Postsystolic shortening of ischemic myocardium: a mechanism of abnormal intraventricular filling

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Submitted 22 April 2002; accepted in final form 28 January 2003

Urheim, Stig, Thor Edvardsen, Kjetil Steine, Helge Skulstad, Erik Lyseggan, Olaf Rodevand, and Otto A. Smiseth. Postsystolic shortening of ischemic myocardium: a mechanism of abnormal intraventricular filling. Am J Physiol Heart Circ Physiol 284: H2343–H2350, 2003.—Acute myocardial ischemia has been associated with abnormal filling patterns in the left ventricular (LV) apex. We hypothesized that this may in part be due to postsystolic shortening of ischemic apical segments, which leads to reversal of early diastolic apical flow. Fourteen open-chest anesthetized dogs were instrumented with micromanometers in the LV apex and left atrium and myocardial sonomicrometers in the anterior apical LV wall. Intraventricular filling by color Doppler and wall motion by strain Doppler echocardiography (SDE) were assessed from an apical view. Measurements were taken before and after 5 min of left anterior descending coronary artery (LAD) occlusion. In four dogs, we measured the pressure difference between the LV apex and outflow tract. At baseline, peak early diastolic flow velocities in the distal one-third of the LV were directed toward apex (9.2 ± 1.6 cm/s). After LAD occlusion, the velocities reversed (−2.3 ± 0.4 cm/s, \( P < 0.01 \)), indicating that blood was ejected from the apex toward the base during early filling. This interpretation was confirmed by wall motion analysis, which showed postsystolic shortening of apical myocardial segments. The postsystolic shortening represented 9.7 ± 1.7% \( (P < 0.01) \) and 14.2 ± 2.4% \( (P < 0.01) \) of end-diastolic segment length by SDE and sonomicrometry, respectively. Consistent with the velocity changes, we found reversal of the early diastolic pressure gradient from the LV apex to outflow tract. In the present model, acute LAD occlusion resulted in reversal of early diastolic apical flow, and this was attributed to postsystolic shortening of dyskinetic apical segments. The clinical diagnostic importance of this finding remains to be determined.

strain-Doppler echocardiography; two-dimensional color Doppler; myocardial ischemia; diastolic filling

AMERICAN PHYSIOLOGICAL SOCIETY

Submitted 22 April 2002; accepted in final form 28 January 2003

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METHODS

Fourteen dogs of either sex and an average body weight of 21.2 kg were given thiopentone (25 mg/kg body wt) and morphine (100 mg) intravenously, followed by an infusion of morphine (50–100 mg/h iv) and pentobarbital (50 mg iv) every hour. The animals were artificially ventilated through a cuffed endotracheal tube using room air with 20% oxygen. A limb lead was monitored. After a median sternotomy, the pericardium was split from the apex to base, and the edges of the pericardial incision were loosely resutured. Inflatable vascular occluders were placed around the proximal third of the left anterior descending coronary artery (LAD). The dog was placed in the right supine position during recordings. The study was approved by the National Animal Experimentation Board.

Pressure Measurements

Via a carotid artery with fluoroscopic guidance, we placed a 5-Fr micromanometer-tipped catheter (model MPC-500, Millar Instruments; Houston, TX) in the LV apical region. Via the appendage, a 5-Fr micromanometer and a fluid-filled catheter were placed in the left atrium (LA). In four dogs, another 5-Fr catheter was positioned in the LV outflow tract just proximal to the aortic valve. All pressure transducers were calibrated with a mercury manometer. The pressures were zero referenced against the fluid-filled LA catheter. Pressure and ECG data were processed via preamplifiers and digitized at 200 Hz for further analysis on a personal computer station.

Sonomicrometry

One pair of ultrasonic crystals was implanted in the inner one-half of the myocardium in the anterior LV wall near the apex, aligned parallel with the LV long axis. In four dogs, another pair of crystals was implanted in a nonischemic region in the anterolateral wall near the base, in the perfusion territory of the left circumflex artery. The crystals were connected to a sonomicrometer (Triton Technology; San Diego, CA, or Sonometrics; London, Ontario, Canada).

Strain Doppler Echocardiography

The method has previously been described in detail (18). With the use of a combined tissue imaging (3.5 MHz) and Doppler (2.75 MHz) transducer (GE Vingmed Ultrasound; Horten, Norway), we recorded images from an apical view with a frame rate varying from 65 to 106 (mean value 88 frames/s). Strain rate was calculated as the time integral of strain rate (18), with a frame rate varying from 65 to 106 (mean value 88 frames/s). The digital color velocity data were transferred to an external computer (Macintosh, Apple Computer) and analyzed with the use of a dedicated analysis program (Echopac, GE Vingmed Ultrasound).

Experimental Protocol

Recordings were first taken at baseline. We then inflated the LAD occluder for a median of 5 min and did recordings during ischemia. Because of interference, sonomicrometry and Doppler echocardiography could not be measured simultaneously. At baseline and during ischemia, we first recorded pressures, ECG and Doppler flow velocities during 10 s and then pressures, and ECG and myocardial segment length during the subsequent 10 s. Because it was not feasible to measure 2-D color flow and strain by Doppler simultaneously, we did the strain Doppler recordings close (within 2 min) to the color flow measurements.

At the end of each recording, we induced ventricular extrasystoles and used long diastoles after premature contractions to adjust absolute pressure levels for the micromanometers. Data were recorded with the respirator off and digitized at 200 samples/s. In four dogs, contrast was injected rapidly into the LA before and during LAD occlusion, and 2-D echocardiographic images were recorded immediately after the injection.

Calculations

Pressure-derived variables. We calculated LV peak systolic pressure, LV end-diastolic pressure, and the time derivative of LV pressure (dP/dt). The time course of the fall in LV pressure from peak –dP/dt to 5 mmHg above end-diastolic pressure was characterized by the time constant (τ) of an assumed exponential decay to zero pressure (19). For definition of end diastole and end systole, we used the peak R wave of the ECG and peak LV –dP/dt, respectively. We calculated the time from end diastole to the first diastolic crossover of LV and LA pressures (onset of transmitral filling). In four dogs, we also calculated the difference between LV apical and LV outflow tract pressures.

Sonomicrometry-derived variables. We calculated the following variables: peak systolic shortening [as the percent change in length (%ΔL)], as

\[
\frac{[\text{end-diastolic length} - \text{minimal segment length}]}{\text{end-diastolic length}} \times 100
\]

systolic lengthening (ischemic segments; %ΔL), as

\[
\frac{[\text{end-diastolic length} - \text{peak systolic length of ischemic segment}]}{\text{end-diastolic length}} \times 100
\]

and postsystolic shortening (%ΔL), as

\[
\frac{[\text{end-systolic length} - \text{minimal segment length}]}{\text{end-diastolic length}} \times 100
\]

During ischemia, we calculated the time from the onset of late systolic segmental shortening to the peak early diastolic LV apex to the outflow tract pressure gradient.

The reported values represent the mean of three beats with the respirator off.

Doppler-derived variables. Doppler measurements of shortening strains were represented by negative values and lengthening strains by positive values. However, to simplify comparison with sonomicrometry, we report strain values in terms of percent shortening: peak systolic shortening and lengthening were calculated as a percentage of end-diastolic dimensions. Postsystolic shortening was calculated as seg-
ment shortening after end systole, as a percentage of end-diastolic dimension.

Flow velocities by 2-D color Doppler were recorded along the mitral-to-apical axis. We measured peak intraventricular velocities in the distal one-third of the LV at the time of the first diastolic crossover of LV and LA pressures.

Statistical Analysis

Data are presented as means ± SE. Statistical analysis was performed with Student’s t-test for paired data. For all statistical comparisons, P < 0.05 was considered significant.

RESULTS

Hemodynamic variables before and during ischemia are presented in Table 1 and Fig. 1. Peak systolic shortening by sonomicrometry and SDE decreased from 12.5 ± 2.4% to −12.5 ± 2.2% (P < 0.01) and from 12.6 ± 1.7% to −9.5 ± 1.1% (P < 0.01), respectively, indicating dyskinesis.

Figure 2 demonstrates marked changes in intraventricular filling after LAD occlusion. During baseline, the early diastolic filling wave by 2-D color Doppler propagated rapidly towards the apex, as indicated by the uniformly red color throughout the LV cavity. During LAD occlusion, however, all experiments showed reversal of early diastolic flow in the apex, i.e., the early diastolic velocities were directed from the apex toward the base. The reversed apical velocities are represented by the blue-colored area in Fig. 2, bottom left. To quantify this change in filling, we measured peak velocities in the distal one-third of the LV at the onset of transmural filling, defined as the time of first diastolic crossover of LV and LA pressures. The peak velocity decreased from 9.2 ± 1.6 cm/s at baseline to −2.3 ± 0.4 cm/s (P < 0.01) during LAD occlusion. The 2-D color pattern suggested that the transmural filling wave propagated only a short distance into the LV and then was redirected toward the LV outflow tract, where it appeared to rotate in a large vortex. These interpretations were confirmed by observations with contrast that was injected into the LA (Fig. 2). Before ischemia, the contrast propagated rapidly toward the apex and filled the entire LV cavity immediately after the onset of transmural filling. During LAD occlusion, the contrast moved toward the midportion of the LV cavity and then rotated toward the LV outflow tract, whereas the apex remained free of contrast. Later in diastole, the contrast moved toward the apex as part of a macrovortex.

The reversed apical flow during early LV filling was associated with postsystolic shortening of the ischemic apical segment (Fig. 1B). Postsystolic shortening by sonomicrometry and SDE changed from 1.3 ± 0.4% and 0.8 ± 0.4%, respectively, to 14.2 ± 2.4 (P < 0.01) and 9.7 ± 1.7% (P < 0.01) during LAD occlusion. Figure 1 also demonstrates the temporal relationships between myocardial segmental motion and transmural driving pressure. During LAD occlusion, the ischemic segment was shortening at the time of LA and LV pressure crossover, and, as demonstrated in Fig. 3, the postsystolic shortening continued while the nonischemic segment was lengthening. The ischemic segment continued to shorten 47 ± 8 and 65 ± 16 ms after the onset of filling by sonomicrometry and SDE, respectively. The time constant of LV relaxation (τ) increased from 47 ± 4 to 64 ± 7 ms during ischemia (P < 0.01).

Figure 4 displays the intraventricular pressure gradients as calculated between the apex and LV outflow tract. During LV ejection, the pressure gradient was directed from the apex toward the LV outflow tract, and there was a small reversal of the pressure gradient in late systole. The systolic pressure gradient decreased after LAD occlusion. During most of the isovolumic relaxation period and during early transmural filling, the pressure gradient at baseline was directed toward the apex (peak value −1.1 ± 0.3 mmHg). During LAD occlusion, however, the gradient was reversed during most of the isovolumic relaxation period (peak value 1.2 ± 0.3 mmHg), consistent with the observed reversal of early diastolic apical flow velocities. The time from onset of late systolic shortening of the ischemic segment by sonomicrometry to the peak early

<p>| Table 1. Hemodynamic parameters before and during LAD occlusion |
|---------------------------------|--------|--------|</p>
<table>
<thead>
<tr>
<th>n</th>
<th>Baseline</th>
<th>Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>14</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>LV peak systolic pressure, mmHg</td>
<td>14</td>
<td>103 ± 4</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mmHg</td>
<td>14</td>
<td>7.3 ± 0.7</td>
</tr>
<tr>
<td>Peak LV intraventricular flow velocities (early diastole), cm/s</td>
<td>10</td>
<td>9.2 ± 1.6</td>
</tr>
<tr>
<td>End-diastolic segment length (LAD region), mm</td>
<td>14</td>
<td>8.3 ± 0.8</td>
</tr>
<tr>
<td>Peak systolic shortening (LAD region)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By sonomicrometry, %</td>
<td>10</td>
<td>12.5 ± 2.4</td>
</tr>
<tr>
<td>By strain Doppler echocardiography, %</td>
<td>10</td>
<td>12.6 ± 1.7</td>
</tr>
<tr>
<td>Postsystolic shortening (LAD region)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By sonomicrometry, %</td>
<td>10</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>By strain Doppler echocardiography, %</td>
<td>10</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Time from end diastole to first diastolic crossover of LV and LA pressures, ms</td>
<td>10</td>
<td>387 ± 18</td>
</tr>
<tr>
<td>τ, ms</td>
<td>14</td>
<td>47 ± 4</td>
</tr>
<tr>
<td>Peak pressure difference between the LV apex and outflow tract during isovolumic relaxation, mmHg</td>
<td>4</td>
<td>−1.1 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE n, no. of animals. LAD, left anterior descending coronary artery; LV, left ventricular; LA, left atrial; τ, time constant of LV relaxation. *P < 0.05 vs. baseline.
diastolic apex-to-outflow tract pressure gradient was 25 ± 3 ms.

DISCUSSION

Slowing of mitral-to-apical flow propagation has been observed in patients with acute myocardial ischemia in different clinical settings (11, 13) and has been reproduced in experimental models (1, 12, 13). The etiology of the impaired apical filling is unclear, but several mechanisms have been proposed (10, 12–14). In the present study, we demonstrated that postsystolic shortening of the ischemic myocardium has a profound effect on intraventricular flow. The postsystolic shortening resulted in early diastolic ejection of blood from the apex toward the base, which resulted in markedly disturbed flow at the base of the ventricle, where flow from the apex encountered the transmitral filling wave. The postsystolic shortening was demonstrated by SDE and was confirmed by sonomicrometry. The present study therefore demonstrates the ability of Doppler echocardiography to quantify interactions between intraventricular flow and regional LV wall motion.

Stugaard et al. (13) reported delayed apical filling by color M-mode Doppler during LAD occlusion. In their study, no early diastolic apical flow was reported. This may be due to their velocity filter setting (12 cm/s), which was above the range of reversed apical velocities measured in the present study. The reversed velocities are very low, so the filter setting is critical to capture these velocities. Edvardsen et al. (2) reported reversed flow during the isovolumetric relaxation period in patients with anterior wall infarction. The velocity filter in that study was between 4 and 8 cm/s.
Mechanisms of Delayed Early Diastolic Mitral-to-Apical Flow Propagation

Currently, we have very limited insight into how LV intracavitary flow relates to myocardial properties. This is in part a consequence of the complex geometry of the ventricle and the continuous change in elastic properties of the myocardium throughout the cardiac cycle, which leads to very complex flow patterns. Furthermore, current imaging methods do not provide full visualization of the three-dimensional pattern that composes LV intracavitary flow. Nikolic et al. (6) have shown that regional deformation of the LV, even during the isovolumetric relaxation period, lead to intraventricular pressure gradients and intraventricular flows. As demonstrated by Greenberg et al. (4), intraventricular pressure gradients can even be assessed by color Doppler echocardiography. In 2-D models of nonischemic ventricles, it appears that the intraventricular flow field is represented by a number of vortexes that expand in a circular fashion from the mitral tip region (20). However, during the early phase of filling, while transmitral flow is accelerating, the dominant flow vectors are directed toward the apex (7). This is demonstrated by the 2-D color flow image shown in Fig. 2, which from an apical view shows uniformly red-encoded velocities throughout the ventricle. During this early phase of filling, the propagation velocity of mitral-to-apical flow can be measured by color M-mode.

Fig. 2. Top: LV early diastolic filling by two-dimensional (2-D) color Doppler (left) and contrast echocardiography (right) from an apical view. At baseline, the dominant flow wave propagated rapidly toward the apex, as demonstrated by 2-D color Doppler (red-encoded velocities represent flow toward the apex) and by contrast echocardiography. Bottom: LV early diastolic flow by 2-D color Doppler (left) and contrast echocardiography (right). During LAD occlusion, the 2-D color image recorded immediately after mitral valve opening demonstrates a dramatic change of the flow pattern compared with baseline. A counterflow, coded blue, is directed toward the red-encoded transmitral inflow. The echo-contrast propagates toward the midcavity but does not reach the apex on this early diastolic frame.
Doppler and has been proposed as a measure of diastolic function (1, 3, 4, 13). Experimental data suggest that slowing of flow propagation is in part due to slowing of myocardial relaxation, which leads to a decrease in the mitral-to-apical pressure gradient (12). It also appears that enhanced vortex formation in the diseased ventricle may contribute to slowing of flow propagation as measured by color M-mode Doppler (10). The present study clearly demonstrates that postsystolic shortening of apical myocardial segments may contribute to the impairment of apical filling that is observed during acute ischemia. These different mechanisms are probably related.

As demonstrated by sonomicrometry, the ejection of blood from the ischemic apical region started during isovolumic relaxation and persisted for some time after the onset of transmitral filling. Therefore, lengthening of the nonischemic segment (Fig. 3) during early filling may be ascribed not only to transmitral flow but also to redistribution of blood caused by postsystolic shortening. Blood that was ejected from the ischemic segment during early diastole encountered the transmitral jet, which was hindered from propagating toward the apex. As suggested by 2-D color flow and echocontrast, the transmitral flow appeared to propagate only a short distance in the ventricle and then formed macrovortexes that rotated toward the LV outflow tract.

The observed reversal of the intraventricular pressure gradient during ischemia supported the interpretation that postsystolic shortening caused early diastolic ejection of blood from the apical region. At baseline, the pressure gradient during isovolumic relaxation and early filling was directed from the base toward the apex, and intraventricular flow velocities by color flow imaging were directed toward the apex. During LAD occlusion, the pressure gradient during isovolumic relaxation reversed and was directed toward the base, along with reversal of flow velocities. During ischemia, there was a small time delay of ~25 ms between the onset of late systolic segmental shortening and the peak apex-to-outflow tract pressure gradient, which is consistent with the notion that the gradient is caused by the segmental shortening.

Yellin et al. (20) described intraventricular vortexes that occurred during LV filling due to shear between blood and mitral leaflet surface. The flow reversal described in the present study, however, started during isovolumic relaxation and therefore cannot be attributed to a similar mechanism.

Apical Flow Reversal: Diagnostic Implications

The mechanisms of postsystolic shortening were investigated by Skulstad et al. (9), and it was found that postsystolic shortening was a relatively nonspecific feature of the ischemic myocardium. It could occur in severely ischemic myocardium by an entirely passive process, then representing passive recoil of dyskinetic segments. Postsystolic shortening also occurred in moderately ischemic myocardium and was in part due to delayed active contraction, although passive components did contribute.

The present study suggests that color flow imaging may be helpful as an additional diagnostic tool for identifying regions with suspected postsystolic shortening. The finding of early diastolic velocities that are directed from the apex toward the LV base is consistent with postsystolic shortening. Therefore, the two methods are complementary, and their combined use could increase the diagnostic power of echocardiogra-

Fig. 3. LV and LA pressure tracings, LV dP/dt, segment lengths in the LAD and left circumflex (Cx) regions, and ECG before and during LAD occlusion. Before ischemia, both segments shorten during systole and lengthen during early diastole. During LAD occlusion, the ischemic segment shortens during systole and shortens during early diastole. Line A indicates end diastole; line B indicates the time of peak LV –dP/dt, which was used as a marker of end systole; and line C indicates the first diastolic crossover of LV and LA pressures, which was used as a marker of the onset of transmitral filling.

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phy in the assessment of regional myocardial function. The clinical potential of this approach remains to be investigated.

Limitations

The present animal model differs from a clinical setting in many regards, in particular due to the thoracotomy, the extensive instrumentation, and the use of general anesthesia. However, the regional myocardial responses to coronary occlusion in terms of segmental function should be relatively similar. Therefore, we believe the principal findings of this study may be valid for a clinical situation. This, of course, should be tested in a population with acute myocardial infarction.

One significant limitation of SDE is a strong angle dependency (18). In the present study with open-chest animals, we could easily optimize transducer position and therefore minimized this problem. In a clinical setting, however, the problem of angle dependency of the echobeam relative to myocardial fiber orientation may be significant, in particular when studying apical segments.

The present study was limited to short-term ischemia. Potentially, with ischemia of longer duration, resulting in tissue necrosis and stiffening of the myocardium, one might see less passive systolic distension and subsequently less marked postsystolic shortening (5). This in turn may reduce the early diastolic flow reversal.
In conclusion, in the present experimental study, we demonstrated that delayed early diastolic LV apical filling during LAD occlusion may be due to postsystolic shortening of ischemic segments. During isovolumic relaxation and during the early phase of transmitral filling, blood was ejected from the apical region and redistributed toward the basal portions of the cavity. This implies that, in addition to global factors such as the rate of LV relaxation and ventricular geometry, one should consider asynchronous wall motion, and in particular postsystolic shortening, as a mechanism of disturbed intraventricular flow. Potentially, the use of color flow imaging along with SDE may represent a clinical tool for studying interactions between regional function and intraventricular flow. This combined imaging might increase the diagnostic power of echocardiography in the assessment of myocardial function.

S. Urheim, T. Edvardsen, and H. Skulstad were and E. Lyseggen is a recipient of a research fellowship from the Norwegian Council on Cardiovascular Diseases.

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