Assessment of Nonuniformity of Transmural Myocardial Velocities by Color-Coded Tissue Doppler Imaging
Characterization of Normal, Ischemic, and Stunned Myocardium

Geneviève Derumeaux, MD, PhD; Michel Ovize, MD, PhD; Joseph Loufoua, PhD; Gérard Pontier, BS; Xavier André-Fouet, MD; Alain Cribier, MD

Background—Transmural myocardial contractile performance is nonuniform across the different layers of the left ventricular wall. We evaluated the accuracy of color M-mode tissue Doppler imaging (TDI) to assess the transmural distribution of myocardial velocities and to quantify the severity of dysfunction induced by acute ischemia and reperfusion in the inner and outer myocardial layers.

Methods and Results—Thirteen open-chest dogs underwent 15 minutes of left anterior descending coronary artery occlusion followed by 120 minutes of reperfusion. M-mode TDI was obtained from an epicardial short-axis view. Systolic velocities were calculated within endocardium and epicardium of the anterior and posterior walls. Regional myocardial blood flow was assessed by radioactive microspheres. Segment shortening was measured by sonomicrometry in endocardium and epicardium of both the anterior and posterior walls. At baseline, endocardial velocities were higher than epicardial velocities, resulting in an inner/outer myocardial velocity gradient. Ischemia caused a significant and comparable reduction in endocardial and epicardial systolic velocities in the anterior wall with the disappearance of the velocity gradient. Systolic velocities significantly correlated with segment shortening in both endocardium and epicardium during ischemia and reperfusion. In the first minutes after reflow, endocardial velocities showed a greater improvement than epicardial velocities, and the velocity gradient resumed although to a limited extent, indicative of stunning.

Conclusions—TDI is an accurate method to assess the nonuniformity of transmural velocities and may be a promising new tool for quantifying ischemia-induced regional myocardial dysfunction. (Circulation. 2000;101:1390-1395.)

Key Words: echocardiography • ischemia • reperfusion • stunning, myocardial

Experimental studies have demonstrated that circumferential fiber thickening varies across the different layers of myocardial walls and is more pronounced in endocardium than in epicardium.1–4 This transmural inhomogeneity is important to take into account in the setting of ischemic cardiomyopathy to differentiate the various patterns of contractile abnormalities that may occur during acute ischemia, hibernation, or stunning. Conventional assessment of contractile function is based on the measurement of transmural thickening. Previous ultrasonic studies of myocardial contractility based on M-mode or 2-dimensional images have assessed the differences between end-systolic and end-diastolic myocardial wall thicknesses or have involved digitization of endocardial and epicardial echoes.5,6 However, neither of these approaches provides information regarding the transmural distribution of contractile performance.

Tissue Doppler imaging (TDI) is a recent ultrasound technique that enables quantification of intramural myocardial velocities by detection of consecutive phase shifts of the ultrasound signal reflected from the contracting myocardium.7–9 TDI may display velocities with B-mode, M-mode, or pulsed Doppler. M-mode TDI overcomes the temporal resolution problems inherent in the B-mode approach, analyzes in real time endocardial and epicardial velocities, and provides new indexes of myocardial function such as the myocardial velocity gradient (MVG).10,11 Recent experimental studies using 2-dimensional and pulsed TDI have demonstrated that TDI can quantify ischemia-induced regional myocardial dysfunction, but there has been no report that M-mode TDI can characterize transmural distribution of velocities during ischemia and reperfusion.12,13

Therefore, the objectives of this study, performed in the open-chest canine model of ischemia-reperfusion, were (1) to assess the ability of M-mode TDI to quantify endocardial and epicardial velocities with sonomicrometry as a reference method, (2) to analyze the variations of the transmural...
artery (LAD) occlusion resulted in a dramatic decrease in both endocardial and epicardial RMBF from 0.88 ± 0.05 to 0.12 ± 0.04 and 0.94 ± 0.04 to 0.27 ± 0.07 mL · min^-1 · g^-1, respectively (P < 0.01 versus baseline for both). At 30 minutes after reflow, endocardial and epicardial RMBF in the anterior wall averaged 3.81 ± 0.93 and 3.18 ± 0.84 mL · min^-1 · g^-1, respectively, indicative of hyperemia (P < 0.01 versus baseline) (Table 1). In nonischemic myocardium, RMBF increase during occlusion was not statistically significant. At 30 minutes after reflow, RMBF increased significantly in the nonischemic zone although to a lower extent than in the ischemic zone (P < 0.01 versus baseline, P < 0.05 versus ischemic zone).

Normal Pattern of Myocardial Velocities
Pericardial opening induced a significant decrease in diastolic velocities but did not significantly alter systolic velocities (Table 2). Myocardial velocities recorded after pericardial opening were used as baseline values for further comparison during ischemia/reperfusion. Velocity profiles derived from M-mode TDI traces indicated that distribution of transmural velocities was inhomogeneous across the myocardial wall. Velocities significantly and progressively increased from epicardium to endocardium (Figure 1A). In the anterior wall, baseline endocardial and epicardial systolic velocities (Vs) averaged −4.9 ± 0.7 and −1.7 ± 0.4 cm/s, respectively (Figure 1B). In the posterior wall, endocardial and epicardial Vs averaged 6.8 ± 0.6 and 3.2 ± 0.2 cm/s, respectively. Thus, a MVG could be measured (Figure 1C). This MVG profile displayed 2 distinct negative peaks during systole and 2 positive peaks during diastole. During systole, the first peak was brief and occurred during isovolumic contraction, whereas the second peak was more prolonged, of smaller amplitude, and occurred during the ejection phase. The first diastolic peak occurred during isovolumic relaxation; the second, during the early ventricular filling phase. MVG was

**Table 1. Hemodynamics and Regional Myocardial Blood Flow**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Occlusion</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>159 ± 7</td>
<td>155 ± 4</td>
<td>152 ± 6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>135 ± 6</td>
<td>138 ± 5</td>
<td>138 ± 4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83 ± 6</td>
<td>84 ± 5</td>
<td>86 ± 3</td>
</tr>
<tr>
<td>RMBF, mL · min^-1 · g^-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>0.88 ± 0.05</td>
<td>0.12 ± 0.04†</td>
<td>3.81 ± 0.93†</td>
</tr>
<tr>
<td>Epicardium</td>
<td>0.94 ± 0.04</td>
<td>0.27 ± 0.07†</td>
<td>3.18 ± 0.84†</td>
</tr>
<tr>
<td>Nonischemic zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>1.05 ± 0.06</td>
<td>1.52 ± 0.09</td>
<td>2.26 ± 0.33†</td>
</tr>
<tr>
<td>Epicardium</td>
<td>0.99 ± 0.07</td>
<td>1.37 ± 0.09</td>
<td>1.90 ± 0.27†</td>
</tr>
</tbody>
</table>

*HR indicates heart rate; SBP, systolic blood pressure; and DBP, diastolic blood pressure. All values are expressed as mean ± SE. †P < 0.05 vs nonischemic zone RMBF; †P < 0.01 vs baseline.

**Table 2. Comparison of Myocardial Velocities and Myocardial Velocity Gradients Within Anterior Wall Before and After Pericardial Opening**

<table>
<thead>
<tr>
<th></th>
<th>Before Pericardial Opening</th>
<th>After Pericardial Opening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Ischemia</td>
</tr>
<tr>
<td>Systole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{epi}</td>
<td>−1.8 ± 0.2</td>
<td>−1.7 ± 0.4</td>
</tr>
<tr>
<td>V_{endo}</td>
<td>−5.2 ± 0.5</td>
<td>−4.9 ± 0.7</td>
</tr>
<tr>
<td>MVG s</td>
<td>−3.5 ± 0.4</td>
<td>−3.2 ± 0.5</td>
</tr>
<tr>
<td>Diastole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{epi}</td>
<td>2.7 ± 0.6</td>
<td>1.5 ± 0.2†</td>
</tr>
<tr>
<td>V_{endo}</td>
<td>8.8 ± 0.8</td>
<td>4.4 ± 0.3†</td>
</tr>
<tr>
<td>MVG E</td>
<td>5.8 ± 0.4</td>
<td>3.1 ± 0.2‡</td>
</tr>
<tr>
<td>V_{epi}</td>
<td>1.1 ± 0.2</td>
<td>0.6 ± 0.1*</td>
</tr>
<tr>
<td>V_{endo}</td>
<td>1.8 ± 0.1</td>
<td>0.7 ± 0.1*</td>
</tr>
<tr>
<td>MVG A</td>
<td>0.6 ± 0.1</td>
<td>0.1 ± 0.2*</td>
</tr>
</tbody>
</table>

V indicates velocity; s, systole; epi, epicardium; endo, endocardium; E, early diastole; and A, late diastole.

*P < 0.05, †P < 0.01, ‡P < 0.001 vs before pericardial opening.

§P < 0.01, †P < 0.001 vs baseline.
abolished during atrial contraction, indicating that during this time period, inner and outer myocardial layers were contracting at a similar speed.

Myocardial Velocity Changes During Ischemia-Reperfusion

Ischemic Wall
Anterior wall thickening decreased from 55±9% at baseline to 3±1% during ischemia (P<0.0001). As depicted in Figure 2, Vₐ, dramatically decreased to a similar extent in the inner and outer layers. Vₐ averaged 0.4±0.1 cm/s in endocardium (P<0.0001 versus baseline) and 0.2±0.2 cm/s in epicardium (P<0.0001 versus baseline) (P=NS between endocardium and epicardium). Consequently, the MVG during the ejection phase was significantly reduced from 3.2±0.5 at baseline to 0.3±0.1 s⁻¹ during ischemia (P<0.0001). The whole MVG profile was dramatically altered, with only 1 brief and small negative peak persisting during isovolumic contraction and mean MVG back to nearly zero during the ejection phase. As opposed to systolic velocities, diastolic velocities failed to change significantly (Table 2).

Thirty minutes after reflow, anterior wall thickening remained severely depressed, averaging 11±5% (P<0.0001 versus baseline) (Figure 3). Similarly, epicardial Vₐ remained dramatically low and not significantly different from the preceding ischemic values. In contrast, endocardial Vₐ tended to increase yet failed to fully recover. At 30 minutes of reperfusion, Vₐ recovered to 42±21% of baseline in endocardium (P<0.05 versus occlusion) but only to 9.5±12% of baseline in epicardium (P=NS versus occlusion). At that same time, MVG averaged 2.1±0.3 s⁻¹, a value lower than baseline but significantly higher than the ischemic values (P<0.01).

Nonischemic Wall
During occlusion, wall thickening slightly but not significantly increased in the nonischemic territory to 115% of normal at baseline. During reperfusion, wall thickening increased to 118% of baseline.

Figure 1. Transmural distribution of velocities across anterior wall at baseline. Top, M-mode TDI image of anterior wall at baseline. Anterior wall is divided into 2 layers (epicardial and endocardial) by off-line tracing lines. In each layer, mean velocities are analyzed throughout cardiac cycle, and their corresponding waveforms are displayed in B. Bottom, Different ways to analyze myocardial velocities. A, Instantaneous velocities during mid-systole across anterior wall. This velocity profile clearly demonstrates increase in velocities from epicardium to endocardium. B, Curves of mean epicardial (top) and endocardial (bottom) velocities. C, MVG profile throughout cardiac cycle. Arrows indicate peak values of MVG during isovolumetric contraction (IC), ventricular ejection (Ej), isometric relaxation (IR), early ventricular filling (E), and atrial contraction (A).
baseline values. Endocardial $V_s$ and SS increased to 121% and 119% of control values, respectively ($P_{NS}$), whereas epicardial $V_s$ and SS remained unchanged. After 30 minutes of reperfusion, all parameters returned to baseline values.

**Correlations Between $V_s$, SS, and Myocardial Blood Flow**

To evaluate whether the severity of regional contractile dysfunction induced by ischemia could be accurately evaluated by TDI, $V_s$ was plotted versus SS (both expressed as percentage of baseline values) within endocardium and epicardium. $V_s$% was significantly correlated to SS% within both endocardium ($r=0.94$, $P_{0.0001}$) and epicardium ($r=0.91$, $P_{0.0001}$) (Figure 4).

The relationship between $V_s$ and RMBF in the anterior wall at baseline, during ischemia, and after 30 minutes of reperfusion is summarized in Figure 5. During occlusion, the decrease in endocardial and epicardial RMBF was accompanied by a dramatic reduction in endocardial and epicardial $V_s$. Thirty minutes after reflow, despite hyperemia in both layers of the anterior wall, $V_s$ remained significantly depressed to $42\pm21\%$ and $9.5\pm12\%$ of baseline values in endocardium and epicardium, respectively.

**Discussion**

The present study demonstrates that M-mode TDI can accurately assess the nonuniformity of the transmural distribution of myocardial contractile performance. Specifically, M-mode TDI was able to differentiate and quantify ischemia- and reperfusion-induced endocardial and epicardial contractile dysfunction and assess the transmural MVG.

**Nonuniformity of Left Ventricular Circumferential Thickening in Normal Myocardium**

Conventional quantitative echocardiographic methods classically address transmural but not inner or outer layer myocardial function. Their principle is to analyze the displacement of the endocardial border, which does not take into account the nonuniformity of wall thickening. In a previous study, we used pulsed-wave TDI to analyze septal wall velocity resulting from left ventricular (LV) long-axis shortening and...
its variations after LAD occlusion. We demonstrated that pulsed-wave TDI is accurate to quantify online ischemia-induced dysfunction. But we were unable to discriminate endocardial and epicardial velocities.

In the present study, M-mode TDI allowed interrogation of intramural velocities to quantify LV circumferential contraction. This TDI modality is the first noninvasive method that can quantify in the in situ heart the velocity of myocardial thickening that has been recognized as an index of regional contractility in isolated papillary muscle preparations. Theoretical considerations based on various models of the LV and numerous in vivo experiments have clearly demonstrated that wall thickening is not uniform and the ratio of inner to outer half-thickening approximates 2.0:1.0. The present M-mode TDI data are consistent with these previous studies. As depicted in Figure 7, the ratio of endocardium to epicardium systolic velocities was close to 2.0:1.0. This progressive increase in velocities from inner to outer layer created, under baseline conditions, a velocity gradient that may represent an interesting new index of regional myocardial function.

Detection and Quantification of Ischemia- and Reperfusion-Induced Wall Motion Abnormalities by M-Mode TDI

During LAD occlusion, endocardial and epicardial SS was replaced by passive bulging consistent with a severe reduction in myocardial blood flow. TDI data were closely related to sonomicrometric measurements, indicating that M-mode TDI allows accurate quantification of contractile function during ischemia and reperfusion. Importantly, this accuracy of M-mode TDI applied for any severity of regional dysfunction exhibited by endocardium and epicardium. Both endocardial and epicardial velocities were markedly and uniformly decreased during ischemia and resulted in the disappearance of MVG. This absence of MVG across the anterior wall during severe flow reduction is congruent with previous investigations that reported the abolition of the transmural thickening gradient during dramatic flow deprivation. It is worth noting that no significant decrease occurred in diastolic velocities during ischemia. This may be related to the fact that the pericardial opening had already significantly reduced diastolic velocities, thereby possibly blunting further reduction related to ischemia.

After reperfusion, wall motion in the distribution of the LAD remained severely depressed, indicative of stunning. Conventional M-mode imaging failed to detect any significant improvement in transmural wall thickening. In contrast, M-mode TDI was able to detect a slight but significant increase in endocardial (but not epicardial) velocities, resulting in the resumption of a MVG. This MVG, however, was short lived because endocardial and epicardial velocities were no longer different at 90 minutes of reperfusion. The greater improvement in endocardial velocities early after reflow was likely a consequence of the hyperemic response to the preceding ischemic insult, as suggested by Figure 4. Despite hyperemia, epicardium failed to recover early after reperfusion, suggesting the development of severe stunning and possible tethering to endocardium. These data are in close agreement with those from a study by Bolli et al that reported comparable time course of nonuniform transmural functional recovery after reflow in dogs submitted to 15 minutes of LAD occlusion followed by 7 days of reperfusion. In that study, dogs exhibited a transmural systolic thickening gradient at baseline that disappeared during ischemia. On reperfusion, the inner/outer gradient first resumed, was maximal during the first hour after reflow, and decreased thereafter.

**Figure 5.** Systolic velocities versus myocardial blood flow in anterior wall during ischemia and reperfusion. Velocities ($V_s$%) are expressed as percentage of baseline values. Endocardial (left) and epicardial (right) ischemic zone myocardial blood flow is expressed as fraction of nonischemic zone myocardial blood flow (RMBF ratio). LAD occlusion caused severe flow reduction in both endocardium and epicardium that resulted in similar reduction in $V_s$. RMBF ratio decreased from 0.89 ± 0.05 to 0.08 ± 0.02 within endocardium and from 1.24 ± 0.08 to 0.21 ± 0.06 within epicardium. At 30 minutes after reflow, endocardial and epicardial RMBF ratio averaged 2.01 ± 0.57 and 1.77 ± 0.5, respectively, indicative of hyperemia. After 30 minutes of reperfusion, $V_s$ remained depressed to greater extent in epicardium than in endocardium. (Bold characters indicate mean values and normal characters individual values.) *$P<0.05$ vs occlusion.
Study Limitations
During reperfusion, RMBF and TDI velocities were simultaneously measured 30 minutes after reflow. At that time point, as previously demonstrated,\textsuperscript{22} there is considerable variability in the response of both RMBF and myocardial wall velocity to reperfusion and no relationship between wall velocity and myocardial perfusion (Figure 5).

Our data demonstrate that M-mode TDI is a sensible technique that can detect and quantify mild changes in regional wall motion that may occur during ischemia or reperfusion. The present study has potential important clinical implications, ie, identification and quantification of the regional endocardial or epicardial contractile dysfunction that may arise during or as a consequence of acute coronary syndromes. However, further studies are needed to determine whether these data can apply to human patients.

References
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