EXPERIMENTAL STUDIES

Mechanisms of Diastolic Intraventricular Regional Pressure Differences and Flow in the Inflow and Outflow Tracts

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OBJECTIVES We sought to investigate the mechanisms of left ventricular (LV) intracavitary early diastolic flow during changes in contractility and loading.

BACKGROUND There is limited understanding of how intracavitary flow velocities relate to intraventricular driving pressures.

METHODS In 12 anesthetized dogs, we measured pressures in the left atrium (LA), LV at the mitral tip, apex, and subaortic region; intraventricular velocities by color M-mode Doppler echocardiography (CMD); and volume by sonomicrometry. We also investigated responses to isoprenaline, ischemic failure, and volume loading.

RESULTS During rapid, early filling, the mitral to apical pressure gradient (LVP mitral-apex) correlated with the peak mitral to apical velocity (r = 0.92). The LVP mitral-apex increased from 1.4 ± 0.6 (SD) to 3.2 ± 1.8 mm Hg during isoprenaline (p < 0.05) and decreased to 0.6 ± 0.5 during ischemic failure (p < 0.01). The pressure gradient correlated positively with the time constant of isovolumic relaxation (tau) (r = 0.82) and negatively with LV end-systolic volume (ESV) (r = −0.77). Volume loading increased LA pressure, tau, and ESV, but caused no significant change in LVP mitral-apex. At baseline and during isoprenaline, tau was shorter (p < 0.05) at the apex than at the base. When the mitral to apical gradient approached zero, filling velocities were directed toward the LV outflow tract, and a pressure gradient was established between the apex and subaortic region.

CONCLUSIONS Changes in LVP mitral-apex induced by inotropic stimuli, loading, and ischemia appeared to reflect dependency of the pressure gradient on the rate of relaxation, ESV, and LA pressure. Regional differences in the rate of relaxation may also contribute to intraventricular pressure gradients. These findings have implications for how to interpret intraventricular filling in a clinical context.

Clinical studies have shown marked changes in the intraventricular filling pattern in patients with myocardial ischemia and in those with congestive heart failure (1–3). Accordingly, intraventricular filling, as measured by color M-mode Doppler echocardiography (CMD), has been proposed as a noninvasive method for assessing diastolic dysfunction (1–3). However, there is very limited understanding of how intracavitary flow velocities relate to intraventricular driving pressures. The aim of the present study was to determine the mechanisms of changes in LV early diastolic flow during changes in contractility and loading and during acute ischemic LV failure.

METHODS

Instrumentation

Animal preparation. Twelve dogs of either gender, weighing 18.1 to 30.0 kg (22.2 ± 3.5), were anesthetized, artificially ventilated and instrumented, as previously described (4,5). After finishing the data collections, the dogs were sacrificed by means of an overdose of pentobarbital, 20 mg/kg per body weight. The protocol was approved by the Ethical Committee of the institution.

Positioning of pressure transducers (Fig. 1). Micromanometer-tipped catheters were placed in the left atrium (LA) (model SPC-471A, Millar Instruments, Houston, Texas), LV inflow tract (model MPC-500), and LV outflow tract (model MPC-500) (4,5). A micromanometer (Koningsberg Instruments, Pasadena, California) was located in the LV apex. The micromanometers were calibrated and zero-referenced, as previously described (4,5).

Color M-mode Doppler echocardiography. Ultrasonic measurements were performed using a Vingmed CFM 700 cardiac scanner (Vingmed Sound, Horten, Norway), as previously described (4,5). Guided by an apical long-axis two-dimensional image, the CMD cursor line could be placed centrally in the LV inflow and outflow tracts (Figs. 1–3). The data were digitized and transferred to an external computer (Macintosh 11ci, Apple Computer Inc.).

Sonomicrometry. Three pairs of ultrasonic crystals were implanted in the LV endocardium to measure the equatorial anteroposterior, septolateral, and long-axis base-apex dimensions (6). The crystals were connected to a
sonomicrometer (Triton Technology Inc., San Diego, California).

**Experimental Protocol**

Pressures, dimensions, electrocardiograms, and Doppler flow velocities were recorded and digitized, as previously described (4,5). The recordings were done under the following experimental conditions: recordings during baseline were obtained in 12 dogs (Fig. 4, A and B).

**Isoprenaline.** After the baseline recordings, six of these dogs received intravenous isoprenaline (0.075 µg/kg per min).

**Left ventricular failure.** Approximately 1 h after termination of the isoprenaline infusion, acute ischemic LV failure was induced by coronary microembolization (7).

**Volume loading.** After the baseline recordings, six dogs received an infusion of saline until LV end-diastolic pressure of −18 mm Hg was reached.

**Data analysis**

**Pressure measurements.** Pressure and dimension calculations were performed using the software program CVSOFT (Odessa Computers, Calgary, Canada). Left atrial pressure (LAP) was measured at the first diastolic crossover (onset of filling) of the three LV pressures. The time constant of isovolumic relaxation (tau) was calculated using the derivative method (8). The correlation coefficient (r) for the natural logarithm of the first derivative of LV pressure (dP/dt) versus pressure for the three different LV pressure tracings was > 0.93.

**Calculation of pressure gradients.** The following pressure differences were calculated: along the inflow tract: LAP – LVP$_{mitral}$, LAP – LVP$_{apex}$, and LVP$_{mitral}$ – LVP$_{apex}$; along the LV outflow tract: LVP$_{apex}$ – LVP$_{aorta}$. We also calculated LVP$_{mitral}$ – LVP$_{aorta}$. All reported values are peak gradients during early diastole.

**Color M-mode Doppler analyses and calculations.** The CMD measurements were performed using the software program EchoDisp (Vingmed Sound, Horten, Norway), as previously described (2).

The apically directed velocities in the inflow tract were coded in a rainbow-colored system: from red by decreasing velocities to a lighter shade of red and to yellow and blue (aliasing) by increasing velocities (Fig. 2). The spreadsheet of the digitized data was used to identify the mitral to apical peak velocity and the start and cessation of flow.

In the outflow tract, the velocities were directed toward the aortic valve and were coded from dark blue by low velocities to a lighter shade of blue by higher velocities (Fig.
The timing of the first diastolic LA/LV pressure crossover was similar for the three LV pressures (Fig. 4A). The minimal dP/dt (dP/dt_{min}) of the LVP_{apex} was slightly delayed relative to the dP/dt_{min} of the LVP_{aorta} and LVP_{mitral}, by 9 ± 6 and 6 ± 5 ms, respectively (both p < 0.05). However, tau was significantly shorter in the apex than at the base (LVP_{aorta} and LVP_{mitral}) (p < 0.05) (Table 1); therefore, the pressure nadir of the LVP_{apex} occurred significantly earlier than that of the LVP_{aorta} and LVP_{mitral}, by 31 ± 14 and 31 ± 16 ms, respectively (both p < 0.001). The differences in tau disappeared after coronary microembolization and after volume loading (Tables 1 and 2, respectively). A representative recording during isoprenaline is displayed in Figure 5.

Mitral to Apical (LV Inflow Tract) Velocities and Pressure Differences

Isoprenaline and LV failure. The mitral to apical peak velocities and the pressure difference (ΔLVP_{mitral-apex}) increased markedly during inotropic stimulation with isoprenaline and decreased after induction of LV failure by coronary microembolization (Fig. 6 and Table 1). In the pooled data, the mitral to apical peak velocity correlated strongly with ΔLVP_{mitral-apex} (r = 0.92, p < 0.001).

Volume loading. Intravenous volume loading increased the peak mitral to apical filling velocities slightly (Table 2). However, in contrast to the observations during isoprenaline, we found no significant increase of the mitral to apical pressure gradient (Table 2).

Apex to Subaortic (LV Outflow Tract) Velocities and Pressure Differences

Isoprenaline and LV failure. With the color M-mode Doppler cursor oriented from the apex toward the aortic valve, blue-encoded velocities directed toward the subaortic region dominated during early diastole (Fig. 3). These velocities were first observed during deceleration of the mitral to apical flow and continued into late diastole (Fig. 3 and 4B). Peak velocities in the LV outflow tract occurred 48 ± 27 ms after the peak mitral to apical velocities and were associated with a positive pressure difference from the apex to the subaortic region. This pressure difference increased with isoprenaline and decreased after coronary microembolization (Table 1). At baseline, the peak pressure difference in the LV outflow tract (ΔLVP_{apex-aorta}) preceded peak velocity by 18 ± 11 ms. In the pooled data, ΔLVP_{apex-aorta} correlated strongly with peak velocities in the LV outflow and inflow tracts (r = 0.82, p < 0.01 and r = 0.85, p < 0.001, respectively).

Volume loading. Volume loading caused a significant increase in ΔLVP_{apex-aorta} from 3.5 ± 0.7 to 5.1 ± 1.0 mm Hg (p < 0.01) and tended to increase the peak velocity from 0.36 ± 0.12 to 0.44 ± 0.13 m/s (p = NS) (Table 2).
Pressure Differences Between the Mitral and Subaortic Regions

At baseline, there was a small, early diastolic pressure gradient (1.3 ± 0.4 mm Hg) between the sensors in the LV mitral and subaortic region (Fig. 4A,a). This pressure gradient was established 23 ± 21 ms (p < 0.01) after the start of the mitral to apical pressure gradient.

Relationship Between the Intraventricular Pressure Gradient and Other Hemodynamic Variables

Isoprenaline and LV failure. In the pooled data, \( \Delta LVP_{mitral-apex} \) correlated with tau (\( r = 0.82, p < 0.05 \)) and ESV (\( r = -0.77, p < 0.05 \)).

Volume loading. However, volume loading caused a significant increase in tau, from 26 ± 10 to 34 ± 3 ms (p <
Furthermore, in early diastole, we demonstrate a significant gradient reversed. In most cases, we could also observe reversal of the transmitral pressure gradient or the mitral to apical pressure gradient. This could reflect the significant change in the transmitral pressure gradient or the mitral to apical pressure gradient. This could reflect the pressure gradient from the mitral tip region to the LV subaortic region, and this gradient could also play an important role in intraventricular flow and vortex formation.

**Mitral to Apical Pressure Gradient During Changes in Contractility and Loading**

Early diastolic mitral to apical flow was associated with a significant pressure gradient. During mitral to apical flow acceleration, the gradient was directed toward the apex, and during the subsequent flow deceleration, the pressure gradient reversed. In most cases, we could also observe reversal of flow in the apical region (i.e., velocities directed toward the mitral region) (Fig. 2). The peak mitral to apical pressure gradient and flow velocities decreased during myocardial ischemia, and enhancement of LV inotropy by isoprenaline led to a marked increase in the peak pressure gradient and flow velocities.

In the present model, volume loading caused no significant change in the transmitial pressure gradient or the mitral to apical pressure gradient. This could reflect the

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic Variables Measured at Baseline, During Isoprenaline, and After Induction of LV Failure by Coronary Microembolization in Six Dogs*</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
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<tr>
<td>LAP (mm Hg)</td>
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<tr>
<td>LVP_{apex} (mm Hg)</td>
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<td>LVEDP (mm Hg)</td>
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<tr>
<td>dp/dt_{max} (mm Hg/s)</td>
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<td>CO (ml)</td>
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<tr>
<td>SV (ml)</td>
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<td>EDV (ml)</td>
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<tr>
<td>ESV (ml)</td>
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<td>LVEF (%)</td>
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Peak early diastolic pressure differences

- ΔLAP-LVP_{apex} (mm Hg) | 3.8 ± 0.8 | 5.9 ± 1.9§ | 2.0 ± 1.1|| | 6 |
- ΔLAP-LVP_{mitral} (mm Hg) | 2.4 ± 0.8 | 2.8 ± 1.3# | 1.8 ± 0.9§# | 6 |
- ΔLVP_{mitral-apex} (mm Hg) | 1.4 ± 0.6 | 3.2 ± 1.8§# | 0.6 ± 0.5†# | 6 |
- ΔLVP_{apex-aorta} (mm Hg) | 3.4 ± 0.9 | 4.4 ± 1.9 | 1.2 ± 0.6| | 6 |

Peak velocity (m/s) in LVTT

- 0.54 ± 0.04 | 0.76 ± 0.13§ | 0.38 ± 0.09† | 6 |

Peak velocity (m/s) in LVOT

- 0.26 ± 0.07 | 0.43 ± 0.10§ | 0.18 ± 0.04§ | 6 |

Early diastolic pressure nadirs

- LVP_{apex} (mm Hg) | 3.4 ± 2.3 | 2.0 ± 3.3 | 11.7 ± 3.0† | 6 |
- LVP_{mitral} (mm Hg) | 3.9 ± 2.3** | 4.0 ± 1.5# | 11.9 ± 3.8# | 6 |
- LVP_{aorta} (mm Hg) | 3.1 ± 2.6** | 2.4 ± 2.1 | 11.4 ± 3.5† | 6 |

Time constant of isovolumic relaxation (tau)

- LVP_{apex} (ms) | 32 ± 3 | 23 ± 7§ | 53 ± 18§ | 6 |
- LVP_{mitral} (ms) | 37 ± 7†# | 28 ± 4# | 48 ± 16# | 6 |
- LVP_{aorta} (ms) | 36 ± 6†† | 31 ± 7†† | 50 ± 14§ | 6 |

*Body weight 20.5 ± 2.6 kg, †p < 0.01 vs. baseline, §p < 0.05 vs. baseline. ¶Sonomicrometry in only five dogs. #p < 0.001 vs. baseline. *LVP_{mitral} in only five dogs. ¶¶p < 0.001 vs. baseline. ¶¶¶p < 0.05 when local pressures were compared. †† †p < 0.05 when local tau LVP_{mitral} and tau LVP_{aorta} were compared with tau LVP_{apex}. Data are presented as the mean value ± SD. CO = cardiac output; dp/dt_{max} = maximal first derivative of left ventricular pressure; EDV and ESV = end-diastolic and end-systolic volume, respectively, by sonomicrometry; LAP = left atrial pressure at first crossover with left ventricular pressures; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction by sonomicrometry; LVTT and LVOT = left ventricular inflow and outflow tract, respectively; LVP_{apex} = maximal systolic left ventricular pressure; ΔLAP-LVP_{apex} = peak early diastolic pressure difference from LA to LV apical region; ΔLAP-LVP_{mitral} = peak early diastolic pressure difference from LA to LV mitral tip region; ΔLVP_{mitral-apex} = peak early diastolic pressure difference from LV mitral tip to apical region (LV inflow tract); ΔLVP_{apex-aorta} = peak early diastolic pressure difference between LV apical and subaortic regions (LV outflow tract); LVP_{apex}, LVP_{mitral}, and LVP_{aorta} nadirs = early diastolic pressure nadirs of LV apical, mitral and subaortic pressures, respectively; tau LVP_{apex}, LVP_{mitral}, and LVP_{aorta} = time constant of isovolumic pressure decay in LV apical, mitral and subaortic regions, respectively; SV = stroke volume by sonomicrometry.
The combined effect of a rise in LAP, which tends to increase the gradient, and prolongation of tau, which has the opposite effect. There was, however, a small increase in peak filling velocities along the inflow tract, which could mean that we were not able to measure minor changes in pressure gradients induced by volume loading.

The different effects of changes in inotropy and changes in loading on the mitral to apical pressure gradient may be attributed to entirely different effects on the active and passive myocardial determinants of 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Volume</th>
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<tr>
<td>Heart rate (beats/min)</td>
<td>131 ± 13</td>
<td>136 ± 13</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>8.7 ± 2.5</td>
<td>16.9 ± 4.3§</td>
</tr>
<tr>
<td>LVPmax (mm Hg)</td>
<td>102 ± 7</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.8 ± 3.3</td>
<td>18.0 ± 7.6§</td>
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<tr>
<td>dP/dt max (mm Hg/s)</td>
<td>2,456 ± 788</td>
<td>2,269 ± 511</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>959 ± 309</td>
<td>1,688 ± 451§</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>7.0 ± 2.2</td>
<td>12.5 ± 3.1§</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>19.4 ± 3.7</td>
<td>28.2 ± 2.4§</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>12.4 ± 3.1</td>
<td>16.2 ± 1.7§</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37 ± 10</td>
<td>43 ± 8§</td>
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**Regional Differences in the Rate of Relaxation**

The peak –dP/dt at the apex was slightly delayed relative to that at the subaortic region and mitral tip. These small temporal differences probably reflect the ventricular activation time and lead to a small delay in the onset of relaxation in the apex, relative to the basal region. During most of the isovolumic relaxation time, however, pressure was falling at a faster rate at the apex than at the base; therefore, the early diastolic pressure nadir was reached first in the apex. During volume loading and after coronary microembolization, however, tau became similar in all regions. It seems likely that the regional differences in tau contribute to the early diastolic mitral to apical pressure gradient measured at baseline and during isoprenaline infusion. The mechanisms of the observed nonuniformity of tau remain to be investigated.

**Pressure Gradients and Flow Toward the Subaortic Region**

In the present study, we could observe how the intraventricular driving pressures and flow directions shifted during rapid, early filling. Immediately after LAP/LVP early diastolic crossover, an intraventricular pressure gradient was established, and flow accelerated from the mitral region toward the apex, and ~50 ms later, from the apex toward the subaortic region. The pressure gradient toward the subaortic region then increased progressively, whereas the mitral to apical gradient reversed. The present study does not determine whether the velocities in the LV outflow tract represent blood that flows directly from the mitral tip region or blood that has propagated through the apex or other portions of the LV cavity. The observation of a significant pressure gradient from the apex toward the subaortic region, however, suggests that the latter mechanism may have contributed. Moreover, the strong and positive relationship between this pressure gradient and the peak velocities in the outflow tract adds further evidence to this notion.

In a recent clinical study, Radevand et al. (14) investigated patterns of intraventricular flow using high-frame-rate two-dimensional color Doppler echocardiography. The initial intraventricular filling was dominated by velocities directed toward the apex, and this flow pattern persisted as long as there was transmitral flow acceleration. At peak transmitral early filling (E wave), there was a shift in the filling pattern. During transmitral flow deceleration, the intraventricular flow pattern was dominated by velocities toward the LV outflow tract, and blood appeared to circulate toward the outflow tract as part of a high-velocity vortex near the mitral tip. These observations fit with the predictions of Yellin et al. (15), who said that the LV
The diastolic flow field is represented by a number of vortices that expand in a circular fashion from the mitral region. Kim et al. (16), utilizing magnetic resonance velocity mapping, confirmed the existence of a counterclockwise vortex around the anterior mitral leaflet. Such vortices may have contributed to the flow velocities in the LV outflow tract.

From the present data and background information, we suggest the following sequence: immediately after mitral valve opening, blood propagates rapidly toward the apex, driven by its momentum and by the mitral to apical pressure gradient. Vortices will form lateral to this flow column and initiate flow toward the LV free wall and septum. The presence of a pressure gradient from the mitral tip toward the subaortic region will strengthen vortex formation and contribute to filling of the outflow tract. In addition, reversal of the mitral to apical pressure gradient will decelerate flow toward the apex.

Study Limitations

Because of the anesthesia and extensive surgical instrumentation employed, the present model does not represent normal physiology. The patterns of filling by CMD, however, are qualitatively similar to those observed in humans (2,4). Therefore, we believe the present model is valid for studying principles involved in the regulation of LV intracavitary flow in early diastole.

Color M-mode Doppler echocardiography has no lateral resolution and does not allow imaging of more complex flow patterns. Ischemic failure and volume loading probably enhanced vortex formation lateral to inflowing blood. Such a principle was demonstrated by Steen and Steen (17) in an in vitro study where vortex formation increased when the ratio between the nozzle area and cavity cross-sectional area decreased. This important aspect of filling was not investigated in the present study.

Conclusions

The present study demonstrates differences in the direction and timing of pressure gradients along the LV inflow and outflow tracts during rapid, early filling. The mitral to apical pressure gradient responded differently to isoprenaline and volume loading, which may be attributed, at least in part, to different effects on ESV and the rate of LV relaxation. The decrease in the mitral to apical pressure gradient during

Figure 5. Representative experiment showing left ventricular (LV) pressure and volume during isoprenaline infusion. Note that the pressure in the left ventricle at the apex (LVP_{apex}) declined at a faster rate than LVP_{mitral} and LVP_{aorta} during isovolumic pressure decay (upper panel). However, minimal first derivative of LV pressure (dP/dt\text{min}) of the LVP_{apex} (middle vertical broken line) was delayed, as compared with the dP/dt\text{min} of the LVP_{aorta} and LVP_{mitral} (left vertical broken line). The right vertical broken line indicates the first crossover between all three LV and left atrial pressures.
myocardial ischemia was attributed to marked prolongation of tau, a loss of nonuniformity of tau between the apex and base, and a marked increase in ESV. In early diastole, we observed a positive pressure gradient from the apex to subaortic region and from the mitral tip to the subaortic region, which could play an important role in intraventricular formation and may contribute to filling of the LV outflow tract.

Acknowledgments
We thank engineer Roger Ødegaard for his important technical assistance and Maureen Raw, university secretary, for her helpful advice and assistance in the computer management.

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REFERENCES