Assessment of Left Ventricular Relaxation by Doppler Echocardiography

Comparison of Isovolumic Relaxation Time and Transmitral Flow Velocities With Time Constant of Isovolumic Relaxation

Yngvar Myreng, MD, and Otto A. Smiseth, MD, PhD

Isovolumic relaxation time (IVRT) and events of early transmitral flow measured by Doppler echocardiography were validated against the time constant of left ventricular relaxation (τ) in open-chest dogs. During increased inotropy (by isoproterenol infusion) at constant preload, enhancement of relaxation was indicated by a decrease in τ from 48±12 (mean±SD) to 33±5 msec (p=0.04) with a concomitant decrease in IVRT from 74±18 to 38±8 msec (p=0.03). During decreased inotropy (by propranolol infusion) at constant preload, slowing of relaxation was indicated by an increase in τ from 40±8 to 51±13 msec (p=0.02) with a concomitant increase in IVRT from 71±15 to 83±21 msec (p<0.05). A significant correlation between changes in τ and changes in IVRT was found (r=0.66, p<0.001). In contrast, when left ventricular end-diastolic pressure was increased from 7±2 to 24±4 mm Hg at constant inotropy, τ increased from 47±14 to 64±25 msec (p=0.03), whereas no change in IVRT was observed (76±19 and 71±19 msec, respectively). Aortic pressure was not significantly changed during any intervention, and heart rate was kept constant by pacing. Peak early transmitral velocity was unchanged by propranolol but increased during isoproterenol and saline infusion (p<0.001 and p<0.01, respectively). During volume loading, left atrial V wave pressure was a positive predictor (p=0.002) and τ was a negative (p=0.06) predictor of the flow-adjusted transmitral flow velocity. Thus, IVRT reflected τ during changing contractility at constant preload, but not during increasing preload. Prolongation of IVRT as a sign of slowing of relaxation during volume loading was counteracted by an earlier opening of the mitral valve caused by increasing atrial pressure, thus leaving IVRT unchanged. (Circulation 1990;81:260–266)

Abnormal relaxation of the left ventricle (LV) is present in a variety of cardiac diseases and is an early manifestation of LV dysfunction.\(^1\)\(^–\)\(^5\) The most accepted index of LV relaxation is the time constant of LV pressure decay (τ).\(^6\) However, calculation of τ requires LV pressure recordings. Accordingly, attempts have been made to assess LV relaxation noninvasively by M-mode\(^7\)\(^–\)\(^8\) and Doppler echocardiography\(^9\)\(^–\)\(^10\) and by radionuclide technique.\(^11\)\(^–\)\(^12\) Isovolumic relaxation time (IVRT), comprising the time interval during which the principal LV pressure fall takes place, can be measured by combining phonocardiography and M-mode echocardiography, by M-mode technique alone, or from the signals of valve movements by Doppler echocardiography. We have previously reported that reproducible measurements of IVRT can be achieved by Doppler technique in patients.\(^13\) The aim of the present study was to validate IVRT and events of early transmitral filling as measured by Doppler technique against τ during changing inotropy and LV filling pressure, respectively. This was done in an experimental model in dogs, which allowed monitoring of the pressure determinants of IVRT.

**Methods**

**Animal Preparation**

The experiments were performed in 11 dogs weighing 23±2 kg (range, 19–26 kg). Anesthesia was induced with thiopentone and continued with intravenous morphine injections (50–100 mg/hr) supplemented with sodium pentobarbital as needed. The dogs were ventilated with room air by use of a Servo Ventilator (model 900B, Siemens Elema, Stockholm, Sweden). Blood gases and body temperature were
kept within physiologic ranges. The chest was opened through a median sternotomy, and the pericardium was left open throughout the experiment. Through peripheral vessel incisions a high-fidelity catheter (Millar, Houston, Texas) and a fluid-filled reference catheter were placed in the left ventricle. A fluid-filled catheter was advanced to the ascending aorta. In eight of the dogs, a catheter was introduced into the left atrium by means of the left auricle; four of these dogs received a fluid-filled catheter, and the other four dogs received a Millar catheter, which was zero-referenced against the LV fluid-filled catheter during long diastases. The fluid-filled catheters were connected to transducers (model AE 840, SensoNor, Horten, Norway). Both external jugular veins were cannulated to allow for rapid volume infusion. The pressure tracings and electrocardiograms were printed on paper at a speed of 200 mm/sec by a recorder (model 2600 S, Gould, Cleveland, Ohio). Sinus node function was abolished by injection of 20% formaldehyde in the frontal aspect of the right atrial wall to the left of and below the superior caval vein. Pacing electrodes were sutured to the right atrial appendage and to the frontal aspect of the interventricular septum immediately subjacent to the atrophicventricular groove. The heart was paced in atrophicventricular sequence (atrioventricular delay, 130 msec) at rates below 118 beats/min.

**Doppler Echocardiography**

A dedicated Doppler instrument (SD-100, Vingmed Sound, Horten, Norway) with a 3-MHz probe was used for the Doppler measurements. During data acquisition, the dog was placed in the semilateral left decubitus position. The Doppler probe was applied manually directly on the apex. Continuous wave mode was used to locate the highest velocities and, thus, to align the ultrasound beam parallel to the flow direction, whereas pulsed wave mode was used for recording the signals. In the measuring depth (40–60 mm) the sample volume was approximately 7 mm in diameter and 7 mm in length. The sample volume was placed in the depth at which the spikes caused by mitral valve opening were most distinctly seen in the Doppler spectrum and amplitude tracing; this corresponds to the tip of the mitral valve.\(^4\) Care was taken to display distinct aortic valve closure and mitral valve opening signals simultaneously. Transmitial inflow velocities were visualized in the same spectrum (Figure 1). Probe position and angulation were adjusted to achieve optimal signals as judged from the spectral display and the audible Doppler shift. All Doppler recordings were videotaped.

**Procedure**

Pressures and Doppler signals were recorded simultaneously during suspension of ventilation for 15–30 seconds. Atrioventricular sequential pacing was used to keep heart rate constant (range, 71–118 beats/min) during each intervention.

**FIGURE 1.** Upper panel: Recordings of transmitral flow velocities from the apical approach. Positive velocities (above zero line) depict phasic transmitral diastolic flow, and negative velocities (below zero line) depict systolic left ventricular outflow. Lower panel: Line drawing demonstrating the identification of aortic valve closure (AVC) and mitral valve opening (MVO). E-wave depicts the maximal velocity during early inflow.

In seven dogs, inotropy was changed by isoproterenol and by propranolol. After baseline measurements, isoproterenol was infused intravenously at rates of 50, 100, and 150 \(\mu\)g/kg/min, and recordings were acquired during steady state at each infusion level. LV end-diastolic pressure (LVEDP) was kept constant by infusing saline. After the isoproterenol infusion had been terminated, at least 10 minutes was allowed for return to baseline. Then 1 mg/kg propranolol was injected intravenously. LVEDP was adjusted to baseline, and the recordings were repeated at least 10 minutes later.

In 11 dogs, LV diastolic pressure was increased by rapid saline infusion. Propranolol (1 mg/kg) was injected intravenously at least 10 minutes before the volume loading was started. Pressures and Doppler signals were recorded at three different levels of LVEDP: less than 10 mm Hg, 11–18 mm Hg, and greater than 19 mm Hg.

**Data Analysis and Calculations**

**Doppler measurements.** The Doppler recordings were replayed from the sound track of the videotape. This yields high quality Doppler signals, identical with the real-time recordings. On the frozen images,
TABLE 1. Invasive and Doppler Characteristics During Isoproterenol, Propranolol, and Saline Infusion

<table>
<thead>
<tr>
<th></th>
<th>Isoproterenol (µg/kg/min)</th>
<th>Propranolol (mg/kg)</th>
<th>Saline infusion (EDP, mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 50 100 150</td>
<td>Control 1</td>
<td>≤10 11-18 ≥19</td>
</tr>
<tr>
<td><strong>τ (msec)</strong></td>
<td>48±12 35±6* 38±4 33±5*</td>
<td>40±8 51±13*</td>
<td>47±14 59±17* 64±25*</td>
</tr>
<tr>
<td>Asymptote (mm Hg)</td>
<td>-6±4  -3±7  -8±3 -6±6</td>
<td>-3±4  -4±2</td>
<td>-4±2  -7±10 -6±4</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>74±18 54±11* 43±7* 38±8*</td>
<td>71±15 83±21*</td>
<td>76±19 76±23 71±19</td>
</tr>
<tr>
<td>AT (msec)</td>
<td>70±9  70±12 72±9 72±5</td>
<td>69±7  71±10</td>
<td>70±10 73±5 78±8</td>
</tr>
<tr>
<td>E (cm/sec)</td>
<td>80±26 94±27* 97±26† 106±25†</td>
<td>79±28 82±22</td>
<td>68±12 83±20 90±24†</td>
</tr>
<tr>
<td>Dec (m/sec²)</td>
<td>6.3±1.7 6.1±2.9 6.3±2.8 7.4±2.8</td>
<td>6.0±2.7 5.6±1.7</td>
<td>4.9±0.7 6.3±1.9* 7.9±3.3*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>7±2   8±2 8±3 8±2</td>
<td>6±2   7±3</td>
<td>7±2  15±2 24±4</td>
</tr>
<tr>
<td>V wave (mm Hg)</td>
<td>9±2   10±1 11±3 10±2</td>
<td>8±4   9±6</td>
<td>9±3  15±3 30±4</td>
</tr>
<tr>
<td>Aortic SBP (mm Hg)</td>
<td>97±11 103±11 109±8 111±9</td>
<td>92±13 89±12</td>
<td>102±17 104±17 99±17</td>
</tr>
<tr>
<td>Aortic DBP (mm Hg)</td>
<td>53±20 49±5 47±10 45±11</td>
<td>45±8  50±12</td>
<td>59±12 58±10 62±12</td>
</tr>
<tr>
<td>Aortic end-systolic BP (mm Hg)</td>
<td>70±20 67±11 65±17 69±16</td>
<td>64±15 64±16</td>
<td>71±8 79±12 75±6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>111±6 111±6 111±6 111±6</td>
<td>104±15 104±15</td>
<td>100±19 99±18 96±18</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.
EDP, end-diastolic pressure; τ, time constant of left ventricular isovolumic pressure fall; IVRT, isovolumic relaxation time; AT, acceleration time; E, early transmural velocity peak; Dec, deceleration after E; LVEDP, left ventricular EDP; V wave, left atrial V wave pressure; SBP, systolic blood pressure (BP); DBP, diastolic BP.
*tp<0.05 vs. control or EDP≤10 mm Hg (saline infusion).
†tp<0.01 vs. control or EDP≤10 mm Hg (saline infusion).
‡tp<0.001 vs. EDP≤10 mm Hg (saline infusion).

Statistics

The results are presented as mean±1 SD. The data were analyzed by two-way analysis of variance, Student's t test with Bonferroni correction, and single and multiple linear regression analysis (least squares). The relative importance of independent variables in the multivariate analysis was assessed by the standardized regression coefficients: The regression coefficient of each independent variable was multiplied by the ratio of the standard deviation of the independent variable to the standard deviation of the dependent variable. Variation between separate recordings of Doppler parameters was calculated as the difference between pairs of measurements divided by their mean and expressed as a positive percent.

Results

The results of the Doppler and pressure measurements during the various interventions are summarized in Table 1.

Isovolumic Relaxation Time and τ

Inotropic stimulation with isoproterenol induced a significant shortening of τ and a concomitant decrease in IVRT (Table 1). Individual data are presented in Figure 2. No significant change in aortic pressure was observed. Heart rate and LVEDP were kept constant during the isoproterenol infusion. Compared with baseline, increasing doses of isoproterenol (50, 100, and 150 µg/kg/min) caused an increase in maximum LV dP/dt by 72±38, 83±41, and 140±48%, respectively.

β-Adrenergic blockade with propranolol induced a significant prolongation of τ and a concomitant increase in IVRT (Table 1). Individual data are
presented in Figure 2. No significant change in LVEDP or aortic pressure was observed. Compared with baseline, propranolol caused a reduction in maximum LV dP/dt by 31±17%.

During the saline infusion, which increased LVEDP from 7±2 to 24±4 mm Hg, a progressive prolongation of τ was observed, whereas IVRT was not altered (Table 1). Individual data are presented in Figure 3. Left atrial V wave pressure increased from 9±3 to 30±4 mm Hg. Aortic pressure was not significantly changed, and heart rate was kept constant.

Regression analyses were done separately for the data obtained during constant and increasing LVEDP. When LVEDP was kept constant, as during the isoproterenol and propranolol injections, a significant correlation between changes in τ and changes in IVRT was found ($r=0.66$, $p<0.001$); with few exceptions, the changes were directionally similar (Figure 4). In contrast, when LVEDP was increased by saline infusion, no significant correlation between changes in τ and changes in IVRT existed (Figure 4).

Table 2 demonstrates the results of the multiple regression analysis of IVRT as the dependent variable against τ, left atrial V wave pressure, and peak systolic LV pressure as independent variables (eight dogs); a significant correlation (multiple $r=0.66$, $p<0.001$) was found. τ was a positive predictor and left atrial V wave pressure was a negative predictor of IVRT ($p<0.001$ and $p=0.02$, respectively). LV systolic pressure was not significantly changed and exerted no independent influence.

**Transmirtal Flow Parameters and τ**

The E velocity increased during isoproterenol infusion ($p<0.001$). After normalization against control values in the respective dogs, a weak negative correlation with τ was found ($r=-0.44$, $p<0.05$). The E velocity remained unchanged during β-adrenergic blockade. Alterations of inotropy induced no significant changes in acceleration or deceleration rate of early inflow nor in left atrial V wave pressure or in aortic pressure.

During saline infusion, the E velocity and deceleration rate of early inflow increased significantly (Table 1) and reflected increased transmirtal flow; acceleration was, however, unchanged. To adjust for changes in flow, the E velocity was normalized against the respective transmirtal velocity time integral. Table 2 demonstrates the results of multiple regression analysis of the normalized E velocity as the dependent variable against left atrial V wave pressure, τ, and LV systolic pressure as independent variables; this analysis was performed on the values for the dogs in which phasic left atrial pressure was recorded during volume loading ($n=8$). A significant correlation (multiple $r=0.60$, $p<0.001$) was found. Left atrial V wave pressure was a positive predictor of the normalized E velocity ($p=0.002$). τ was a weak negative predictor ($p=0.06$) and LV systolic pressure was a weak positive predictor ($p=0.07$) of the normalized E velocity.

**Reproducibility**

No significant difference was found between pairs of Doppler measurements at baseline. The percent differences between the paired measurements of IVRT, acceleration time, peak E velocity, and deceleration rate of early flow were 6±4%, 9±7%, 6±6%, and 12±7%, respectively.

**Discussion**

In the present animal model, IVRT as measured by Doppler ultrasound was found to reflect LV relaxation during constant preload. Changes in the time constant of isovolumic relaxation induced by changing inotropy at constant transmural filling pressure and heart rate were accompanied by similar changes in IVRT. During the β-adrenergic pharma-
cological interventions, end-systolic aortic pressure was unchanged, and LV filling pressure was kept constant.

However, during increasing preload, changes in IVRT did not parallel the prolongation of \( \tau \). Since IVRT is measured as the time interval between aortic valve closure and mitral valve opening, determinants of the valve movements will also influence IVRT. Therefore, together with the rate of LV pressure fall, end-systolic aortic pressure as well as left atrial pressure constitute the determinants of IVRT. Multivariate analysis of data acquired during increasing volume load showed a direct relation between IVRT and \( \tau \), whereas an inverse relation between left atrial V wave pressure and IVRT existed. Thus, a progressive rise in left atrial pressure would tend to cause an earlier opening of the mitral valve,\(^{18}\) which explains why IVRT remained unchanged despite the apparent slowing of relaxation during saline infusion as indicated by \( \tau \). A decline in end-systolic aortic pressure could have a similar effect, but no such change was observed in the present study.

LV relaxation is not complete at the start of the diastolic filling period,\(^{19,20}\) and variation of relaxation rate would be expected to influence the early atrioventricular pressure gradient\(^{21}\) and, hence, the E velocity. Despite unchanged left atrial pressure, we found an increased E velocity during isoproterenol infusion. This could be related to the inverse relation between the E velocity and \( \tau \). During saline infusion, multivariate analysis revealed that left atrial V wave pressure was a stronger predictor of the E velocity than \( \tau \) (Table 2). These findings are consistent with the study of Choong et al.,\(^{22}\) who in addition demonstrated that increasing afterload (peak LV systolic pressure) was associated with a decline in the E velocity. In apparent contrast to the latter, a weak tendency (\( p=0.071 \)) toward an increase in the E velocity by increasing LV systolic pressure was found in the present study. However, this finding probably reflects random variation of the data, because no significant change in LV systolic pressure was observed. In accordance with Ishida et al.,\(^{23}\) who showed that IVRT corresponded with the time constant of LV relaxation but that the acceleration time was not a meaningful index of early filling dynamics, we found no consistent changes in acceleration time during any intervention. The increased deceleration rate during volume loading probably reflects increased transmitral flow with a more rapid atrioventricular pressure equalization.

The derivative method of calculating \( \tau \)\(^{16} \) was used as the reference method for measurement of LV relaxation. This method accounts for LV pressure

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**TABLE 2. Results of Multiple Regression Analysis**

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>Standardized regression coefficient</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVRT</td>
<td>( \tau )</td>
<td>0.60</td>
<td>0.63</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>V wave</td>
<td>-0.76</td>
<td>-0.39</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>LVP</td>
<td>0.12</td>
<td>0.11</td>
<td>0.47</td>
</tr>
<tr>
<td>E</td>
<td>( \tau )</td>
<td>-0.012</td>
<td>-0.33</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>V wave</td>
<td>0.042</td>
<td>0.56</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>LVP</td>
<td>0.013</td>
<td>0.29</td>
<td>0.071</td>
</tr>
</tbody>
</table>

The relative importance of the independent variables was assessed by the standardized regression coefficients.\(^{17}\)

IVRT, isovolumic relaxation time; \( \tau \), time constant of left ventricular (LV) isovolumic pressure fall; V wave, left atrial V wave pressure; LVP, LV systolic pressure; E, peak early transmitral velocity.
decay toward a nonzero asymptote. Although the pericardium was open during the experiments, some external pressure may have resulted from contact with the Doppler probe, chest wall, lungs, and fluid in the thoracic cavity.

The observed changes in $\tau$ during the isoproterenol and propranolol interventions reflect changing inotropy and are in accordance with previous knowledge.6,24,25 Like others23,26 we found a significant increase in $\tau$ when LV diastolic pressure was increased by blood volume expansion. However, the increased $\tau$ during volume loading might be due to increased LV afterload (systolic wall stress) rather than increase in preload per se.27

The advantage of the present animal model is that it allowed control of several of the hemodynamic determinants of LV diastolic function. A limitation of the model is, however, the rather extensive chest surgery and the absence of the physiologic influence of the lungs and the pericardium. Therefore, the present data should be interpreted with care, and the findings may not be readily extrapolated to other situations. Furthermore, the pacing protocol may have caused some asynchrony of relaxation, although placing the electrode high on the septum probably provided a more physiologic transmission of the electrical impulse than conventional right ventricular apical pacing.

Dedicated Doppler offers high sensitivity and precision for velocity measurements and prevents bias due to concomitant imaging.28 Because the pericardium was open during the experiments, the mitral orifice may have become dilated when filling pressure was elevated. Thus, the E velocity may not have reflected the true transmitral volume transport, in particular during saline infusion. Calculation of flow rather than measurement of peak velocity might have improved the possibility of detecting relaxation-related changes in early diastolic filling parameters. This problem was partly overcome by adjusting the E velocity according to the transmitral velocity time integral. Measurement of mitral flow area would have introduced significant measurement error, and this might have increased variability substantially.

Despite the limitations inherent in the present experimental study, the clinical implications of our findings are important. Taking the advantage of noninvasive methods into consideration, IVRT assessed by Doppler echocardiography appears to be a useful parameter of LV relaxation and is more reliable than indirect indexes derived from the transmitral Doppler velocity curve. However, IVRT is influenced by its pressure determinants and is not valid as a relaxation parameter when they are significantly changed. This limitation reduces the applicability of IVRT in clinical practice.

References


**KEY WORDS** - diastole • isoproterenol • propranolol
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