Myocardial Strain Analysis in Acute Coronary Occlusion

A Tool to Assess Myocardial Viability and Reperfusion

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Background—This study proposes 2 new echocardiographic indices with potential application in acute coronary artery occlusion to differentiate between viable and necrotic myocardium and to identify reperfusion. We investigated whether the ratio between systolic lengthening and combined late and postsystolic shortening (L-S ratio) could identify viable myocardium and whether systolic myocardial compliance, calculated as systolic lengthening divided by systolic pressure rise, could identify necrotic myocardium.

Methods and Results—In anesthetized dogs, we measured left ventricular (LV) pressure and long-axis strain by Doppler echocardiography (SDE) and sonomicrometry. The left anterior descending coronary artery was occluded for 15 minutes with 3-hour reperfusion (n/H11005/6), for 4 hours with 3-hour reperfusion (n/H11005/6), or for 4 hours with no reperfusion (n/H11005/6). Myocardial work was quantified by pressure–segment length analysis, necrosis by triphenyltetrazolium chloride staining, and edema by water content. L-S ratio and systolic compliance were calculated by SDE. The L-S ratio ranged between 0.00 and 1.00 and was well correlated with regional myocardial work (r/H11005/0.77, P/H11021/0.0001). In entirely passive myocardium, the L-S ratio approached 1 and was similar in viable (0.88 ± 0.02) and necrotic (0.81 ± 0.03) myocardium. Compliance, however, was reduced in necrotic myocardium owing to edema (0.07 ± 0.01%/mm Hg) but was preserved in viable myocardium (0.15 ± 0.01%/mm Hg, P/H11021/0.05). Reperfusion of viable myocardium caused a reduction of the L-S ratio after 15 minutes (0.57 ± 0.06, P/H11021/0.05), reflecting recovery of function. Reperfusion of necrotic myocardium caused no change in the L-S ratio, but compliance was further reduced within 15 minutes (0.03 ± 0.01%/mm Hg, P/H11021/0.05).

Conclusion—Myocardial L-S ratio and compliance by SDE identified active contraction and necrosis, respectively. These indices should be tested clinically for assessment of myocardial viability and reperfusion. (Circulation. 2005;112:3901-3910.)

Key Words: echocardiography • ischemia • infarction • reperfusion • myocardial contraction

Fibrinolytic therapy in acute coronary occlusion is often unsuccessful, and the patient may need transferal for rescue coronary intervention. Optimal patient triage, however, requires methods that can identify reperfusion precisely and early after fibrinolytic therapy. Furthermore, it is essential to know whether the myocardium distal to the occluded artery is viable, and we therefore need methods that can differentiate between viable and necrotic myocardium.

The first principle behind our hypothesis is that combined analysis of systolic and postsystolic strain patterns may identify actively contracting and therefore, viable, myocardium. In general, myocardium that generates an active force will shorten in systole when left ventricular pressure (LVP) is rising, whereas myocardium with no active force will lengthen passively when LVP is rising, and recoil during late systole and early diastole when pressure is falling. We hypothesized that the remaining active forces in dyskinetic segments are likely to limit systolic lengthening and enhance late and postsystolic shortening. Thus, by relating myocardial strain patterns to the timing of LV systole in dyskinetic segments, it may be possible to identify actively contracting and therefore, viable, myocardium.

The other principle behind our hypothesis relates to the assessment of viability in passive segments. We suggest that strain analysis in combination with systolic pressure may...
provide a measure of tissue compliance in passive segments, and this measure may be used to differentiate between necrotic and viable myocardium. The rationale behind this approach is that necrotic myocardium is edematous7–9 and therefore less compliant than viable myocardium.10–12

Therefore, the aims of the study were to determine whether deformation characteristics by strain Doppler echocardiography (SDE) in the setting of acute coronary occlusion can (1) identify viable as opposed to necrotic myocardium and (2) serve as a method to diagnose successful coronary reperfusion. The study was performed in a series of acutely anesthetized dogs, and measurements of strain were made with SDE and implanted ultrasonic crystals as the reference method. To document tissue edema, we calculated myocardial water content. To define active as opposed to passive segments, we used regional LVP–segment length (LVP-SL) loops, and an active segment was defined as one that generates work. Myocardial blood flow was measured by radionuclide-labeled microspheres.

Methods

Thirty-four mongrel dogs of either sex and a mean body weight of 25.9 ± 0.7 kg were anesthetized with a bolus of thiopental (25 mg/kg body weight), followed by continuous infusion of morphine (3.5 mg · kg⁻¹ · h⁻¹) and pentobarbital (2 mg · kg⁻¹ · h⁻¹), the latter being reduced to half the dose after 4 hours of infusion. The animals were ventilated and surgically prepared as previously described. Final analysis included data from 22 complete experiments. Twelve animals were excluded because of complications during surgery (n = 2), sustained arrhythmia (n = 2), small infarcts (n = 3), and/or regional crystals outside the infarcted myocardium (n = 5). The study was approved by the National Animal Experimentation Board. The laboratory animals were supplied by the Center for Comparative Medicine, Rikshospitalet University Hospital, Oslo, Norway.

Hemodynamic Measurements

Aortic, left atrial, and LV pressures were measured by micromanometers (MPC-500, Millar Instruments Inc), and myocardial dimensions, by sonomicrometry (Sonometrics Corp). In the anterior LV wall, 1 pair of ultrasonic crystals was implanted in the inner third of the myocardium, aligned parallel with the LV long axis. Guided by inspection of coronary anatomy, we placed the crystals in what appeared to be the center of the left anterior descending coronary artery (LAD) perfusion territory. Furthermore, ligatures were placed under all dominant collaterals from the circumflex coronary artery. Thus, when crystals did not show dyskinesis within a few minutes of LAD occlusion, we could occlude the collaterals without opening the pericardium again. At the end, we verified that the crystals were located within a region with transmural necrosis as defined by triphenyltetrazolium chloride (TTC) staining. In 4 dogs, another pair of crystals was implanted in the same region, with 1 crystal in the epicardium and the other in the subendocardium to measure wall thickness. A pair of longitudinal crystals was positioned in the inner third of the posterior LV wall (circumflex artery region) for nonischemic reference. Data were digitized at 200 Hz.

Echocardiography

We used system FiVe and Vivid 7 ultrasound scanners (GE Vivimed Ultrasound AS). Recordings were done from the apex, with image plane and beam direction through the region in which the LAD crystals were positioned. Myocardial strain was measured in the center of the ischemic regions, midway between the crystal pair. In the 12 dogs with reperfusion, end-diastolic wall thickness (EDWT) was measured in a 2D gray-scale, short-axis recording (LAD region).

Figure 1. Two representative SL recordings from partly active (left) and entirely passive (right) myocardium. The L-S ratio was calculated by dividing systolic shortening (L) by the sum of late and post systolic shortening (S). In example 1, shortening far exceeds lengthening (L-S ratio < 0.50), and the loop rotates counter-clockwise, indicating active contraction. In example 2, shortening approaches lengthening (L-S ratio approaching 1), and the loop rotates clockwise, indicating entirely passive behavior of the segment. Systolic myocardial compliance was calculated by dividing systolic shortening (L) by LV systolic pressure rise (ΔP). ED indicates end diastole.

Calculations

Longitudinal systolic shortening (nonischemic segments), systolic lengthening and late systolic shortening (dyskinetic segments), and post systolic shortening (segmental shortening after LV dP/dt max) by sonomicrometry were calculated as the percentage of end-diastolic dimension. Total segmental shortening was defined by the sum of late systolic and post systolic shortening.

Longitudinal strain by SDE was calculated offline. To facilitate comparison between methods, we report SDE and sonomicrometry data with similar terminology, i.e., as systolic shortening and lengthening and post systolic shortening. Ischemic myocardial segments with dyskinesia were assessed by the ratio between systolic lengthening and total shortening (L-S ratio). See Figure 1.

The area of the LVP-SL loop was calculated by CVSOFT (Odesa Computers) and used as an index of regional segmental work. All values represent the mean of 3 consecutive heart cycles. In passive myocardial segments (>90% reduction in LVP-SL loop area compared with baseline), systolic myocardial compliance was calculated as systolic lengthening divided by systolic pressure rise (Figure 1, right).

After excision of the heart, the LV was cut into 10-mm-thick, transverse slices, which were incubated in a 1% solution of TTC for 15 minutes. The extent of nonstaining area (necrosis) in each slice was quantified by computerized planimetry and summed for each heart. The water content [(wet weight–dry weight)/wet weight] of 100% was calculated in ischemic and nonischemic regions to assess edema.

Regional Myocardial Blood Flow

Myocardial blood flow was determined in 6 dogs by radionuclide-labeled microspheres, as previously described. We injected 15.5 ± 0.1-μm microspheres labeled with ¹⁵⁵⁵Cs, ¹⁵⁷¹Ce, ¹⁰⁹⁴Nb, and ⁸⁵⁵Sr (New England Nuclear) into the left atrium at baseline, after 4 hours of occlusion, and after 15 minutes and 3 hours of reperfusion. Regional blood flow was determined in the central ischemic region and in adjacent and nonischemic regions. Microvascular obstruction...
was defined as regional blood flow <50% of flow in the remote nonischemic myocardium after reperfusion. Transmural infarcts were obtained in 4 of 6 experiments.

Experimental Protocol
After a 30-minute period of stabilization, baseline recordings were performed. To avoid interference between sonomicrometry and TDI measurements, we first recorded pressures, ECG, and echocardiographic data during 10 seconds and then pressures, flow, ECG, and SLs during the subsequent 10 seconds. Data were recorded with the ventilator off.

Acute myocardial ischemia was induced by LAD occlusion for 15 minutes, followed by reperfusion for 3 hours (group 1, n=6). Another group had sustained LAD occlusion for 4 hours without reperfusion (group 2, n=6) to evaluate necrosis and edema without reperfusion. The last group of dogs (group 3, n=6) and the dogs with microspheres underwent 4 hours of occlusion followed by 3 hours of reperfusion.

Statistics
Values are expressed as mean±SEM unless otherwise stated. We used 1-way repeated-measures ANOVA followed by the Bonferroni correction on predefined clinically relevant comparisons.17 (GraphPad Prism 4.02, GraphPad Software). \( P<0.05 \) after Bonferroni correction was considered significant. L-S ratio and LVP-SL loop area measurements were compared by least-squares linear regression. Agreement between indices was assessed by the intraclass correlation coefficient (\( R_c \)) and the method of Bland-Altman.18 (SPSS 12.0.1, SPSS Inc).

Results
Representative recordings of regional function by sonomicrometry and SDE are displayed in Figures 2 and 3, and mean data are presented in Tables 1 through 3. During LAD occlusion, the ischemic segments became dyskinetic and segmental work dropped to near 0, indicating purely passive motion. In these segments, the profile of the myocardial strain curve resembled the LVP curve, consistent with pressure-dependent deformation, and the L-S ratio therefore approached 1. During reperfusion of viable segments, there was gradual recovery of function and the L-S ratio increased accordingly.

The utility of the LVP-SL loop analysis in differentiating between actively contracting and passive myocardium is illustrated by considering strain tracings during reperfusion. As shown by the strain tracing in Figure 2A, there was marked dyskinesis and apparently severe impairment of function in segments that were reperfused for 15 minutes. The LVP-SL loop displayed in Figure 2B, however, rotated counterclockwise with a large loop area, indicating substantial active work.
In a pooled analysis that included recordings during ischemia and reperfusion, the L-S ratio correlated well with regional myocardial work: \( y = 0.01x + 0.79, \) \( r = 0.77, P < 0.0001 \) (Figure 4). When the L-S ratio was < 0.50, the segments performed active work (specificity, 99%; sensitivity, 67%), and when the L-S ratio was > 0.80, the segments were entirely passive (specificity, 90%; sensitivity, 74%). The L-S ratio by SDE correlated well with L-S ratio by sonomicrometry \((R = 0.90)\). Regional myocardial compliance was calculated only in segments that were passive, as defined by the LVP-SL analysis. There was good correlation between myocardial compliance calculated with SDE and with sonomicrometry as a dimension estimate \((R = 0.76)\). Furthermore, compliance estimates were essentially similar when calculated with peak systolic pressure instead of developed LVP in the denominator \((R = 0.73)\) (Tables 2 and 3 and Figure 5). There was no significant change in segmental shortening of the nonischemic region during ischemia and reperfusion (Tables 1 and 3).

**Viable Myocardium (Group 1)**

Ischemia for 15 minutes increased the L-S ratio from 0.01±0.00 to 0.72±0.08 \((P < 0.05)\), and segmental work decreased from 127±34 to −1±5 mm×mm Hg \((P < 0.05)\). Reperfusion for 15 minutes reduced the L-S ratio to 0.48±0.04 \((P < 0.05)\), and regional work increased to 84±29 mm×mm Hg \((P < 0.05)\).

There were moderate changes in EDWT during ischemia and reperfusion of viable segments, and these were attributed to changes in end-diastolic SL (Table 1 and Figure 2B). During ischemia, systolic myocardial compliance was high in viable ischemic segments \((0.21±0.04%/mm Hg)\). After reperfusion, passive systolic compliance could not be assessed because the segments were actively contracting (Table 1).

The water content of the viable ischemic region was slightly increased compared with the nonischemic region \((P < 0.01)\). There were no signs of myocardial necrosis by TTC staining.

**Necrotic Myocardium (Groups 2 and 3)**

Fifteen minutes of LAD occlusion increased the L-S ratio in groups 2 and 3, from 0.06±0.05 and 0.14±0.09, respectively, at baseline to 0.78±0.03 \((P < 0.05)\) and 0.76±0.04 \((P < 0.05)\). There was no further change in the L-S ratio when the myocardium underwent necrosis or after reperfusion (Tables 2 and 3). Segmental myocardial work decreased from 47±4 and 92±30 mm×mm Hg to −4±6 \((P < 0.05)\) and
−4±3 mm×mm Hg (P<0.05) after 15 minutes with ischemia and remained unchanged thereafter.

Development of necrosis was associated with a decrease in myocardial compliance. After 15 minutes of ischemia, myocardial compliance in group 3 was 0.23±0.07%/mm Hg, which is comparable to compliance after 15 minutes of ischemia in the viable myocardium group. A marked reduction of compliance was found after 4 hours of ischemia, to 0.12±0.01%/mm Hg (P<0.05), and a further reduction to 0.05±0.04%/mm Hg after 15 minutes of reperfusion (P<0.05). The reductions in compliance can be appreciated visually by considering the strain and pressure tracings in

### Table 1. Viable Myocardium Group (Group 1, n=6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 Minutes Ischemia</th>
<th>15 Minutes Reperfusion</th>
<th>3 Hours Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min⁻¹</td>
<td>90±6</td>
<td>104±3</td>
<td>100±7</td>
<td>90±5</td>
</tr>
<tr>
<td>LV peak systolic pressure, mm Hg</td>
<td>96±5</td>
<td>85±5</td>
<td>84±6</td>
<td>91±3</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>7.9±0.9</td>
<td>10.6±1.3</td>
<td>7.8±0.4</td>
<td>8.8±1.0</td>
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<tr>
<td>LV dP/dt max, mm Hg/s</td>
<td>1419±120</td>
<td>1657±219</td>
<td>1358±166</td>
<td>1573±103</td>
</tr>
<tr>
<td>EDWT by 2D echocardiography, mm</td>
<td>14.4±0.8</td>
<td>9.7±0.7*</td>
<td>11.5±1.0†</td>
<td>13.4±0.9‡</td>
</tr>
<tr>
<td>End-diastolic SL by sonomicrometry, mm</td>
<td>10.0±1.5</td>
<td>11.6±1.9*</td>
<td>10.8±1.8</td>
<td>10.5±1.7†</td>
</tr>
<tr>
<td>Systolic shortening by sonomicrometry, %</td>
<td>0.1±0.1</td>
<td>15.4±3.8*</td>
<td>9.5±1.6</td>
<td>1.7±0.9†</td>
</tr>
<tr>
<td>Late systolic shortening by sonomicrometry, %</td>
<td>17.2±2.7</td>
<td>4.0±1.3*</td>
<td>12.1±3.3†</td>
<td>9.6±1.5</td>
</tr>
<tr>
<td>Postsystolic shortening by sonomicrometry, %</td>
<td>2.5±0.9</td>
<td>16.8±3.1*</td>
<td>7.9±1.0†</td>
<td>3.4±1.2</td>
</tr>
<tr>
<td>Segmental work (loop area), mm×mm Hg</td>
<td>127±34</td>
<td>−1±5*</td>
<td>84±29†</td>
<td>75±21</td>
</tr>
<tr>
<td>L-S ratio by sonomicrometry</td>
<td>0.01±0.00</td>
<td>0.72±0.08*</td>
<td>0.48±0.04†</td>
<td>0.13±0.07‡</td>
</tr>
<tr>
<td>Systolic compliance (ΔLVP§) by sonomicrometry, %/mm Hg</td>
<td>Active</td>
<td>0.21±0.04</td>
<td>Active</td>
<td>Active</td>
</tr>
<tr>
<td>Systolic compliance (LVP max§) by sonomicrometry, %/mm Hg</td>
<td>Active</td>
<td>0.18±0.04</td>
<td>Active</td>
<td>Active</td>
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<tr>
<td>Systolic shortening by sonomicrometry, circumflex region, %</td>
<td>15.0±0.6</td>
<td>16.5±2.5</td>
<td>14.0±1.1</td>
<td>16.2±1.2</td>
</tr>
<tr>
<td>L-S ratio by Doppler</td>
<td>0.01±0.00</td>
<td>0.85±0.03*</td>
<td>0.57±0.06†</td>
<td>0.10±0.05‡</td>
</tr>
<tr>
<td>Systolic compliance (ΔLVP§) by Doppler, %/mm Hg</td>
<td>Active</td>
<td>0.14±1.5</td>
<td>Active</td>
<td>Active</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*P<0.05 vs baseline.
†P<0.05 vs 15-minute ischemia.
‡P<0.01 vs 15-minute reperfusion. One-way repeated-measures ANOVA P values after Bonferroni correction.
§Pressure used in the denominator for calculation of compliance.
||LVP-SL loop area >10% of baseline value.

### Table 2. Necrotic Myocardium Group, No Reperfusion (Group 2, n=6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 Minutes Ischemia</th>
<th>4 Hours Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min⁻¹</td>
<td>108±5</td>
<td>115±7</td>
<td>107±6</td>
</tr>
<tr>
<td>LV peak systolic pressure, mm Hg</td>
<td>103±4</td>
<td>99±3</td>
<td>98±6</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>5.7±0.4</td>
<td>8.9±0.6</td>
<td>8.7±1.2</td>
</tr>
<tr>
<td>LV dP/dt max, mm Hg/s</td>
<td>2235±220</td>
<td>1770±79</td>
<td>1680±107</td>
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<tr>
<td>End-diastolic SL by sonomicrometry, mm</td>
<td>12.1±1.4</td>
<td>13.6±1.5*</td>
<td>13.4±1.4</td>
</tr>
<tr>
<td>Systolic shortening by sonomicrometry, %</td>
<td>0.5±0.5</td>
<td>15.2±2.5*</td>
<td>7.7±0.8†</td>
</tr>
<tr>
<td>Late systolic shortening by sonomicrometry, %</td>
<td>6.5±0.9</td>
<td>2.2±0.1*</td>
<td>1.4±0.4*</td>
</tr>
<tr>
<td>Postsystolic shortening by sonomicrometry, %</td>
<td>1.0±0.4</td>
<td>16.3*</td>
<td>7.0±0.6†</td>
</tr>
<tr>
<td>Segmental work (loop area), mm×mm Hg</td>
<td>47±4</td>
<td>−4±6*</td>
<td>−2±2*</td>
</tr>
<tr>
<td>L-S ratio by sonomicrometry</td>
<td>0.06±0.05</td>
<td>0.78±0.03*</td>
<td>0.87±0.02*</td>
</tr>
<tr>
<td>Systolic compliance (ΔLVP§) by sonomicrometry, %/mm Hg</td>
<td>Active</td>
<td>0.17±0.04</td>
<td>0.09±0.01†</td>
</tr>
<tr>
<td>Systolic compliance (LVP max§) by sonomicrometry, %/mm Hg</td>
<td>Active</td>
<td>0.16±0.03</td>
<td>0.08±0.01†</td>
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<tr>
<td>L-S ratio by Doppler</td>
<td>0.07±0.05</td>
<td>0.88±0.04*</td>
<td>0.94±0.03*</td>
</tr>
<tr>
<td>Systolic compliance (ΔLVP§) by Doppler, %/mm Hg</td>
<td>Active</td>
<td>0.12±0.01</td>
<td>0.06±0.01†</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*P<0.05 vs baseline.
†P<0.05 vs 15-minute ischemia. One-way repeated-measures ANOVA P values after Bonferroni correction.
§Pressure used in the denominator for calculation of compliance.
||LVP-SL loop area >10% of baseline value.
TABLE 3. Necrotic Myocardium Group, With Reperfusion (Group 3, n=6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 Minutes Ischemia</th>
<th>4 Hours Ischemia</th>
<th>15 Minutes Reperfusion</th>
<th>3 Hours Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min⁻¹</td>
<td>104±10</td>
<td>116±10</td>
<td>118±10</td>
<td>115±5</td>
<td>113±9</td>
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<tr>
<td>LV peak systolic pressure, mm Hg</td>
<td>99±6</td>
<td>82±6*</td>
<td>92±4</td>
<td>84±5</td>
<td>82±7</td>
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<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>8.3±0.8</td>
<td>11.1±1.6</td>
<td>11.9±1.9*</td>
<td>10.3±1.6</td>
<td>9.8±2.2</td>
</tr>
<tr>
<td>LV dP/dt max, mm Hg/s</td>
<td>1638±180</td>
<td>1248±128</td>
<td>1808±75</td>
<td>1724±128</td>
<td>1582±143</td>
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<tr>
<td>EDTW by 2D echocardiography, mm</td>
<td>14.0±0.5</td>
<td>11.1±0.9*</td>
<td>11.6±0.9</td>
<td>17.5±0.9†</td>
<td>16.3±1.1</td>
</tr>
<tr>
<td>End-diastolic SL by sonomicrometry, mm</td>
<td>12.3±1.1</td>
<td>13.5±1.2*</td>
<td>13.6±1.3</td>
<td>12.1±1.1†</td>
<td>12.0±1.1</td>
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<tr>
<td>Systolic lengthening by sonomicrometry, %</td>
<td>1.3±0.8</td>
<td>17.2±3.8*</td>
<td>7.4±1.3†</td>
<td>2.5±0.3‡</td>
<td>2.5±0.3</td>
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<tr>
<td>Late systolic shortening by sonomicrometry, %</td>
<td>8.9±2.0</td>
<td>3.3±1.0*</td>
<td>1.6±0.5</td>
<td>0.65±0.2</td>
<td>0.67±0.1</td>
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<td>Post systolic shortening by sonomicrometry, %</td>
<td>1.9±0.5</td>
<td>18.8±4.0*</td>
<td>7.9±1.7†</td>
<td>2.3±0.3‡</td>
<td>2.3±0.3</td>
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<tr>
<td>Segmental work (loop area), mm x mm Hg</td>
<td>92±30</td>
<td>−4±3*</td>
<td>−1±3</td>
<td>−2±4</td>
<td>−4±3</td>
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<tr>
<td>L-S ratio by sonomicrometry</td>
<td>0.14±0.09</td>
<td>0.76±0.04*</td>
<td>0.80±0.05</td>
<td>0.83±0.08</td>
<td>0.85±0.05</td>
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<tr>
<td>Systolic compliance (ΔLVP§) by sonomicrometry, %/mm Hg</td>
<td>Active</td>
<td>0.23±0.07</td>
<td>0.12±0.04†</td>
<td>0.05±0.01‡</td>
<td>0.05±0.01</td>
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<tr>
<td>Systolic compliance (LVP max§) by sonomicrometry, %/mm Hg</td>
<td>Active</td>
<td>0.22±0.06</td>
<td>0.09±0.02†</td>
<td>0.05±0.01‡</td>
<td>0.05±0.01</td>
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<tr>
<td>Systolic shortening by sonomicrometry, circumflex region, %</td>
<td>18.5±3.4</td>
<td>19.8±4.4</td>
<td>21.0±4.4</td>
<td>20.0±4.3</td>
<td>18.8±4.9</td>
</tr>
<tr>
<td>L-S ratio by Doppler</td>
<td>0.0±0.0</td>
<td>0.90±0.03*</td>
<td>0.81±0.05</td>
<td>0.94±0.03</td>
<td>0.89±0.05</td>
</tr>
<tr>
<td>Systolic compliance (ΔLVP§) by Doppler, %/mm Hg</td>
<td>Active</td>
<td>0.18±0.04</td>
<td>0.06±0.01†</td>
<td>0.03±0.01‡</td>
<td>0.03±0.01</td>
</tr>
</tbody>
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Values are mean±SEM.
*P<0.05 vs baseline.
†P<0.05 vs 15-minute ischemia.
‡P<0.05 vs 4-hour ischemia. One-way repeated-measures ANOVA P values after Bonferroni correction.
§Pressure used in the denominator for calculation of compliance.
[ΔLVP-SL loop area >10% of baseline value.

Figure 3. As shown in Figure 3A, development of necrosis was associated with a marked decrease in systolic lengthening at essentially similar developed LV systolic pressure. Figure 3B illustrates that the slope of the LVP-SL relation became much steeper after development of necrosis, meaning that a larger pressure rise was needed to obtain a given lengthening. After 15 minutes of reperfusion, the relation became even steeper. The most dramatic change with reperfusion, however, was a marked leftward-shift of the LVP-SL relation, indicating markedly stiffer myocardium. These changes in myocardial elastic properties occurred rapidly and reached a maximum after 15 minutes of reperfusion. Group 2 had compliance values similar to those of group 3 before reperfusion.

The increase in LV end-diastolic pressure and end-diastolic SL with the onset of ischemia was accompanied by a decrease in EDWT (Table 3). Reperfusion, however, caused an immediate and marked increase in EDWT. Most of the increase occurred within 3 minutes of reperfusion, and EDWT leveled off after 15 minutes (Table 3 and Figure 6A). No additional change in compliance or EDWT occurred during the rest of the reperfusion period.

Myocardial staining by TTC demonstrated transmural (>90%) necrosis in both groups, with average infarct sizes of 28±3% and 32±6% in groups 2 and 3, respectively. The water content of necrotic myocardium with no reperfusion (group 2) was 80.3±0.4% compared with 78.7±0.3% (P<0.01) in viable ischemic myocardium (group 1). Reperfusion of necrotic myocardium (group 3) caused a further increase in water content, to 82.8±0.4% (P<0.01).

Microvascular Obstruction and Regional Function

During LAD occlusion, perfusion in the central ischemic region (between the ultrasonic crystals) decreased from 89±8 to 3±1 mL·100 g⁻¹·min⁻¹ (P<0.01). Two of the 4 dogs demonstrated preserved microvascular perfusion after reperfusion, with relative myocardial blood flow of 80% and 66%, respectively, after 3 hours. Two of the dogs, however, demonstrated microvascular obstruction, defined as flow <50% of that in remote myocardium. In these 2 experiments, flow was depressed during the entire reperfusion period, and after 3 hours, relative flow was 17% and 41%, respectively. The reperfusion-induced decrease in compli-
In the present experimental study, we introduce a new method to assess myocardial viability and to evaluate responses to reperfusion during acute coronary occlusion. This is a TDI-based approach that used systolic and postsystolic myocardial strain patterns as markers of active force generation and myocardial necrosis. In dyskinetic myocardium with active force, early systolic lengthening was much less than combined late and postsystolic shortening. In dyskinetic myocardium that was entirely passive, however, the magnitude of systolic lengthening was nearly as large as late and postsystolic shortening, and the L-S ratio approached 1. Thus, in dyskinetic segments, the L-S ratio proved to be a marker of active wall tension.

In segments that developed necrosis, there was a marked reduction in systolic lengthening owing to a decrease in myocardial compliance, as defined by LVP-SL loops. We also estimated systolic compliance as systolic lengthening by SDE divided by systolic pressure, and this measure was well correlated with compliance calculated from the LVP-SL relation (Figure 5). We could show that this ratio was a powerful marker of tissue necrosis.

Thus, the present findings suggest that the combined use of the L-S ratio and systolic compliance by SDE may represent a means to assess viability in acutely ischemic myocardium and to determine responses to coronary reperfusion.

**Identification of Viable Myocardium by L-S Ratio**

In severely ischemic myocardium, there is typically systolic lengthening, and end-systolic length may exceed end-diastolic length. Although such segments obviously do not contribute to LV stroke volume, one cannot readily rule out a component of active contraction that may be offset by the forces that cause lengthening of the segment. The present study shows that the L-S ratio represents a method to differentiate between dyskinetic segments that generate active force and those that are entirely passive. As demonstrated in Figure 4, the L-S ratio increased progressively and approached 1 as regional work approached 0, supporting the concept that the L-S ratio is a marker of active force. These characteristics of active segments are explained in part by a reduction in systolic lengthening caused by active wall tension and in part by active late and postsystolic shortening. The latter mechanism was demonstrated by Skulstad et al in a similar animal preparation and was confirmed in the present study by the LVP-SL loops (Figure 2B).

An entirely passive myocardial segment is analogous to a stretched elastic spring; i.e., the myocardium will recoil passively to its original length when the stretching force is removed, resulting in an L-S ratio of 1. In the present study, however, the L-S ratio was < 1, even in segments that were entirely passive according to LVP-SL loop analysis. This apparent inconsistency between predicted and observed L-S ratios can be explained by a lower LVP in the early filling phase than at end diastole, which causes the segment to recoil passively to a smaller length than at the preceding end diastole. Therefore, the L-S ratio in passive segments never reached 1 but was in the range of 0.47 to 0.98 and 0.63 to 0.99 by sonomicrometry and TDI, respectively.

These results imply that assessment of the L-S ratio in dyskinetic segments can identify myocardium that generates active tension and therefore is viable. Furthermore, after reperfusion of segments that were passive but viable, the L-S ratio decreased rapidly. In segments that were passive and necrotic, the L-S ratio did not change after reperfusion.

**Identification of Necrosis by Systolic Myocardial Compliance**

After 4 hours of coronary occlusion, the myocardium developed transmural necrosis, as evidenced by TTC staining, and

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**Figure 5. Relations between systolic myocardial compliance as measured by SDE and sonomicrometry. Developed LVP was used in the denominator for the sonomicrometric calculations, whereas systolic LVP (LVP$_{max}$) was used for the SDE calculations to mimic the potential noninvasive measurement of compliance. A, Correlation between systolic myocardial compliance as measured by SDE and sonomicrometry. B, Agreement between systolic myocardial compliance by the 2 methods.**

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**Discussion**

In the present experimental study, we introduce a new method to assess myocardial viability and to evaluate responses to reperfusion during acute coronary occlusion. This is a TDI-based approach that used systolic and postsystolic myocardial strain patterns as markers of active force generation and myocardial necrosis. In dyskinetic myocardium with active force, early systolic lengthening was much less than combined late and

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**Reproducibility of L-S Ratio and Compliance by SDE**

All SDE recordings from groups 1 and 3 were analyzed by 2 observers who were blinded to the measurement conditions. Interobserver and intraobserver agreement was expressed as mean differences (±SD) and intraclass correlation coefficient ($R_i$). Mean differences for interobserver agreement for L-S ratio and myocardial compliance were 0.00 ± 0.13 and −0.02 ± 0.04%/mm Hg, and $R_i$ values were 0.95 and 0.77, respectively, indicating good agreement. Mean differences for intraobserver agreement were 0.02 ± 0.12 and 0.00 ± 0.02%/mm Hg, and $R_i$ values were 0.96 and 0.97, respectively.

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**Analyses of the Infarcted Segment**

1. The area at risk tended to be larger in the 2 dogs with microvascular obstruction (52% and 56%, respectively) than in the 2 dogs with preserved microvascular flow (both 42%).

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**Figures and Tables**

1. **Figure 5. Relations between systolic myocardial compliance as measured by SDE and sonomicrometry. Developed LVP was used in the denominator for the sonomicrometric calculations, whereas systolic LVP (LVP$_{max}$) was used for the SDE calculations to mimic the potential noninvasive measurement of compliance. A, Correlation between systolic myocardial compliance as measured by SDE and sonomicrometry. B, Agreement between systolic myocardial compliance by the 2 methods.**

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**Table 1. Interobserver and Intraobserver Agreement for L-S Ratio and Compliance**

<table>
<thead>
<tr>
<th>Method</th>
<th>Interobserver</th>
<th>Intraobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-S Ratio</td>
<td>Mean difference (±SD)</td>
<td>0.00 ± 0.13</td>
</tr>
<tr>
<td>Compliance</td>
<td>Mean difference (±SD)</td>
<td>−0.02 ± 0.04%/mm Hg</td>
</tr>
</tbody>
</table>

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**Figure 4. Identification of Viable Myocardium by L-S Ratio**

In severely ischemic myocardium, there is typically systolic lengthening, and end-systolic length may exceed end-diastolic length. Although such segments obviously do not contribute to LV stroke volume, one cannot readily rule out a component of active contraction that may be offset by the forces that cause lengthening of the segment. The present study shows that the L-S ratio represents a method to differentiate between dyskinetic segments that generate active force and those that are entirely passive. As demonstrated in Figure 4, the L-S ratio increased progressively and approached 1 as regional work approached 0, supporting the concept that the L-S ratio is a marker of active force. These characteristics of active segments are explained in part by a reduction in systolic lengthening caused by active wall tension and in part by active late and postsystolic shortening. The latter mechanism was demonstrated by Skulstad et al in a similar animal preparation and was confirmed in the present study by the LVP-SL loops (Figure 2B).

An entirely passive myocardial segment is analogous to a stretched elastic spring; i.e., the myocardium will recoil passively to its original length when the stretching force is removed, resulting in an L-S ratio of 1. In the present study, however, the L-S ratio was < 1, even in segments that were entirely passive according to LVP-SL loop analysis. This apparent inconsistency between predicted and observed L-S ratios can be explained by a lower LVP in the early filling phase than at end diastole, which causes the segment to recoil passively to a smaller length than at the preceding end diastole. Therefore, the L-S ratio in passive segments never reached 1 but was in the range of 0.47 to 0.98 and 0.63 to 0.99 by sonomicrometry and TDI, respectively.

These results imply that assessment of the L-S ratio in dyskinetic segments can identify myocardium that generates active tension and therefore is viable. Furthermore, after reperfusion of segments that were passive but viable, the L-S ratio decreased rapidly. In segments that were passive and necrotic, the L-S ratio did not change after reperfusion.
there was a marked increase in myocardial water content, reflecting tissue edema. The development of necrosis was accompanied by reductions in systolic lengthening and in postsystolic shortening, which is consistent with previous work. As shown in the present study, the reductions in systolic lengthening and postsystolic shortening were associated with myocardial edema and a decrease in systolic compliance. Reperfusion of infarcted myocardium caused further marked reductions in systolic lengthening and postsystolic shortening and was accompanied by aggravated edema with a further decrease in systolic compliance. As suggested by our microvascular flow data, the reduction in compliance of necrotic myocardium after reperfusion was found in necrotic myocardium with or without microvascular obstruction. In keeping with the recent publications by Gerber et al.20 and Azevedo et al.21 however, reperfusion-induced reductions in compliance tended to be larger in segments with microvascular obstruction (Figure 6B). Additional studies are needed to better define the relation between microvascular obstruction and regional compliance. From a practical standpoint, however, the marked decrease in compliance, even in segments without microvascular obstruction, suggests that the TDI-based indices might be applicable as coronary (epicardial) reperfusion markers regardless of microvascular integrity.

Potential Diagnostic Application of L-S Ratio and Systolic Myocardial Compliance

In this section, we outline how combined use of the L-S ratio and systolic myocardial compliance may have a role in the assessment of viability in dyskinetic myocardium and in the evaluation of responses to coronary reperfusion therapy.

When using SDE to assess viability in acute ischemia, the first step should be to identify signs of active myocardial contraction. This is achieved by calculating the L-S ratio, and if the ratio is <0.50, the segment is most likely active and therefore viable. However, if the L-S ratio approaches 1, the segment is entirely passive, indicating the absence of significant active force. As confirmed in the present study, however, an entirely passive segment may still be viable. Therefore, an additional method is needed to differentiate between viable and necrotic segments. The second step is assessment...
of systolic compliance. If compliance is high, it is likely that the segment is viable. However, if an entirely passive segment demonstrates reduced compliance, it is consistent with myocardial necrosis.

Our results suggest that these measures may also be used to evaluate responses to coronary reperfusion. The present experimental model illustrates 2 principally different responses to reperfusion therapy. First, in myocardium that was severely ischemic but viable, reperfusion resulted in recovery of function measured as either systolic shortening or reduced L-S ratio. Second, when myocardium was necrotic before reperfusion, systolic compliance decreased abruptly and markedly, and EDWT increased owing to further tissue edema. There was no change in the L-S ratio, indicating no recovery of contractile function.

Taken together, these observations indicate that the combined use of the L-S ratio and systolic compliance may represent a new approach for evaluating responses to reperfusion therapy. Although compliance as calculated in this study was based on invasive LVP measurements, it will be feasible to use arterial systolic pressure to approximate LVP. Therefore, the present data suggest that this simple approach may serve as a guide to assess responses to reperfusion therapy. These concepts need to be tested in clinical trials. As suggested by the present study, the reduction in systolic compliance may in part be related to tissue damage associated with microvascular obstruction during reperfusion.

Limitations of the Model
In the present study, we used a model of coronary occlusion that resulted in transmural myocardial infarcts. Therefore, the present findings and proposed methodologies may not be applicable to subendocardial infarctions, which account for a substantial fraction of clinical infarctions. Furthermore, in patients, the duration of acute ischemia varies widely, and there may be substantial changes in the intensity of ischemia over time. The present study should be considered a demonstration of a principle with potential clinical importance, and further studies are definitely needed.

Calculation of the L-S ratio and systolic myocardial compliance requires high-quality strain tracings. Because of significant problems with signal noise and drift when using SDE, it may be difficult to obtain accurate values for these indices. Ongoing developments of the technology are likely to reduce these problems.

When LV end-diastolic pressure is elevated, the myocardium operates on a steeper portion of the LVP-SL curve, which implies a decrease in chamber compliance. This in turn will reduce systolic thickening for a given LV developed pressure and cause a reduction in the L-S ratio. The magnitudes of these load dependencies are difficult to predict but are likely to impact the L-S ratio as well as the systolic compliance estimate. As illustrated in Figure 3B, the LVP-SL relation of necrotic myocardium has essentially the same slope over a wide range of pressures, and therefore, the L-S ratio may not be as load dependent. As shown in the same figure, viable myocardium has a curvilinear LVP-SL relation and is more load dependent. Potentially, noninvasive estimation of LV end-diastolic pressure may help to define preload as a confounder in this setting.

Importantly, any active force in a segment will tend to reduce systolic compliance and will confuse the interpretation with regard to tissue necrosis. Therefore, it is essential that the first step is to assess L-S ratio and to proceed to estimation of compliance only if the segment appears entirely passive.

Conclusions
The present experimental study demonstrates that SDE can be used to assess viability and to evaluate responses to reperfusion in acute coronary occlusion. These methods should be tested clinically to determine whether the L-S ratio and myocardial systolic compliance by SDE might add unique diagnostic information when decisions are to be made with regard to revascularization and other therapies in acute myocardial infarction.

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Disclosures
After completing the work on this study, Dr Rabben changed employers and currently works for GE Vingmed Ultrasound, which supplied some of the equipment used in this study. The other authors report no conflicts of interest.

References
CLINICAL PERSPECTIVE

This experimental article proposes a novel approach to assess myocardial viability and reperfusion in acute coronary occlusion. The method is based on measurement of myocardial strain by SDE, with sonomicrometry used as the reference method. First, in dyskinetic myocardium, the ratio between early systolic lengthening and total shortening (L-S ratio) proved to be a marker of active myocardial force: When the L-S ratio approached 1, the segment was entirely passive and generated essentially no active force. When the L-S ratio was <0.5 and shortening dominated over lengthening, there was a component of active contraction, consistent with preserved tissue viability. Second, in entirely passive segments (L-S ratio approaching 1), low systolic myocardial compliance, calculated as systolic lengthening divided by systolic LVP, proved to be a marker of necrosis. This relation was in part accounted for by marked tissue edema, which caused stiffening of necrotic myocardium. Reperfusion of necrotic myocardium caused no change in the L-S ratio but resulted in a rapid, further reduction in compliance. Reperfusion of viable myocardium, however, caused an immediate reduction in the L-S ratio. These observations suggest that the myocardial L-S ratio and systolic compliance by SDE may differentiate between necrotic and viable myocardium and identify reperfusion in acute coronary occlusion. Bedside assessment of these new indices is feasible, and clinical studies should be conducted to test the principles in patients.
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