two different approaches. First, because restoring forces are generated when myocardium contracts to dimensions less than unstressed or slack length (\( L_0 \)), we used the extent of compression level in case of a nonfilling diastole.12,13 LV relaxation was measured in terms of \( \tau \).14 The potential mechanisms that regulate \( e' \) were studied in a dog model during different levels of contractility, different loading conditions, and acute myocardial ischemia.

**Methods**

Twelve mongrel dogs of either sex and with a body weight of 28±4 kg were anesthetized with a bolus of 25 mg of thiopental per 1 kg of body weight, followed by continuous infusion of morphine (3.5 mg · kg⁻¹ · h⁻¹) and pentobarbital (2 mg · kg⁻¹ · h⁻¹), the latter reduced to half dose after 4 hours of infusion. The animals were ventilated and surgically prepared as described previously15 and studied with open chest and pericardium loosely resutured. Two animals were excluded owing to complications that occurred during surgery. In addition, 1 dog was excluded during dobutamine and ischemia because of persistent arrhythmia. The study was approved by the National Animal Experimentation Board. The laboratory animals were supplied by the Center for Comparative Medicine, Rikshospitalet University Hospital, Oslo, Norway.

**Measurements**

**Pressure Measurements and Sonomicrometry**

Left atrial (LA) and LV intracavitary pressures were measured by micromanometer-tipped catheters (MPC-500, Millar Instruments Inc, Houston, Tex). To serve as an absolute pressure reference for the dial pressure was measured with a fluid-containing flat balloon.16 Left atrial (LA) and LV intracavitary pressures were measured by micromanometers, a fluid-filled catheter was placed in the LA.17

**Echocardiography**

A Vivid 7 ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway) was used. LV TDI (color Doppler) recordings were obtained from 4- and 2-chamber views. Mitral annulus velocities were measured at both sides of the annulus in each projection with a region of interest size of 12×6 mm. Anterior annular velocities are reported, as well as average values of the 4 sample sites. To facilitate comparison between the methods, we report TDI and sonomicrometry data with similar polarity (ie, positive velocities indicate elongation). All recordings were obtained with the animals in a supine position with the ventilator off. The ECG was monitored from a limb lead.

**Data Analysis and Definitions**

Figure 1 illustrates measurement of hemodynamic variables. The following definitions were applied:

- \( e' \) (cm/s): peak early-diastolic LV lengthening velocity, calculated as the time derivative of the LV long-axis diameter.
- \( \tau \) (ms): Time constant of the exponential LV transmural pressure decay during isovolumic relaxation, which indicates the rate of LV relaxation.14
- Transmural LV pressure (mm Hg): LV intracavitary pressure minus pericardial pressure, which represents the effective LV distending pressure.
- LVP_{MVO} (mm Hg): The transmural LV pressure at first diastolic LV intracavitary pressure crossover with LA pressure, used as a measure of LV lengthening load.
- Unstressed LV diameter (\( L_0 \), mm): LV diameter at a transmural LV pressure of zero, which represents the slack length or resting length of LV myocardium.
- Estimated fully relaxed LV transmural pressure (FRP_{est}, mm Hg): Derived from the end-diastolic transmural LV pressure-diameter curve during caval constriction as the pressure coordinate that corresponded to minimum LV diameter (detailed explanation below).
- LV volume (mL): calculated as a modified general ellipsoid \((\% \cdot D_a \cdot D_L \cdot D_{trans})\)15
- Peak E (mL/s): Peak early-diastolic transmitral flow rate, calculated as the time derivative of LV volume.
- Operating stiffness (mm Hg/mm): Slope of linear regression of the end-diastolic LV pressure-diameter relation during caval constriction.

**Calculation of LV Restoring Forces**

The first step in the assessment of restoring forces was to define the transmural LV diastolic pressure-diameter relationship. The influ-
ence from the pericardial constraint was adjusted for by subtracting pericardial pressure from LV intracavitary pressure. Because early- and mid-diastolic pressure may be markedly influenced by inertial and viscous forces and by ongoing relaxation, we used only end-diastolic pressure-diameter points to construct the passive-elastic curve. End diastole represents an approximately stationary LV configuration. A line fitted through end-diastolic pressure-diameter coordinates during caval constriction defined the pressure-diameter relationship that was assumed to reflect LV passive-elastic myocardial properties.

Figure 2A shows how $L_0$ was measured as the LV diameter at zero transmural pressure. Figure 2B shows how the 2 different measures of LV restoring forces were obtained: Shortening below unstressed length was measured as $L_{min} - L_0$, and $FRP_{est}$ was obtained by projecting minimum LV diameter down to the transmural end-diastolic pressure-diameter curve.

**Experimental Protocol**

Baseline recordings were performed after a 30-minute period of stabilization. To avoid interference between sonomicrometry and TDI measurements, we first recorded pressures, ECG, and echocardiographic data during 10 seconds and then pressures, ECG, and dimensions during the subsequent 10 seconds.

To determine how $e'$ responded to changes in loading, we performed the following interventions: Preload was reduced by transient caval constrictions and was elevated by rapid intravenous infusion of isotonic saline ($n=10$). To determine how $e'$ responded to increased inotropy and to acute ischemia, we performed the following interventions: Inotropy was enhanced by intravenous dobutamine administration ($5.0 \mu g \cdot kg^{-1} \cdot min^{-1}$; $n=9$), and ischemia was induced by constricting a snare applied around the left anterior descending coronary artery immediately distal to the first diagonal branch. Recordings were obtained after 15 minutes of left anterior descending coronary artery occlusion ($n=9$).

We compared $e'$ from heartbeats during dobutamine with postextrasystolic beats during ischemia, induced by a tap on the right atrium. This analysis was performed to isolate the effect of large variation of $r$ on $e'$, because the beats during the 2 interventions have similar lengthening load, and postextrasystolic beats cause increased shortening similar to dobutamine.

**Statistical Analysis**

Values are expressed as mean±SD. Variables were analyzed by a mixed-model procedure with structured covariance matrix (SPSS 15, SPSS Inc, Chicago, Ill) to handle the dependencies in repeated measurements within the same subject.

The proposed determinants of $e'$ were assessed by the inclusion of $r$, $LVPMVO_{2}$, and $L_{min} - L_0$ (or $FRP_{est}$) as independent variables into the model:

$$e' = \beta_0 + \beta_1 r + \beta_2 (L_{min} - L_0) + \beta_3 LVPMVO_{2}.$$ 

The parameter estimate ($\hat{\beta}$) indicates the magnitude and directional change in $e'$ for a 1-unit increase in the corresponding variable. Quadratic terms and interaction terms were included if appropriate and removed if nonsignificant. Interventions were analyzed together and in 2 separate groups that included dobutamine, baseline, and ischemia or volume loading, baseline, and caval constriction. The covariance structure with the lowest information criteria (Akaike) was chosen provided it was appropriate to the experimental protocol. Residuals were inspected to assess goodness of fit. Statistical differences were considered significant at $P<0.05$.

The 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

Figure 3 displays representative recordings from the different interventions, and the Table presents mean data. Increments in e' with volume loading and dobutamine infusion were observed, as well as reductions with caval constriction and left anterior descending coronary artery occlusion.

A close association was observed between TDI measurements of e' from the anterior annulus and the average values of the 3 other sampling sites (β=0.83; P<0.001). During ischemia, however, anterior e' was reduced (P<0.001) compared with average e' of the other 3 sampling sites.

Values of e' by TDI were consistently larger than by sonomicrometry, but e' by the 2 methods showed close association (β=0.97; P<0.001). Because of interference between sonomicrometry and Doppler signals, e' by TDI could not be measured simultaneously with LV dimensions. Therefore, in the subsequent presentation, we use e' (anterior wall) by sonomicrometry, because this allowed analysis of all variables from the same heartbeat.

A close association was found between Lmin−L0 and FRPest (β=0.94; P<0.001), and their relation to e' was similar. For simplicity, we mainly show the result for Lmin−L0 as the measure of restoring forces in the subsequent presentation.

Relationships Between e' and Hemodynamic Variables During All Interventions

To determine the magnitude of the individual effect of the 3 proposed determinants of e', we evaluated the mixed model that included all interventions (Figure 4). A strong association was observed between e' and LVP_MVO (β=0.49; P<0.001), which indicates an independent effect of lengthening load, and between e' and L_min−L_0 (β=−0.38; P<0.002), and between e' and FRP_est (β=−0.31; P<0.002), consistent with an independent contribution of restoring forces. τ showed no significant association with e'.

Relationships Between e' and Hemodynamic Variables During Dobutamine Infusion and Ischemia

The increase in e' during dobutamine was associated with a reduction of τ, consistent with faster relaxation, and with more negative values for L_min−L_0 and FRP_est, consistent with stronger restoring forces (Table). The reduction in e' during ischemia was associated with prolongation of τ, consistent with slower relaxation, and L_min−L_0 and FRP_est approached zero, consistent with reduction of restoring forces (Table). Minor changes in LVP_MVO were seen. No significant change was found in operative LV diastolic stiffness during dobutamine infusion and ischemia.

Including data from baseline, dobutamine, and ischemia, we entered τ, LVP_MVO, and L_min−L_0 into the mixed model. As shown in Figure 5, a strong negative association was found between e' and L_min−L_0 (β=−0.52; P<0.001), which indicates that shortening below the unstressed LV diameter was associated with a progressive increase in e'. Figure 5 also demonstrates a strong association between e' and LVP_MVO (β=0.44; P<0.001), which supports the concept of effect from lengthening load. The association between e' and τ did not reach statistical significance.

In the plots of e' versus L_min−L_0 and of e' versus FRP_est, data points during dobutamine did not appear to be shifted relative to measurements during baseline. This may have been due to only a relatively small difference in τ. To define how e' responded to a selective change in τ, we compared e' during dobutamine and postextrasystolic beats during ische-
mia, which were the 2 interventions with the lowest and highest $\tau$, respectively. As demonstrated in Figure 6, at comparable $L_{\text{min}} - L_0$, an increased $\tau$ during postextrasystolic beats in the ischemic ventricle was associated with a marked reduction of $e’$. This is consistent with a direct effect of rate of relaxation on $e’$, because no significant difference in LVPMVO was found. To investigate the possible interaction between $L_{\text{min}} - L_0$ and $\tau$, the modeling was repeated with the

### Table. Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cavalc Constriction</th>
<th>Volume Loading</th>
<th>Dobutamine Infusion (n=9)</th>
<th>LAD Occlusion (n=9)</th>
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</thead>
<tbody>
<tr>
<td>$e’$, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sonomicrometry</td>
<td>3.8±1.4</td>
<td>2.3±0.9*</td>
<td>6.4±1.5*</td>
<td>4.9±1.4*</td>
<td>2.5±1.0*</td>
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<td>TDI</td>
<td>4.7±1.2</td>
<td>6.4±1.3*</td>
<td>5.3±1.5*</td>
<td>3.1±1.1*</td>
<td></td>
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<tr>
<td>$a’$, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonomicrometry</td>
<td>1.7±0.7</td>
<td>0.5±0.2*</td>
<td>2.5±1.0*</td>
<td>2.6±0.8*</td>
<td>1.4±0.7</td>
</tr>
<tr>
<td>TDI</td>
<td>1.2±0.5</td>
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<td>1.7±0.8*</td>
<td>0.6±0.7</td>
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<tr>
<td>Heart rate, bpm</td>
<td>105±15</td>
<td>109±16</td>
<td>111±24</td>
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<td>113±24</td>
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<td>Peak systolic LVP, mm Hg</td>
<td>90±10</td>
<td>57±13*</td>
<td>97±14</td>
<td>114±8*</td>
<td>83±13</td>
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<td>LV dP/dt$_{eas}$, mm Hg/s</td>
<td>1590±366</td>
<td>859±216*</td>
<td>1750±410</td>
<td>3061±479*</td>
<td>1254±392</td>
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<td>FRPEst, mm Hg</td>
<td>2.9±1.0</td>
<td>6.4±1.3*</td>
<td>5.3±1.5*</td>
<td>3.1±1.1*</td>
<td></td>
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<tr>
<td>Pericardial pressure at MVO, mm Hg</td>
<td>2.0±2.9</td>
<td>10±16</td>
<td>29±3.0</td>
<td>15±1.6</td>
<td>4.5±2.6*</td>
</tr>
<tr>
<td>Transmural LVPMVO, mm Hg</td>
<td>10.6±1.4</td>
<td>3.3±1.9*</td>
<td>15.9±2.3*</td>
<td>11.6±1.3</td>
<td>11.0±2.5</td>
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<tr>
<td>Peak systolic LVP, mm Hg</td>
<td>8.6±1.9</td>
<td>2.3±2.2*</td>
<td>12.9±2.4*</td>
<td>10.1±1.8*</td>
<td>6.5±1.7</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>54±17</td>
<td>40±16*</td>
<td>62±18*</td>
<td>56±19</td>
<td>53±23</td>
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<td>LV end-systolic volume, mL</td>
<td>37±13</td>
<td>34±13*</td>
<td>40±15*</td>
<td>34±12</td>
<td>41±19*</td>
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<tr>
<td>Minimum LV long-axis diameter, mm</td>
<td>54.2±6.0</td>
<td>52.5±5.9</td>
<td>52.5±5.8</td>
<td>53.9±6.5</td>
<td></td>
</tr>
<tr>
<td>LV long-axis shortening, mm</td>
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<td>1.5±0.7*</td>
<td>5.4±1.4*</td>
<td>4.6±1.4*</td>
<td>2.0±0.8*</td>
</tr>
<tr>
<td>$L_{\text{min}} - L_0$, mm</td>
<td>−1.5±0.7</td>
<td>−2.2±0.7</td>
<td>−0.6±1.1*</td>
<td>−2.5±1.2*</td>
<td>−0.4±1.6*</td>
</tr>
<tr>
<td>Operating stiffness, mm Hg/mm</td>
<td>2.6±0.9</td>
<td>2.5±1.0</td>
<td>2.6±0.8</td>
<td>2.7±0.8</td>
<td></td>
</tr>
</tbody>
</table>

LVPMVO indicates transmural LV pressure; MVO, mitral valve opening; $L_{\text{min}} - L_0$, minimum LV long-axis diameter after end systole ($L_{\text{min}}$) minus unstressed diameter ($L_0$); negative values indicate contraction below $L_0$.

Values are mean±SD.

*P<0.05 vs baseline (mixed model including all interventions).

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\[
e’ = \beta_0 + \beta_1 \tau + \beta_2 (L_{\text{min}} - L_0) + \beta_3 \text{LVPMVO}
\]

\[
e’ = \beta_0 + \beta_1 \tau + \beta_2 \text{FRP}_{\text{est}} + \beta_3 \text{LVPMVO}
\]

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Figure 4. Relationships between $e’$ and $\tau$, $L_{\text{min}} - L_0$, FRP$_{\text{est}}$, and LVPMVO, respectively. Significant relationships were observed between $e’$ and LVPMVO, $L_{\text{min}} - L_0$, and FRP$_{\text{est}}$, which indicates associations with lengthening load and restoring forces. The mixed-model terms and corresponding parameter estimates ($\beta$) are shown. NS indicates not significant. LVPMVO indicates transmural LV pressure at the time of mitral valve opening.
interaction term included and with data from postextrasystolic beats added. A strong association was observed between e' and L_{min} - L_0 (∝ 0.11; P<0.01), and a moderate association was seen between e' and L_{min} - L_0 (∝ 0.06; P<0.01), which confirms that restoring forces and rate of relaxation are independent determinants of e'. Furthermore, a significant association was observed between e' and the interaction between L_{min} - L_0 and L_{min} - L_0 (∝ 0.02; P<0.04).

The relationship between e' and minimum LV long-axis diameter was investigated in a separate mixed model, and the association was found to be significant (∝ 0.94; P<0.05).

The relation, however, lost its significance when L_{min} - L_0 was added to the model, which indicates that this effect was accounted for by restoring forces.

**Relationships Between e' and Hemodynamic Variables**

**During Caval Constriction and Volume Loading**

As indicated by the mean data in the Table and by Figure 4, changes in e' with volume loading and caval constriction could not be attributed to changes in L_{min} - L_0 (∝ 0.01), and a moderate association was observed between e' and τ (∝ 0.02; P<0.01), which confirms that restoring forces and rate of relaxation are independent determinants of e'. Furthermore, a significant association was observed between e' and the interaction between L_{min} - L_0 and τ (∝ 0.02; P<0.04).

The relationship between e' and minimum LV long-axis diameter was investigated in a separate mixed model, and the association was found to be significant (∝ 0.94; P<0.05).

The relation, however, lost its significance when L_{min} - L_0 was added to the model, which indicates that this effect was accounted for by restoring forces.

**Figure 5. Relationships between e' and τ, L_{min} - L_0, FRPEst, and LVP_{MVO}, respectively.** Measurements during baseline, dobutamine infusion and ischemia are included. We observed significant relationships between e' and LVP_{MVO}, L_{min} - L_0, and estimated fully relaxed pressure (FRPEst), indicating associations to lengthening load and restoring forces. The mixed model terms and corresponding parameter estimates (∝) are shown. NS indicates not significant. LVP_{MVO} indicates transmural LV pressure at the time of mitral valve opening.

**Continuous recordings in one dog**

**Figure 7. Relationships between e' and end-systolic diameter from a single experiment.** Beat-to-beat recordings are shown from onset of dobutamine infusion, onset of ischemia, and caval constrictions at baseline and volume loading. The relationship between e' and restoring forces is shifted by large changes in lengthening load.
Volume loading and caval constriction caused marked changes in LVP_{MVO} (Table). A mixed-model analysis that included data from baseline, volume loading, and caval constriction demonstrated a strong association between e’ and LVP_{MVO} (β=0.42; P<0.001) and no significant associations with τ or L_{min}-L_{0}, which suggests that changes in e’ were caused primarily by changes in LVP_{MVO}.

**Discussion**

The present study demonstrates that LV restoring forces and LV lengthening load are independent determinants of e’, in addition to myocardial relaxation. The relative contribution from each of the determinants, however, differed markedly between the hemodynamic interventions that were studied. Changes in e’ during loading interventions were attributed entirely to changes in LV lengthening load and could not be explained by changes in myocardial relaxation or restoring force. Forces in e’ during dobutamine were attributed mainly to stronger restoring forces and during ischemia to both loss of restoring forces and slowing of relaxation. This is consistent with previous studies ten that suggested that increased e’ by dobutamine is attributed mainly to restoring forces, which in turn reflects increased contractility which causes smaller end-systolic myocardial dimension.

During myocardial ischemia, we observed a reduction in e’, and LV minimum length increased and approached L_{0}, which indicates that loss of restoring forces contributed to the reduction in e’. Furthermore, a marked increase in τ was seen, which indicates slowing of LV relaxation. Because LVP_{MVO} was essentially similar during baseline and ischemia, reduced e’ during ischemia could not be attributed to reduced lengthening load. The present data did not allow a clear separation between contributions from loss of restoring forces and slowing of relaxation to the decrease in e’ during ischemia. Most likely, both mechanisms contributed, and reduction of e’ during ischemia is accounted for in part by slowing of LV relaxation and in part by loss of restoring forces.

A direct interaction between τ and e’ was demonstrated when we compared the interventions with lowest and highest τ (dobutamine and ischemia, respectively). At similar LVP_{MVO} and comparable L_{min}-L_{0}, as induced by postextrasystolic beats, prolongation of τ was associated with decreased e’. This is consistent with a direct effect of relaxation rate on e’. Furthermore, Figure 6 and the interaction between L_{min}-L_{0} and τ suggest that slowing of relaxation reduces the effect of restoring forces on e’. The present study, however, was not designed to explore this possible interaction further.

In the present animal model, with near-normal LV end-diastolic pressures during ischemia, no significant change in diastolic stiffness was found. At elevated filling pressures, however, when operating on steeper parts of the pressure-diameter curve, this may be different, and ischemia may reduce e’ because of stiffening of the myocardium.

**Relationship Between Contractility and e’**

In the present study, increased e’ during dobutamine was accompanied by a decrease in τ, which indicates faster myocardial relaxation. A decrease in LV minimum length to values less than L_{0} was found, which indicates stronger restoring forces. This suggests that dobutamine may have increased e’ both by a direct effect on myocardial relaxation and by an effect on restoring forces. To define the contribution from these two mechanisms, we analyzed how dobutamine modified the relationship between e’ and L_{min}-L_{0}. The assumption was that a direct β-adrenergic effect of dobutamine would cause faster LV lengthening than during baseline for any given L_{min}-L_{0}. As illustrated in Figure 5, this was not the case, because no apparent shift in the relationship between e’ and L_{min}-L_{0} during dobutamine was found. This is in keeping with previous studies ten that suggested that increased e’ by dobutamine is attributed mainly to restoring forces, which in turn reflects increased contractility which causes smaller end-systolic myocardial dimension.

Furthermore, acceleration of blood and myocardial mass underestimates restoring forces, because the ventricle has already expanded before the time of minimum pressure. Furthermore, acceleration of blood and myocardial mass and possibly viscous forces account for additional pressure components. Therefore, LV pressure during rapid filling is always higher than predicted by the pressure-volume curve defined during static conditions. Direct measurement of restoring forces or their pressure equivalent is not feasible in the working heart unless additional interventions or complex methods are used. In the present study, we used an estimate of a fully relaxed pressure as an equivalent of restoring forces. When the ventricle contracted to dimensions less than L_{0}, FRP_{est} became increasingly negative and was associated with an increased e’, which supports the hypothesis that restoring forces contribute to e’.

**Relationship Between LV Lengthening Load and e’**

In isolated muscle preparations, late load is defined as forces applied to the myocardium during relaxation and...
filling, and an increase in late load results in faster myocardial lengthening. In a clinical context, it may be more intuitive to use the term “lengthening load” rather than “late load,” because the former refers directly to the physiology of filling. In the present study, we used LVPMVO as a measure of lengthening load. During a wide range of hemodynamic conditions, a close association between e’ and LVPMVO was observed, and neither τ nor measures of restoring forces could explain the relationship. The increase in e’ during volume loading could only be attributed to an increase in LVPMVO because the magnitude of restoring forces did not increase, and τ increased slightly and had no significant association with e’.

Previous studies have shown that e’ is sensitive to changes in LV end-diastolic pressure or preload. As indicated by the present study, this interaction is due to indirect effects of elevated preload. Because preload, defined as end-diastolic transmural pressure or end-diastolic volume, acts as a regulator of LV function at a time when diastolic lengthening has already occurred, preload as such cannot have a direct effect on e’.

**Relationship Between e’ and LV Shortening**

Previous studies have shown a close correlation between systolic shortening and e’. We suggest that the relationship between e’ and systolic shortening reflects that determinants of systolic shortening and determinants of LV lengthening velocity are tightly coupled. First, increasing systolic shortening below unstressed muscle length results in increased restoring forces, which cause faster myocardial lengthening. Second, changes in LVPMVO are associated with parallel changes in LV end-diastolic pressure and length, and therefore, increased diastolic pressure increases e’ as well as systolic shortening through the Frank-Starling mechanism. Finally, changes in LV contractility and systolic shortening tend to be associated with changes of myocardial relaxation. The association between e’ and systolic shortening does not mean that e’ is primarily a marker of systolic function but rather that determinants of systolic shortening are determinants of e’ as well, and this illustrates the tight coupling that may occur between variables that determine systolic and diastolic function. However, the coupling may be weaker in chronic heart disease and in ventricles with concentric hypertrophy, as indicated by the frequent finding of normal LV ejection fraction in combination with abnormal diastolic parameters.

**Study Limitations and Comments on the Methodology**

The present study was performed in an open-chest model with the pericardium loosely resutured. As previously shown, this does not mean that pericardial constraint is absent, and pericardial constraint can be measured accurately with the flat liquid–containing balloon transducer used in the present study.

Sonomicrometry slightly underestimated e’ compared with TDI, and this may have been attributable to the location of the basal crystal, slightly distal to the mitral ring. The strong association between e’ by the 2 methods indicates that sonomicrometry provided results that were comparable to TDI. The strength of sonomicrometry is that e’ can be measured simultaneously with all other variables, and this allows more extensive exploration of the underlying physiology.

In some cases during dobutamine, the LV contracted to diameters less than the end-diastolic diameters obtained during caval constriction, and we were therefore unable to define the pressure that corresponded to minimum diameter. In those cases, we used the lowest pressure on the end-diastolic transmural pressure-diameter curve rather than extrapolating the curve. Therefore, the average value of minimum pressure is somewhat overestimated, which implies that restoring forces were even stronger than indicated by FRPₑₑ.

A limitation of the present study is that animals with myocardial ischemia were studied only in the short term, and we did not study effects of remodeling, which may have major effects on LV filling in the failing heart. The main objective of the present study, however, was to determine mechanisms of changes in e’ in the nonfailing ventricle.

In severe heart failure with marked elevation of LA pressure and elevated transmitral pressure gradient, early transmitral flow is abbreviated owing to the rapid rise in LV pressure due to a stiff ventricle, which causes rapid deceleration of mitral inflow. Therefore, in the failing ventricle with high LA pressure, the early diastolic filling volume is small, and e’ is reduced. Furthermore, intraventricular flow may be disturbed, which leads to delay in timing of e’ relative to transmitral E. Therefore, in the failing ventricle, diastolic stiffness may play a more important role as a determinant of e’.

Heart size may be another factor that influences e’. Basal lengthening velocity is the sum of all myocardial lengthening between apex and base, when one assumes a stationary apex. Thus, if lengthening velocity per length of myocardial tissue is the same, a larger heart will have a higher e’ than a smaller heart. The animals used in the present study had limited variation in weight and heart size. In a clinical population with abnormal LV size and geometry, this factor should possibly be taken into account when e’ is evaluated.

**Conclusions**

The present study supports the hypothesis that in addition to LV relaxation, restoring forces and lengthening load are independent determinants of early-diastolic lengthening velocity. The relative contribution of these determinants, as well as a possible effect of diastolic stiffness, may depend on the functional state of the ventricle, with a more important contribution from rate of relaxation during heart failure.

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DISCLOSURES

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CLINICAL PERSPECTIVE

Measurement of left ventricular early-diastolic lengthening velocity (e’/a) by tissue Doppler echocardiography is used clinically to evaluate diastolic function, and the ratio between peak transmural early-diastolic velocity and e’ has been introduced as a noninvasive estimate of left ventricular diastolic pressure. A number of studies indicate that e’ is closely related to the rate of left ventricular relaxation. The present experimental study indicates that left ventricular transmural pressure at the onset of diastolic filling, which represents a lengthening load (early-diastolic load), is another important independent determinant of e’. Clinically, lengthening load would approximate left ventricular end-diastolic pressure. The present study also indicates that restoring forces, analogous to the elastic recoil after release of a compressed spring, is another important independent determinant of e’. Experimentally, restoring forces were quantified as the magnitude of contraction below myocardial resting length. Clinically, this is reflected in end-systolic length and magnitude of contraction. The present study confirmed that rate of relaxation is an independent determinant of e’. In the normal heart, with rapid relaxation, lengthening load and restoring forces are probably the main determinants of early-diastolic lengthening velocity. The relative contribution of the different determinants may depend on the functional state of the ventricle, with a more important contribution from rate of relaxation during heart failure.
Determinants of Left Ventricular Early-Diastolic Lengthening Velocity: Independent Contributions From Left Ventricular Relaxation, Restoring Forces, and Lengthening Load
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