Doppler Tissue Imaging Quantitates Regional Wall Motion During Myocardial Ischemia and Reperfusion

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Background—Quantification of regional myocardial function is a major unresolved issue in cardiology. We evaluated the accuracy of pulsed Doppler tissue imaging (DTI), a new echocardiographic technique, to quantify regional myocardial dysfunction induced by acute ischemia and reperfusion.

Methods and Results—In nine open-chest anesthetized pigs, various degrees of regional wall motion abnormalities were induced by graded reduction of left anterior descending coronary artery (LAD) blood flow. Pulsed Doppler tissue imaging was performed from an epicardial apical four-chamber view with the sample placed within the middle part of the septal wall. Peak septal velocities were calculated during systole, isovolumic relaxation, and early and late diastole. Regional myocardial blood flow and systolic and diastolic dysfunctions were assessed by radioactive microspheres and ultrasonic crystals, respectively. Ischemia resulted in a significant rapid reduction of systolic velocities and an early decrease in the ratio of early to late diastolic velocities. Both changes were detected by pulsed DTI within 5 seconds of coronary artery occlusion. The decrease in systolic velocity significantly correlated with both systolic shortening ($r = 0.90, P < 0.0001$) and regional myocardial blood flow ($r = 0.96, P < 0.0001$) during reduction of LAD blood flow.

Conclusions—These results suggest that DTI may be a promising new tool for the quantification of ischemia-induced regional myocardial dysfunction. (Circulation. 1998;97:1970-1977.)

Key Words: imaging • ischemia • echocardiography • ultrasonics
Selected Abbreviations and Acronyms

DTI = Doppler tissue imaging
EDL = end-diastolic lengthening
ESL = end-systolic lengthening
LAD = left anterior descending coronary artery
LDL = late diastolic lengthening
LV = left ventricle/ventricular
MBF = myocardial blood flow
SS = segment shortening

dyskinesis: this was done in a stepwise manner to reduce function by ≈40%, 60%, and finally dyskinesis during total occlusion.
Echographic and segment length recordings were performed sequentially at the following time points: at baseline, during partial stenosis, during total occlusion, and after reperfusion of the LAD.
At the end of each experiment, the LAD was briefly reoccluded and 0.5 mg/kg IV Unisperse Blue Pigment (Ciba-Geigy) was injected to delineate the in vivo area at risk as previously described. Under deep anesthesia, the heart was stopped by intravenous injection of potassium chloride (20 mEq), excised, and cut into 5- to 7-mm-thick transverse slices parallel to the AV groove. We verified that the interventricular septum in the five apical transverse slices was unstained, ie, that the Doppler sampling gate was well in the ischemic area. The correct position of the two ultrasonic crystals within the risk region was checked, and two transmural myocardial samples were excised (one from the ischemic and one from the nonischemic zone) for further measurement of regional MBF.

Data Analysis

Hemodynamics
Heart rate and arterial and LV blood pressures were measured and averaged over 5 continuous cardiac cycles in sinus rhythm at baseline, during coronary artery stenosis or occlusion, and after reperfusion.

Echographic Measurements
From the DTI tracings, we measured the peak velocity of (1) isometric contraction (Vd of DTI, Doppler tissue imaging) was continuously recorded on an echocardiographic recording device. Before thoracotomy, a first series of velocity measurements was performed on five pigs that were lying on their right sides, with the transducer placed over the left ventricular apex to obtain an apical four-chamber view. These measurements were performed to determine whether opening the chest might induce some change in myocardial velocities. In the open-chest preparation (all pigs), all velocity measurements were performed with the beam positioned on the anterior wall near the apex to obtain an epicardial apical four-chamber view. A fixed sampling gate of 10 mm was placed within the middle part of the interventricular septum. Care was taken to align the echo image so that the interventricular septum was parallel to the beam direction. Velocities were encoded positive or negative when the Doppler sampling gate was well in the myocardium. The displacement of the myocardium was directed toward or away from the transducer, respectively. The variation of myocardial velocity during or after coronary occlusion (V occl ) was expressed as a percentage of baseline velocity (V basal ) as $V_{occl} = V_{occl}/V_{basal} \times 100\%$.
Intraobserver variability was tested in eight pigs by repeating the measurements on two occasions under the same basal conditions. To test the interobserver variability, the measurements were repeated from the videotape recordings by a second observer who was unaware of the results of the first observer. For measurement of systolic velocity, and early and late diastolic velocities, intraobserver and interobserver variability ranged from 3.9% to 4.5%.

Regional Myocardial Function
SS and LDL were used as indexes of systolic and diastolic function, respectively. To define these parameters, ESL and EDL were obtained from three well-separated cardiac cycles in each sample period. LV dP/dt was used to define the timing of the cardiac cycle for segment length measurements with ultrasonic crystals; EDL was

Surgical Preparation
Nine farm pigs, weighing 28±4 kg, were premedicated with droperidol (1 mg/kg SC) and anesthetized with pentobarbital (15 mg/kg IV). Additional intravenous administration of pentobarbital was performed when needed. Pigs were ventilated with room air through a tracheotomy tube, and tidal volume and rate were adjusted to provide physiological pH and blood gases. Body temperature was monitored with a rectal thermometer and kept constant by means of a heating pad. Cannulas were inserted into the right jugular vein (for administration of drugs and fluids) and the left carotid artery (for measurement of blood pressure). A 5F Gaeltec probe was placed into the LV cavity through the right carotid artery to measure LV pressure and its first derivative, LV dP/dt. A thoracotomy was performed in the fourth left intercostal space, and a segment of the LAD was isolated just before the first diagonal branch. A micrometric constrictor, designed to gradually reduce coronary blood flow, was tightened the micrometric constrictor. In each animal, several incisions in the middle myocardial layer of the left ventricle and assess regional contractile function, was inserted via a small scalpel.
Measurement of Regional MBF
This measurement was performed in each pig to assess the severity of ischemia during partial or total occlusion of the LAD. Regional MBF (in milliliters per minute per gram) was measured by use of radioactive microspheres labeled with either $^{14} \text{Ce}$ or $^{103} \text{Ru}$ (DuPont-New England Nuclear) as previously described.\textsuperscript{22} Regional MBF was measured at baseline ($n=1$), during partial stenosis ($n=6$), or during total coronary occlusion ($n=4$). Briefly, microspheres were injected into the left atrium via the left atrial catheter, and a reference blood sample was obtained from the carotid artery at a fixed rate of 2.0 mL/min. At the end of the protocol, samples were cut from the center of the ischemic and nonischemic zones, weighed, and counted with the reference blood samples in a gamma counter. Blood flow in the ischemic area (in milliliters per minute per gram) was then computed and expressed as percentage of MBF in the nonischemic region.

Statistical Analysis
Differences between baseline measurements and subsequent values were assessed by repeated-measures ANOVA. Standard linear regression analysis was used to relate changes in myocardial velocities to SS or segment lengthening. Polynomial regression analysis was used to study the relationship between systolic velocities and regional MBF. Myocardial velocities and MBF data (expressed as fractions of control values) obtained from 11 measurements in eight pigs were compared by use of the nonparametric Spearman test because of the small sample size. All values are presented as mean±SE. A value of $P<.05$ was considered to indicate a statistically significant difference.

Results
Nine pigs were entered into the present study. Each animal underwent 1 to 5 episodes of either partial stenosis or total occlusion of the LAD, each separated by an intervening reperfusion period. The total duration of these ischemic events averaged 6±2 and 6±1 minutes, respectively. This design allowed us to record 59 matched measurements of DTI velocities and segment lengths among the nine animals.

### Hemodynamics and Regional MBF

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Stenosis</th>
<th>Occlusion</th>
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<tbody>
<tr>
<td>HR, bpm</td>
<td>146±7</td>
<td>131±4</td>
<td>130±4</td>
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<tr>
<td>SBP, mm Hg</td>
<td>94±4</td>
<td>88±5</td>
<td>84±4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>61±4</td>
<td>58±5</td>
<td>56±3</td>
</tr>
<tr>
<td>MBF, mL·min$^{-1}$·g$^{-1}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic zone</td>
<td>0.90±0.19*</td>
<td>0.11±0.03*</td>
<td></td>
</tr>
<tr>
<td>Nonischemic zone</td>
<td>1.58±0.19</td>
<td>1.44±0.35</td>
<td></td>
</tr>
</tbody>
</table>

HR indicates heart rate; SBP, systolic blood pressure; and DBP, diastolic blood pressure. All values are expressed as mean±SE. * $P<.05$ vs nonischemic zone MBF.

### Normal Pattern of Midseptal Wall Velocities
In the open-chest pig under baseline conditions, pulsed DTI of midseptal wall velocities displayed five consecutive waves whose directions varied according to the phase of the cardiac cycle. During systole, two positive waves occurred, one positive and short wave corresponding to the isometric contraction ($V_{IC}$) (starting at the beginning and ending at the end of the QRS complex) and one single ogival wave corresponding to LV ejection ($V_s$) (starting at the end of the QRS complex and ending at the end of the T wave). During diastole, one positive and two negative waves were sequentially observed: a positive isometric relaxation wave ($V_{IR}$) followed by a negative early ($V_e$), rapid-filling wave and a negative late-filling ($V_{A}$) wave corresponding to atrial contraction.

In the five pigs that underwent pulsed DTI analysis before thoracotomy, similar sequential events were observed, but in all cases, the IR wave was negative instead of positive (Fig 1). In addition, peak systolic velocity values were slightly but significantly higher than in open-chest preparations (Table 2). Myocardial velocities obtained in the open-chest preparations were used as control values for further comparison during LAD occlusion.
Time Sequence and Pattern of Myocardial Velocity Changes During Ischemia/Reperfusion

The time to onset of regional myocardial velocity abnormalities in the ischemic myocardium is presented for the first 60 seconds for 10 episodes of total LAD occlusion in eight pigs (Fig 3). Within 5 seconds of occlusion, systolic velocities (VS) in the ischemic segment decreased to 46% of baseline values (P<.0001). Systolic velocities became negative at 30 seconds and peaked at 1 minute of occlusion. These negative velocities corresponded to the paradoxical expansion of the ischemic segment observed on sonomicrometry tracings (Figs 2 and 4). This early decrease in VS was associated with a simultaneous increase in velocities during both isometric systole (V_IC) and isometric (V_IR) relaxation (Fig 3). Velocity during isometric relaxation progressively increased and peaked at 1 minute after coronary artery occlusion (Fig 3). At 1 minute after reflow, VS and V_IR exhibited a transient positive and negative peak, respectively, corresponding to the hyperemic phase (Fig 3). Within 5 minutes of reperfusion, VS progressively decreased, whereas V_IR increased and appeared as a positive wave as reperfused myocardium developed postischemic stunning (Figs 3 and 4).

Diastolic abnormalities also occurred very quickly after the onset of ischemia. Immediately after LAD occlusion, VE significantly decreased, and VA increased (Fig 4). As a consequence, VE/VA ratio decreased and further remained stable until reperfusion (Fig 3). VE/VA peaked at 1 minute after reflow (hyperemic response) and thereafter returned nearly ischemic values as diastolic alterations of myocardial stunning appeared on segment length recordings.

In five pigs, we also measured velocities in the remote nonischemic lateral wall during ischemic episodes induced by partial stenosis of LAD. Ischemia in the LAD territory did not significantly alter systolic or diastolic velocities in the lateral wall: VS averaged 8.9±0.6 versus 9.1±0.6 cm/s at baseline (P=NS) and VE/VA averaged 1.3±0.5 versus 1.3±0.4 at baseline (P=NS).

### Table 2. Comparison of Myocardial Velocities (cm/s) Within Mid Septal Wall in Pigs Before and After Surgery

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>Open Chest</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>V_IC</td>
<td>3.5±1.5</td>
<td>3.6±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>V_S</td>
<td>9.2±0.6</td>
<td>8.4±0.6</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>V_IR</td>
<td>−2.9±1.2</td>
<td>3±2.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>V_E</td>
<td>−17.6±0.9</td>
<td>−7.9±1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>V_A</td>
<td>−7.2±2.2</td>
<td>−9±1.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>V_E/VA</td>
<td>2.63±0.3</td>
<td>1.2±0.4</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

V indicates velocity; IC, isometric contraction; S, systole; IR, isometric relaxation; E, early diastole; and A, atrial contraction. All values are expressed as mean±SE, and velocities are given in centimeters per second.

Figure 3. Graph of the sequential changes during a brief total occlusion of LAD on systolic and isovolumic relaxation velocities (left) and on diastolic velocities (right). Ten episodes of brief total occlusion of LAD were performed in 8 pigs. Immediately after LAD occlusion, early and significant decrease of systolic ejection velocities (V_S) was associated with the increase of velocities during isometric relaxation (V_IR), the decrease of early diastolic velocities (V_E), and the increase of late diastolic velocities (V_A), leading to a significant decrease in the ratio V_E/VA. After 1 minute of occlusion, V_S became negative whereas V_IR markedly increased. Immediately after reperfusion, V_S returned positive and recovered to a significant higher value than at baseline. However, within 3 minutes of reperfusion, V_S decreased again, whereas V_IR increased, identifying myocardial stunning. *P<.05 vs baseline; **P<.01 vs baseline; ***P<.001 vs baseline.
Comparison Between DTI Velocities and Wall Motion Abnormalities

To evaluate whether the severity of ischemia could be accurately predicted by DTI, the individual systolic velocity and diastolic $V_e/V_A$ ratio (both expressed as a percentage decrease from baseline) were plotted versus corresponding modifications in segment length. There was a significant correlation between the variations of systolic velocity ($V_S$ %) and those of SS: $V_S$ % = $0.78(\text{SS}) + 10.6$ ($r = 0.90$, $P < 0.0001$; Fig 5). This strongly supports that the DTI measurement of $V_S$ accurately quantifies the ischemia-related regional wall motion abnormalities. The diastolic ratio $V_e/V_A$ also showed a significant correlation with late diastolic lengthening, but the relationship was weak ($r = 0.39$, $P = 0.0049$) (Fig 6).

Comparison Between DTI Velocities and Regional MBF

Eleven measurements of regional MBF were obtained in eight pigs and plotted versus simultaneous myocardial systolic velocities (Fig 7).

The relationship between the decrease in MBF (MBF%) and in systolic velocity ($V_S$ %) was best fitted by a polynomial expression according to the following equation: $V_S$ % = $-0.004 \text{ MBF}^3 + 1.73 \text{ MBF} % - 49.14$ ($r = 0.96$; Fig 7A).

A similar correlation existed between SS and MBF%, but this relationship was best fitted by a linear regression equation (Fig 7B).

Myocardial function became severely depressed when MBF decreased <40% of baseline values.

Discussion

In the present study, we report for the first time that pulsed DTI can identify and quantify myocardial wall velocities during regional ischemia and reperfusion. As demonstrated by concomitant measurement of wall motion by sonomicrometry and assessment of regional MBF by the radioactive microsphere technique, pulsed DTI appears to be accurate and reproducible.

DTI is a new echocardiographic method based on the Doppler principle, which provides a velocity map of the myocardial wall.\textsuperscript{17–19} DTI velocity maps are available by use of two-dimensional imaging and M-mode and pulsed-wave Doppler. Low frame rates available from two-dimensional acquisition associated with the Doppler angle of insonation of the myocardium preclude two-dimensional DTI for measurement of rapid myocardial velocity changes. M-mode DTI interrogation of intramural velocities overcomes the temporal resolution problems inherent with the two-dimensional approach and allows the assessment of endocardial to epicardial velocity gradient.\textsuperscript{24,25} But it needs the development of special programs for off-line analysis because M-mode quantification of velocities is not yet available on our ultrasound system. Pulsed-wave DTI provides quantitative information available on-line and was therefore used in this study to analyze septal wall velocity resulting from long-axis shortening of the heart and its variations after LAD occlusion.
mitral annular and Isaaz et al.28 within the LV posterior wall. velocities was described by Rodriguez et al.26,27 within the recordings of midseptal velocities. The same pattern of the cardiac cycle, can be described for the first time from velocity measurement.

In the present experimental preparation, five waves of wall velocity, including two systolic and three diastolic events of the cardiac cycle, can be described for the first time from recordings of midseptal velocities. The same pattern of velocities was described by Rodriguez et al.26,27 within the mitral annular and Isaaz et al.28 within the LV posterior wall.

Normal Patterns of Regional LV Wall Motion and Velocities

Understanding of the normal pattern of myocardial wall movement is necessary for comprehensive assessment of DTI. The complex overall motion of the heart can be divided into three different types of movements: circumferential contraction assessed by short-axis view interrogation, longitudinal contraction assessed by long-axis view, and rotation. The translation of the whole heart also affects the measurement of actual wall velocities, especially in the short-axis view. In the present study, a long-axis recording of mid septal velocities was preferred to a short-axis view to avoid the large incidence angle between the direction of the circumferential septal wall motion and that of the Doppler beam. Indeed, in the short-axis view, a part of the myocardium, particularly the septal or the lateral wall, moves perpendicularly toward the Doppler beam and does not allow accurate myocardial velocity measurement.

In the present experimental preparation, five waves of wall velocity, including two systolic and three diastolic events of the cardiac cycle, can be described for the first time from recordings of midseptal velocities. The same pattern of velocities was described by Rodriguez et al.26,27 within the mitral annular and Isaaz et al.28 within the LV posterior wall.

Both sets of authors reported a good correlation between myocardial velocities derived from M-mode tracings and DTI measurements. However, the determination of myocardial velocities by M-mode appeared difficult, time-consuming, and poorly reproducible, which might explain why M-mode echocardiography has been considered an unreliable tool for assessment of regional wall function.29

It is worth noting that velocity of isometric relaxation shifted from negative to positive values when the chest was opened. Although we did not specifically investigate this issue, we speculate that it may be related to modifications of the transeptal interaction between the two ventricles, secondary to reduction of loading conditions and pericardectomy in the open-chest preparation.30

Detection and Quantification of Ischemia-Related Wall Motion Abnormalities by DTI Velocities

To investigate whether pulsed DTI could accurately identify and quantify the alterations of myocardial wall motion induced by ischemia, we compared the changes in velocities to those in segment lengths as measured by the reference method, ie, sonomicrometry.21 Within 15 seconds of coronary occlusion, systolic contraction decreased and resulted in passive bulging of the myocardium in case of severe ischemia. As expected, these modifications of systolic wall motion were also significantly correlated with the reduction of regional MBF as measured by the radioactive microsphere technique.31–33 Simultaneous diastolic dysfunction developed with a rapid increase in EDL and LDL.34

Our DTI data are in close agreement with these observations. Pulsed DTI was able to detect significant systolic and diastolic velocity changes as soon as 5 seconds after LAD occlusion, a time frame comparable to those reported when sonomicrometry was used.31–33 Systolic velocity during the ejection phase was well correlated with segment shortening, whatever the severity of ischemia. During isometric relaxation, velocity became positive and markedly increased. This paralleled post–SS observed on segment length recordings and suggests an asynchrony in myocardial contractility as previously reported by Gibson et al.35 in patients with coronary artery disease. Early diastolic velocity decreased and late diastolic velocity increased, resulting in an inversion of the $V_s/V_a$ ratio. Its correlation with LDL, as described with sonomicrometry, was statistically significant but obviously much weaker than analysis of the systolic pattern. The reason for the poor correlation between diastolic indexes is unclear but might be related to the complex translation/rotation of the heart during the cardiac cycle. It might also be related to the fact that DTI analyzed septal wall motion, which is affected by right ventricular pressures whose influence is likely more important in diastole.

Although $V_s$ slightly overestimated the degree of regional wall motion abnormalities, it appears to be a useful index for assessment of regional wall motion impairment related to severe, moderate, or even mild ischemia. This was also confirmed by the correlation of ejection systolic velocity and regional MBF. Even slight reductions in regional MBF were associated with a decrease in both myocardial velocities and segment shortening. We observed that ejection systolic ve-
locity became negative for a reduction in MBF reaching 40% of baseline values, which is also associated with the onset of regional bulging as previously described.22

Interestingly, pulsed DTI was able to identify the hyperemic response after reperfusion of the ischemic myocardium. Although this transient increase in regional contractile function is usually short-lived, its identification may be useful as an indicator of reperfusion in the setting of acute myocardial infarction. When postischemic contractile dysfunction (“myocardial stunning”) developed despite restoration of a normal (or nearly normal) MBF, pulsed DTI clearly identified wall motion abnormalities similar to those observed during ischemia.30–38 In other words, as expected, pulsed DTI (as any other technique) failed to distinguish ischemia from reperfusion-induced contractile dysfunction. With respect to this, estimation of myocardial perfusion through measurement of myocardial wall velocities must be done cautiously and is valid only in situations of ischemia but not reperfusion.

Potential Clinical Implications

There are major potential clinical implications to the use of pulsed DTI. In particular, we currently lack a reliable technique to accurately quantify regional contractile function in humans. Contrast and radionuclide ventriculography and conventional two-dimensional echocardiography only allow semiquantitative evaluation of LV function. Today, only cine MRI can quantify wall motion, but it is not easily accessible for a large number of patients. Pulsed DTI appears to be a sensitive, reproducible, accurate, noninvasive echographic technique that may become a very useful clinical tool for the diagnostic, follow-up, and evaluation of the prognosis of cardiac diseases. Whereas effective clinical application of DTI was hampered by low acquisition frame rates and a lack of postprocessing software, a new third generation of Doppler myocardial imaging system, with high temporal and spatial resolution, has been developed that allows real-time acquisition with subsequent on-line analysis of regional mean velocities. This new system has recently been shown to provide reproducible and accurate quantification of LV circumferential and longitudinal contraction in all myocardial segments and therefore will allow stress echocardiography to be quantified.29,39 However, further studies are needed to determine whether data in this experimental preparation can be extrapolated to human patients.

Study Limitations

Because of the version of the ultrasound machine used in this study, we could not record simultaneously DTI velocities and two-dimensional regional wall motion abnormalities. The DTI velocity measurements were performed in the middle part of the interventricular wall septum, whereas segment length data were recorded from the anterior wall. However, these two regions are supplied by the LAD; moreover, the middle part of the interventricular wall septum was clearly included in the area at risk as shown by the Uniposer Blue Pigment injection in the heart slices. It is therefore likely that wall motion abnormalities in the septum were comparable to those observed in the anterior wall.

DTI measurements, as any other method assessing myocardial excursion, are affected by cardiac translation and/or rotation. Nonetheless, the correlation with segment length measurements (that are poorly influenced by cardiac translation) is good (r = .90), suggesting that movements of the heart did not dramatically alter DTI measurements.

Conclusions

DTI is a new, accurate, sensitive, noninvasive tool to quantify on-line systolic and diastolic ischemia-induced myocardial dysfunction. It appears to be a promising method to quantify regional wall motion abnormalities in the setting of ischemic heart disease.

References


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