Mechanisms of Retarded Apical Filling in Acute Ischemic Left Ventricular Failure

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**Background**—We examined the hypothesis that retardation of apical filling as measured by color M-mode Doppler echocardiography in the diseased left ventricle (LV) reflects a decrease in the intraventricular mitral-to-apical pressure gradient.

**Methods and Results**—In 9 open-chest anesthetized dogs, micromanometers were placed near the mitral tip and in the apical region. From the color M-mode Doppler images, the time delay (TD) between peak velocity at the mitral tip and the apical region was determined as an index of LV flow propagation. Acute ischemic LV failure was induced by coronary microembolization. Induction of ischemia caused a marked increase in LV end-diastolic pressure and a decrease in LV ejection fraction. The time constant of LV isovolumic apical pressure decay (τ) increased from 31±8 to 49±16 ms (P<0.001). The peak early diastolic mitral-to-apical pressure gradient (ΔPLV_mitral-apex) decreased from 1.9±0.9 to 0.7±0.5 mm Hg (P<0.01), and TD increased from 5±3 to 57±26 ms (P<0.001). The slowing of flow propagation was limited to the apical portion of the LV cavity. The TD correlated with ΔPLV_mitral-apex (r=−0.94, P<0.01) and with τ (r=0.92, P<0.01). Before ischemia, the mitral-to-apical flow propagation velocity far exceeded the velocity of the individual blood cells, whereas during ischemia, flow propagation velocity approximated the blood velocity.

**Conclusions**—Retardation of apical filling in acute ischemic failure was attributed to a decrease in the mitral-to-apical driving pressure, reflecting slowing of LV relaxation. The slowing of flow propagation appeared to represent a shift in apical filling from a pattern of column motion to a pattern dominated by convection. *(Circulation. 1999;99:2048-2054.)*

**Key Words:** diastole ■ echocardiography ■ ischemia ■ heart failure ■ pressure

Several clinical studies that used color M-mode Doppler echocardiography (CMD) have demonstrated marked disturbances of left ventricular (LV) intracavitary flow in acute myocardial ischemia and in ischemic and nonischemic cardiomyopathy.1–6 A consistent finding in the diseased ventricle has been retardation of early diastolic apical filling as measured by CMD.1–6 Furthermore, the impairment of apical filling in the ischemic and failing ventricle is associated with prolongation of the time constant of isovolumic pressure decay (τ).1–4 Accordingly, intraventricular flow propagation has been proposed as a noninvasive method to assess LV relaxation.1–4 One potential mechanism could be that slowing of relaxation leads to a decrease in driving pressures for intraventricular flow, and this in turn causes slowing of flow propagation.

Nearly 2 decades ago, Ling et al7 described an early diastolic intraventricular pressure gradient between LV base and apex, probably representing the driving force for base-to-apical flow during early filling. More recently, Courtois et al8 demonstrated reduction of the base-to-apical pressure gradient after induction of acute ischemia in dogs. The present study was designed to test the hypothesis that retardation of early diastolic apical filling in acute myocardial ischemia reflects reduction of the intraventricular base-to-apical pressure gradient subsequent to impairment of LV relaxation.

**Methods**

**Animal Preparation**

Nine dogs of either sex weighing 18 to 30 kg (21.8±3.9 kg) were anesthetized by thiopental sodium 25 mg·kg⁻¹·body wt⁻¹ and 100 mg of morphine IV, followed by infusion of morphine 50 to 100 mg/h IV and pentobarbital 50 mg IV every 1.5 hours. The animals were artificially ventilated through a cuffed endotracheal tube.

The chest was opened by a median sternotomy. After instrumentation, the edges of the pericardial incision were loosely resutured. A pacing lead was placed in the right ventricle and connected to an external pacemaker (Medtronic 5325). After the data collections were finished, the dogs were killed by an overdose of pentobarbital.

The protocol was approved by the ethical committee of the institution.

**Instrumentation and Measurements**

**Pressure**

A 7F fluid-filled catheter was placed in the aortic arch for monitoring of aortic pressure. A micromanometer (Konigsberg Instruments) was placed in the apex via a stab wound in the apical dimple. A 5F micromanometer-tipped catheter (model MPC-500, Millar Instru-
mements) was introduced into the LV via a pulmonary vein and placed near the mitral tip (Figure 1). Another micromanometric catheter (7F) with a fluid lumen (model SPC-471A, Millar) was inserted into the left atrium (Figure 1).

At the end of each recording, we induced extrasystoles by the right ventricular pacing catheter in the right ventricle. Long diastoles after premature contractions were used to adjust absolute pressure levels. By comparing the LV peak pressures during nonejecting premature contractions (ie, LV pressure rise with no rise in aortic pressure), we confirmed that the gain setting was similar for the 2 LV manometers.

**Sonomicrometry**

Three pairs of ultrasonic crystals were implanted in the endocardium of the LV to measure the anterior-posterior (Dap), septal-lateral (Dsl), and the base-apex (Dla) dimensions. The crystals were connected to a sonomicrometer (Trition Technology Inc).

**Color M-Mode Doppler**

Ultrasonic measurements were performed with a Vingmed CFM 700 cardiac scanner (Vingmed Sound). The cursor line was placed centrally in the LV inflow tract, including both mitral and apical flow, and velocities were measured along this line. The velocity filter was set to 8 to 12 cm/s. The recorded velocity, time, and depth values were digitized and transferred to an external computer (Macintosh 11ci, Apple Computer, Inc).

**Experimental Protocol**

Pressures, dimensions, and ECG were recorded by a Gould ES 2000, and the data were simultaneously digitized for later analysis (CVSOFT, Odessa Computers). Recordings were done with the dogs in the supine position at end expiration and with the ventilator off. Pressures, ECG, and Doppler flow velocities were recorded for 10 seconds, followed by pressures, ECG, and dimensions during the subsequent 10 seconds. The recordings were obtained first at baseline and then during acute ischemic LV failure by repeated injections of plastic microspheres (50 μm) according to the method of Smiseth and Mjøs.9

**Data Analysis**

**Pressures**

From the LV apical pressure tracing (PLV apex), the following pressures were calculated: peak-systolic, end-diastolic, and the maximum time derivative (dP/dt max). We calculated \( t \) for both PLV apex and PLV min using the derivative method.10 \( R \) values for ln dP/dt versus pressure for PLV min and PLV apex were >0.97 in all the dogs at baseline and at LV failure. Left atrial pressure (PLA) was measured at first diastolic crossover with the 2 LV pressures. Transmural and intraventricular pressure differences were calculated as PLA minus PLV min and PLV min minus PLV apex, respectively. For both LV pressures, we measured early diastolic pressure nadirs and the time from LA/LV crossover to pressure nadir.

**Sonomicrometry**

End-systolic and end-diastolic volumes were calculated as a general ellipsoid by use of the equation, volume = \( \pi/6 \times Dap \times Dsl \times Dla \).11

**Color M-Mode Doppler**

Analyses were performed as described by Stugaard et al2,3 with the software program EchoDisp (Vingmed Sound).

The CMD images were decoded into numerical values. Each pixel represented a velocity, averaged over a distance of 2.3 mm in the mitral-to-apical (depth) axis and 5 ms in the time (horizontal) axis. An algorithm was used to identify the peak velocity at the mitral tip level and at every second pixel (0.46 cm) toward the apical region. The time delay (TD) in milliseconds between occurrence of peak velocity at the mitral tip (first level) and the apical region (fifth level) was used as an index of early diastolic mitral-to-apical flow propagation.

**TABLE 1. Hemodynamic Variables Before and After Coronary Microembolization**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LV Failure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>134±14</td>
<td>127±27</td>
<td>9</td>
</tr>
<tr>
<td>PLA, mm Hg</td>
<td>8.9±2.1</td>
<td>15.2±4.9†</td>
<td>9</td>
</tr>
<tr>
<td>PLV apex max, mm Hg</td>
<td>95±12</td>
<td>76±25*</td>
<td>9</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>7±3</td>
<td>17±4‡</td>
<td>9</td>
</tr>
<tr>
<td>LV dP/dt max, mm Hg/s</td>
<td>2107±726</td>
<td>1182±486†</td>
<td>9</td>
</tr>
<tr>
<td>rPLV apex, ms</td>
<td>31±8</td>
<td>49±16†</td>
<td>9</td>
</tr>
<tr>
<td>rPLV apex, ms</td>
<td>34±4</td>
<td>46±15*</td>
<td>9</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>978±339</td>
<td>957±444</td>
<td>8</td>
</tr>
<tr>
<td>SV, mL</td>
<td>7±2</td>
<td>8±3</td>
<td>8</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>20±6</td>
<td>32±7†</td>
<td>8</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>13±4</td>
<td>25±5‡</td>
<td>8</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>35±6</td>
<td>23±5‡</td>
<td>8</td>
</tr>
</tbody>
</table>

*PLV apex and PLV apex indicates time constants of isovolumic relaxation of LV pressures in apex and at the mitral tip region, respectively; SV, stroke volume; EDV, LV end-diastolic volume; ESV, end-systolic volume; and LV EF, LV ejection fraction by sonomicrometry. Values are mean±SD.

\( t < 0.05, \dagger t < 0.01, \ddagger t < 0.001 \) LV failure vs baseline.
As an estimate of the time for 1 blood cell to travel from the mitral tip to apex, we used the average of the peak velocities at all 5 levels along this distance.

Statistics
Data are presented as mean±SD. For comparisons of the data, paired t test and ANOVA were performed. Regression analyses were done according to Glantz and Slinker with a multiple regression model, including dummy variables to account for between-subject differences. The level of significance was a value of P<0.05.

Results

LV Function Before and After Coronary Microembolization
Coronary microembolization caused a marked increase in LV end-diastolic apical pressure (EDP), from 7±3 to 17±4 mm Hg (P<0.001), and a decrease in LV ejection fraction from 0.35±0.06 to 0.23±0.05 (P<0.001). Stroke volume was maintained because of a compensatory increase in end-diastolic volume from 20±6 to 32±7 mL (P<0.001). There was a decrease in LV dp/dt max from 2107±726 to 1182±486 mm Hg/s (P<0.01) and a downward and rightward shift of the end-systolic pressure-volume relationship (Figure 2), consistent with substantial depression of LV systolic function.

The τ of PLV apex increased from 31±8 to 49±16 ms (P<0.01), whereas τ of PLV mitral increased from 34±4 to 46±15 ms (P<0.05) after induction of LV failure. Although τ tended to be shorter for PLV apex than for PLV mitral, the difference did not reach statistical significance during baseline (P=0.08) or during LV failure (P=0.9) (Table 1).

Timing of LV Filling by CMD
Before induction of LV failure, the CMD recordings showed rapid and nearly simultaneous onset of diastolic flow along the entire LV inflow tract, with peak velocity almost at the same time in the apical and in the mitral region. Accordingly, the TD between peak velocity at the mitral tip and that in the apical region was small (Figure 3A and Table 2).

After induction of LV failure, the onset of diastolic apical flow became retarded, and the TD index increased from 5±3 to 57±26 ms (P<0.001) (Figure 4A and Table 2). This flow disturbance was predominantly an apical phenomenon, and the retardation of filling was not seen at the measurement level 0.46 cm distal to the mitral tip (Table 2). From the next measurement level (0.92 cm), the TD increased progressively toward the apex (Table 2).

During LV failure, peak early diastolic filling velocities in the apical region were reduced from 0.30±0.07 to 0.19±0.05 m/s (P<0.01), and at the mitral tip from 0.53±0.06 to 0.37±0.12 m/s (P<0.01). Averaged peak velocities at the 5 velocity levels from the mitral tip to apex decreased from 0.44±0.04 m/s at baseline to 0.29±0.9 m/s (P<0.01) during LV failure.

Intraventricular Pressure Gradients
Figure 3 shows simultaneous flow velocities and intraventricular pressures before coronary embolization in a representa-
TABLE 2. Early Diastolic Hemodynamic Variables During Baseline and After Induction of Ischemic LV Failure by Microembolization

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LV Failure</th>
<th>n</th>
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<tbody>
<tr>
<td>ΔPLVmitral-apex, mm Hg</td>
<td>1.9±0.9</td>
<td>0.7±0.5†</td>
<td>8</td>
</tr>
<tr>
<td>ΔPLA−PLVmitral, mm Hg</td>
<td>2.4±0.7</td>
<td>1.7±0.7†</td>
<td>8</td>
</tr>
<tr>
<td>PLVmitral min, mm Hg</td>
<td>3.8±2.1§</td>
<td>11.2±3.1§</td>
<td>8</td>
</tr>
<tr>
<td>PLVapex min, mm Hg</td>
<td>2.8±2.2§</td>
<td>11.0±2.6§</td>
<td>9</td>
</tr>
<tr>
<td>Time to PLVmitral min, ms</td>
<td>65±20</td>
<td>44±16‡</td>
<td>8</td>
</tr>
<tr>
<td>Time to PLVapex min, ms</td>
<td>33±6∥</td>
<td>33±13‡</td>
<td>9</td>
</tr>
<tr>
<td>TD second level (0.46 cm), ms</td>
<td>4±4</td>
<td>6±6</td>
<td>8</td>
</tr>
<tr>
<td>TD third level (0.92 cm), ms</td>
<td>3±6</td>
<td>13±12</td>
<td>8</td>
</tr>
<tr>
<td>TD fourth level (1.38 cm), ms</td>
<td>5±5</td>
<td>28±13‖</td>
<td>8</td>
</tr>
<tr>
<td>TD fifth level (1.84 cm), ms</td>
<td>5±3</td>
<td>57±26¶</td>
<td>8</td>
</tr>
</tbody>
</table>

ΔPLVmitral-apex indicates peak early diastolic difference between LV pressures at the mitral tip and apex; ΔPLA−PLVmitral, peak early diastolic difference between pressures in left atrium and at mitral tip region; PLVmitral min and PLVapex min, minimum early diastolic pressures in the mitral and apical region, respectively; time to PLVmitral min and PLVapex min, time from first crossover between PLA and LV pressures to pressure nadir; and TD, TD between occurrence of peak velocity at mitral tip and second, third, fourth, and fifth (apex) levels down the LV by color M-mode Doppler. Values are mean±SD.

*P<0.05, †P<0.01, ‡P<0.001 LV failure vs baseline.
§P<0.05, ||P<0.001 between baseline, ¶P<0.01 between LV failure.

In the present study, retardation of apical filling during acute ischemic LV failure was associated with marked reduction of the intraventricular mitral-to-apical pressure gradient. There was a strong negative correlation between the intraventricular pressure gradient and τ, suggesting that the decrease in pressure gradient is due to slowing of LV relaxation. The present data therefore suggest that retardation of apical filling during ischemia may be causally related to slowing of relaxation.

Mechanisms of Apical Flow Velocities

Although the present study demonstrates a significant correlation between the mitral-to-apical pressure gradient and flow propagation, the gradient in the nonischemic ventricle varied widely, ie, between 1 and 3 mm Hg, with very little variation in the TD index of flow propagation (Figure 5, upper panel). The prolongation of TD was not evident until the pressure difference dropped to <1 mm Hg, which occurred after induction of ischemic LV failure. Therefore, there may not be a simple linear relationship between the inflow tract pressure gradient and Doppler indices of mitral-to-apical flow propagation. Logarithmic transformation of the intraventricular pressure gradients was consistent with this assumption (Figure 5, lower panel).

Analysis of the color Doppler images of LV filling suggests that the rapid onset of apical flow in the nonischemic ventricle and the retarded apical filling during ischemia reflect entirely different flow phenomena. In the nonischemic ventricle, onset of flow and peak velocities occurred nearly simultaneously along the entire LV inflow tract, with a short TD of 5±3 ms. Given a distance from the mitral tip to the apical level of 1.84 cm and a TD of 5 ms, the apparent flow propagation velocity would be 3.7 m/s. Peak velocity at the mitral tip, however, was 0.53±0.06 m/s, and even if this velocity had been maintained toward the apex, 1 blood cell would use 35 ms to propagate from the mitral tip to the apical level. Therefore, the short TD between peak velocities at the mitral tip and the apical region in the nonischemic ventricle cannot be attributed to convection or motion of the individual volume elements but could reflect the propagation velocity of the blood wave front. This nearly simultaneous onset of flow along the LV inflow tract resembles motion of an entire column of blood in the inflow tract. The latter interpretation is consistent with the conclusions of Steen and Steen from an in vitro model study that simulated LV filling.

During ischemic failure, there was rapid propagation of flow into the basal portion of the LV cavity, but in the apex, the early flow component was lost. Instead, apical filling occurred later in diastole, and peak apical velocities were seen when transmitral velocities approached zero. These observations are not consistent with column motion of blood in the apical region but rather most likely represent convection. This notion is supported by an additional analysis, which incorporated the flow velocities measured at 5 levels between the mitral tip and the apical region. This gives an estimate of ischemic LV failure, however, apical flow was accelerating while apical pressure was rising.

Discussion

In the present study, retardation of apical filling during acute ischemic LV failure was associated with marked reduction of the intraventricular mitral-to-apical pressure gradient. There was a strong negative correlation between the intraventricular pressure gradient and τ, suggesting that the decrease in pressure gradient is due to slowing of LV relaxation. The present data therefore suggest that retardation of apical filling during ischemia may be causally related to slowing of relaxation.
the time for 1 blood cell to move from the mitral tip to apex. By this analysis, we calculated a mitral-to-apical propagation time of 63 ms, which compares well with the measured TD of 57 ± 26 ms during failure. Therefore, in the present heart failure model, it appears that blood enters the LV as a column, but propagation of flow into the apical portion is slow and compatible with convection. In 2 additional dogs, we did supplementary measurements with high-frame-rate 2-dimensional color Doppler (Vingmed system 5). Before ischemia, the flow wave propagated rapidly toward the apex, whereas during ischemia, the early rapid filling wave was aborted in the basal portion of the LV, similar to the findings with CMD. Accordingly, the TD, as measured by CMD, appears to represent different flow phenomena during baseline and during ischemia. This may limit the ability of TD index of flow propagation to serve as a quantitative index of LV relaxation.

Mitral-to-Apical Flow Propagation, “Diastolic Suction,” and Inertial Forces

Courtois et al 8 hypothesized that loss of the early-diastolic base-to-apex pressure gradient during myocardial ischemia and the subsequent flow disturbance is due to loss of elastic recoil. Nicolic et al 14 demonstrated that the base-to-apical pressure gradient was a function of the diastolic restoring forces. Consistent with this, we observed a strong negative correlation between mitral-to-apical pressure gradient and LV end-systolic volume. The present study was not designed to quantify the contribution from elastic recoil to mitral-to-apical flow propagation. However, by applying principles of wave propagation analysis 15,16 and relating apical pressure and velocities, it may be possible to tell which mechanism is dominating, that is, whether blood is “sucked” or “pushed” toward the apex. If blood is sucked into the apical region, one would predict a decrease in apical pressure while flow accelerates toward the apex. Conversely, if blood is pushed toward the apex, one would predict a rise in apical pressure while flow accelerates toward the apex. Figure 6 displays velocity and pressure in early diastole before ischemia and demonstrates that flow is accelerating and apical pressure is falling. This is compatible with suction of blood toward the apex. During ischemia, however, apical pressure is rising when flow accelerates toward the apex. The latter observation cannot be ascribed to a net suction effect. Therefore, the marked slowing of mitral-to-apical flow propagation during ischemic failure might be attributed to loss of diastolic suction.

The strong correlation between TD and end-systolic volume could in part reflect inertial effects during LV failure, when a larger intraventricular mass needs to be accelerated. This interpretation is consistent with the study by Greenberg.

Figure 4. Representative dog with ischemic LV failure (same dog as in Figure 3). CMD image (A) shows retarded early diastolic filling after induction of acute LV failure. TD between peak velocity at mitral tip and fourth (1.38 cm) and fifth (1.84 cm) level is 55 ms and 95 ms, respectively. B, Markedly reduced early diastolic mitral-to-apical pressure gradient between vertical dotted lines.
et al., which recently demonstrated the importance of inertia for LV filling.

Limitations

The functional differences between the present animal model and patients with coronary artery disease or congestive cardiomyopathy are obvious. In our model, heart rate was high and LV ejection fraction was less than normal, probably because of the combined effect of anesthesia and the extensive instrumentation. A high heart rate will shorten diastole, which might represent a problem in the study of diastolic intraventricular flow. In the present study, however, we investigated early-diastolic filling, and heart rate is less of a problem than for studies of mid or late diastolic filling. Moreover, we have previously demonstrated that pacing tachycardia from 120 bpm to heart rates of 150 bpm caused no significant change in the mitral-to-apical flow propagation velocity. Before induction of ischemia, intraventricular flow propagation in the present model was rapid and resembled flow propagation in the normal human heart.

The microembolization model has proved to be a highly reproducible model for induction of ischemic LV failure, and its hemodynamic characteristics are in many ways similar to the hemodynamic features of patients with acute ischemic LV failure. This includes a decrease in LV systolic pressure, an increase in LV EDP, dilatation of the LV, and elevated systemic vascular resistance. Furthermore, we have previously shown that this model, in a reproducible manner, gives retardation of apical filling similar to that seen in patients with ischemic LV failure. Therefore, although the preparation has significant limitations, we believe the model is valid for investigating mechanisms of impairment of apical filling in the ischemic ventricle, which was the main objective of this study.

The observed mitral-to-apical pressure differences were small, and one might question whether they were beyond the resolution of our system. Throughout each experiment, however, pressures were repeatedly adjusted to zero during pacing-induced long diastoles, and similar gain setting for the 2 pressure sensors was confirmed by comparing peak systolic pressures during nonejecting beats.

Conclusions

Retardation of apical filling in acute myocardial ischemia was associated with slowing of LV relaxation and a marked reduction of the intraventricular mitral-to-apical pressure differences.
gradient. In the nonischemic ventricle, the dominant early-diastolic flow propagated rapidly toward the apex with a speed far exceeding that of the blood cells, thus resembling column motion. During ischemia, however, the penetration of this column flow into the LV was markedly reduced. In the apical region, flow propagation was slower and approximated the velocity of the individual blood cells, which is compatible with a change in apical filling to a pattern dominated by convection.

Acknowledgments

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References
