Demonstration of Functional Border Zone With Myocardial Contrast Echocardiography in Human Hearts

Simultaneous Analysis of Myocardial Perfusion and Wall Motion Abnormalities

Shinsuke Nanto, MD; Tohru Masuyama, MD; Young-Jae Lim, MD; Masatsugu Hori, MD; Kazuhsa Kodama, MD; and Takenobu Kamada, MD

Background. Although the presence of a functional border zone (FBZ), defined as the nonischemic but asynergic myocardium adjacent to the ischemic area, has been demonstrated in animal hearts, it is not known whether this zone exists in humans.

Methods and Results. Myocardial contrast echocardiography (MCE) was performed before and during balloon inflation in the area of coronary stenosis by injecting contrast medium through the guiding catheter in 13 patients with effort angina who underwent successful coronary angioplasty. The area showing MCE defect during balloon inflation was determined with reference to the preangioplasty MCE and was regarded as an ischemic area. The size of the FBZ was assessed by measuring the length of the endocardium that showed asynergy in the echo-enhanced (nonischemic) area. The FBZ measured 13±4 mm in the short-axis view (n=5) and 16±9 mm in the long-axis view (n=8).

Conclusions. Nonischemic contractile dysfunction exists even in human hearts. The presence of an FBZ may limit the use of wall motion analysis in assessing the risk or ischemic area in patients with myocardial infarction. MCE appears to be a unique technique for assessing the risk or ischemic area. (Circulation 1993;88:447-453)

KEY WORDS • echocardiography • ischemia

The size of the damaged or ischemic area is estimated by measuring the abnormal contractile area by two-dimensional echocardiography or left ventriculography on the assumption that the dyskinetic area is equivalent to the malperfused area. However, several animal studies have demonstrated the presence of nonischemic regional dysfunction at the lateral borders of the damaged or ischemic myocardium.1-13 The term "functional border zone" (FBZ) was recently introduced8,9 to identify such myocardium. The existence of an FBZ would explain the disparity between the regional wall motion and the pathological infarct size in animal and clinical studies.14,15 If the FBZ does exist, the malperfused area could not be precisely assessed from the extent of the abnormal contractile segment.

Although previous investigators have demonstrated that contractile dysfunction, measured with sonomicrometers or by two-dimensional echocardiography,9 extended 25° to 30° of circumference into the nonischemic myocardium during occlusion of the circumflex artery in animals, the FBZ has not been evaluated in humans in vivo. Myocardial contrast echocardiography (MCE) is considered to be a readily repeatable, accurate, and real-time method for measuring the size of the abnormal regional myocardial perfusion.16-20 Furthermore, MCE allows us to simultaneously delineate the border between the ischemic and the nonischemic myocardium and evaluate left ventricular wall motion. We evaluated the existence of an FBZ in human hearts by comparing perfusion and wall motion abnormalities in myocardial contrast echocardiograms during occlusion of the coronary artery. Specifically, myocardial contrast echocardiographic measurements of left ventricular wall motion and myocardial perfusion were made before and during occlusion of the coronary artery in patients undergoing percutaneous transluminal coronary angioplasty (PTCA).

Methods

Subjects

Thirty-two consecutive patients with angina pectoris who underwent PTCA in the left anterior descending coronary artery were considered for inclusion in this study. Thirteen patients with prior myocardial infarction were excluded from the study. The remaining 19...
patients were randomized into two groups for a study of the short-axis view and the long-axis view. Five patients with inadequate two-dimensional echocardiographic images obtained just before angioplasty and one patient with an unsuccessful PTCA were excluded from this study. Thus, the study population consisted of 13 patients with narrowing in the left anterior descending coronary artery (Table 1). The short-axis view was studied in 5 patients and the long-axis view in 8 patients. All patients gave informed written consent for both balloon angioplasty and study participation.

**Angioplasty**

Nitrates and calcium channel antagonists were continued in all patients, but none were receiving β-blockers. Hydroxyzine (50 mg) and atropine sulfate (0.5 mg) were given routinely before catheterization. Before the angioplasty, heparin (200 U/kg) was administered intravenously. Coronary dilation was performed with the usual angioplasty balloon catheter system by the femoral approach. Lesions were dilated with angioplasty balloon catheters of the appropriate size (2.5 to 3.5 mm in diameter). Several balloon inflations (two to four inflations with 6 to 10 atm for 60 seconds each) were performed. Dilation was concluded when adequate improvement of the lesion (<50% narrowing) was obtained.

**Myocardial Contrast Echocardiographic Study**

After the successful PTCA, the deflated balloon catheter was kept in the coronary artery, and we obtained two-dimensional echocardiographic images of the long-axis view or the parasternal short-axis view at the midpapillary muscle by use of a commercially available phased-array system (model SSH-160A ultrasound system, Toshiba Corp, Japan) with a 3.8-MHz transducer. Echocardiographic images were recorded with a videotape recorder (model BR 6400, Victor Corp, Japan) when amidotrizoate sodium meglumine (Urografin-76), hand-agitated during its passage through a three-way stopcock, was injected into the left coronary artery via the guiding catheter.

After the control study, MCE was repeated during balloon inflation. Echocardiographic images were recorded beginning 10 seconds before balloon inflation. After 30 seconds of inflation, MCE was performed in the same manner as in the control study. After inflation for 1 minute, the balloon was deflated. The gain setting was adjusted at the beginning of each recording and was not changed during the recording. Levels of serum creatine phosphokinase, creatine phosphokinase-MB, glutamic oxaloacetic transaminase, and lactate dehydrogenase were measured before and at 8 and 48 hours after cardiac catheterization.

**Echocardiographic Analysis**

All of the following echocardiographic analyses were performed by an observer blinded to the hypothesis of the study. Wall motion abnormality was assessed by comparing the endocardial edge of the left ventricle in the control MCE with that during balloon inflation. The endocardial edge of the left ventricle was traced manually with a joy stick–controlled cursor in the end-systolic echocardiographic image of the control MCE obtained at the T-wave termination of the ECG. The endocardial edge was also traced in the end-systolic MCE images during balloon inflation. MCE images with the traces on them were printed out with the strip chart recorder and were superimposed on each other (Figs 1 to 3). The superimposition of the traces of endocardial edge were performed with reference to the aortic root in the long-axis analysis and to the papillary muscle in the short-axis analysis. Separation between the two lines was observed only in the PTCA-related area. Thus, the separating point of these lines was defined as the ends of the wall motion abnormality. Note that end-systolic images at control and during balloon inflation, rather than end-systolic and successive end-diastolic images, were compared to determine the PTCA-induced wall

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**Table 1. Characteristics of 13 Patients With Effort Angina**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Narrowing of LAD (%)</th>
<th>Collaterals</th>
<th>Ejection fraction (%)</th>
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<tbody>
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<tr>
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<td>50</td>
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<td>59</td>
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<td>56</td>
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<tr>
<td>3*</td>
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<td>Male</td>
<td>97</td>
<td>Yes</td>
<td>58</td>
</tr>
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<td>Male</td>
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<td>77</td>
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<td>94</td>
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<td>63</td>
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<td>45</td>
<td>Male</td>
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</tr>
<tr>
<td>8</td>
<td>77</td>
<td>Female</td>
<td>87</td>
<td>None</td>
<td>63</td>
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</table>

Mean±SD | 59±11 | 90±5 | 70±7 |

LAD, left anterior descending coronary artery.
*Denotes a patient with saphenous vein graft to the diagonal artery and the left circumflex artery.
motion abnormalities in this study. FBZ was defined as the area between the separating point and the interface between the echo-enhanced and the nonenhanced areas in the MCE obtained during balloon inflation, since this area was considered nonischemic but dysfunctional. FBZ in the septum was evaluated in the long-axis images (Fig 2), and that in the lateral wall in the short-axis images (Fig 3).

Interobserver and Intraobserver Variability

Ten pairs of control MCE images and MCE images obtained during balloon inflation were randomly selected for the analysis of interobserver and intraobserver variability of the measurements of FBZ length. Five pairs were each selected from the short- and long-axis studies. Intraobserver variability was determined by one observer making duplicate measurements. Interobserver variability was determined by another observer making a single set of measurements. Both observers were blinded to the patient data, the hypothesis tested, and the results of the other observer. The means and SDs of differences between observations were 0.4±2.0 mm (intraobserver variability) and 1.0±2.6 mm (interobserver variability) for the short-axis view and 0.3±1.5 mm (intraobserver variability) and −1.0±1.9 mm (interobserver variability) for the long-axis view. There was no statistically significant difference between observations.

In addition to the reproducibility of the measurements of FBZ size, we assessed the reproducibility of analysis of echocardiographic wall motion and myocardial contrast echocardiograms in the same 10 pairs of echocardiograms (five short-axis and five long-axis images). In terms of the reproducibility of analysis of wall motion abnormalities, the length between the ends of abnormal wall motion was measured by two independent observers (interobserver variability). The differences between observations were 0.2±2.9 mm for the short-axis view and 0.2±2.1 mm for the long-axis view. There was no statistically significant difference between observations. In terms of the reproducibility of the analysis of myocardial contrast echocardiograms, the length between the interfaces between the contrast-enhanced and nonenhanced areas was measured by two independent observers. The differences between observations were 0.3±1.2 mm for the short-axis view and 0.2±1.0 mm for the long-axis view. There was no statistically significant difference between observations.

Statistical Analysis

All data are expressed as mean±SD. Student’s unpaired t test was used to compare the size of FBZ between the short-axis and the long-axis views. The difference between two observations done to assess reproducibility was tested with Student’s paired t test. A level of P<.05 was accepted as statistically significant.

Results

The narrowed coronary arteries in the 13 patients were successfully dilated from 90±5% occlusion to 23±12% occlusion by PTCA. MCE was performed without any trouble, and none of the patients showed an abnormal elevation of cardiac enzymes after angioplasty.

In the control study, the anteroseptal wall motion was normal in 11 patients and hypokinetic in 2 patients. Balloon inflation caused akinetic wall motion in 9 patients and hypokinetic motion in 4 patients.

Both the anteroseptal and posterolateral regions were well opacified in the control MCE study, and no contrast defect was observed. In the MCE observed during balloon inflation, the anteroseptal region was not opacified, but good opacification was obtained in the posterolateral region. The perfusion boundary was somewhat irregular; however, peninsulas in the interface between the enhanced and the nonenhanced regions were within a few millimeters except for one case (patient 2 of short-axis study in Table 2). In this patient, MCE with balloon inflation showed good enhancement in the subendocardial half but poor enhancement in the subepicardial half, which accounts for the peninsula of about 9 mm in the subendocardial site in this patient.

The FBZ measured was 13±4 mm and 35±19° in circumference in the five patients in whom short-axis images were analyzed and 16±9 mm in the eight patients in whom long-axis images were analyzed. There were no significant differences between these values.

Discussion

Our results clearly demonstrated the existence of a substantial area of abnormal wall motion in the nonischemic area, thus verifying the existence of the FBZ in human hearts.

Myocardial Contrast Echocardiogram

MCE can be used to evaluate the perfusion area and wall motion abnormalities simultaneously. The size of the defect area in MCE correlated well with the size of the malperfused area21,22 and of the necrotic area.22 Sakamaki et al21 reported that the perfusion defect
assessed by contrast echocardiography was correlated with the deficiency in perfusion delineated by Monostral blue dye ($r = .91$), although it slightly overestimated the extent of necrosis measured by triphenyl tetrazolium chloride. MCE is a readily repeatable, accurate, and real-time method of measuring the extent of abnormal regional myocardial perfusion during acute coronary occlusion similar to the microsphere methods used in animal experiments. Another advantage of MCE is that wall motion and myocardial perfusion can be analyzed in the same image. We used these advantages to demonstrate the existence of FBZ by evaluating the wall motion and myocardial perfusion in the same image.

Functional Border Zone

This article is the first description of FBZ in human hearts. Although there are no comparable in vivo data in human hearts, two studies have implied the existence of FBZ in autopsied hearts.$^{23,24}$ The FBZ has been demonstrated$^{10,11}$ in animal hearts by sonomicrometry. Kaul et al.$^{25}$ using the methods we used, reported a discrepancy between the extent of abnormal wall motion and the area at risk in dogs.

We found the FBZ to measure $16 \pm 9$ mm in the long-axis view and $13 \pm 4$ mm ($35 \pm 19\%$) in the short-axis view. The size of the FBZ has previously been evaluated only in dogs. Buda et al.$^{10}$ and Force et al.$^{17}$ used two-dimensional echocardiography to evaluate the extent of nonischemic dysfunction after circumflex coronary occlusion. Buda et al.$^{10}$ reported that the dysfunction extended approximately $25\%$ beyond one lateral margin of the ischemic area. In similar fashion, Force et al.$^{17}$ demonstrated that regional wall thickening recovered to normal levels within 8 to 9 mm from the perfusion boundary. Buda et al.$^{16}$ used two-dimensional echocardiography to evaluate circumferential flow-function relations in conscious dogs and found an FBZ averaging $27\%$ at one lateral margin of the ischemic area early after occlusion of the circumflex coronary artery. In similar fashion, Gallagher et al.$^{13}$ reported that the FBZ measured by sonomicrometry was $32\%$ and $28\%$ of circumference at 10 minutes and 3 hours, respectively, after occlusion. Thus, our results on the size of FBZ in humans agree well with the animal data.

Regional variations in FBZ were studied by comparing the length of the FBZ in the posterolateral wall in the short-axis image with that in the septum in the long-axis image. We found no significant difference in the length of FBZ between the posterolateral wall and the septum, suggesting little, if any, variation in the length of FBZ. However, the short- and long-axis images were not analyzed together in any one patient. Also, FBZ has not been studied in other regions. Thus, future studies are needed to fully clarify the regional variations in FBZ size. Thus, we will not emphasize our results concerning the regional variations in the size of FBZ, partially because there is no reason to indicate the absence of FBZ in other sites.

**Figure 2.** Representative myocardial contrast echocardiographic images of the long-axis view obtained at control (left panel) and during coronary occlusion (right panel) in patient 9 (Table 1). Thick lines represent endocardial edges determined in each image. Thin line in the right image is the superimposed line that represents the endocardial edge determined in the control study. Arrow in right panel indicates the ends of the functional border zone.
Possible Mechanism of Nonischemic Dysfunction

This has been discussed previously.4,7-9,11,27,28 Bogen et al27 considered the FBZ to be a mechanical phenomenon that is dictated by the geometry of the left ventricle and the relative levels of stiffness in ischemic and nonischemic areas but that is unrelated to flow restriction or relative ischemia. The similarity of the FBZ obtained in open-chest, anesthetized, and conscious dogs, despite substantial hemodynamic differences between the two types of preparations, supports this view.

### Table 2. Functional Border Zone and Left Ventricular Wall Motion Before and During Balloon Inflation in Myocardial Contrast Echocardiograms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Functional border zone</th>
<th>Anteroseptal wall motion</th>
<th>LVSP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Length (mm)</td>
<td>Degree</td>
<td>Control</td>
</tr>
<tr>
<td>Short-axis study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>43</td>
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</tr>
<tr>
<td>2</td>
<td>12</td>
<td>45</td>
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</tr>
<tr>
<td>3</td>
<td>9</td>
<td>21</td>
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<tr>
<td>4</td>
<td>13</td>
<td>56</td>
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</tr>
<tr>
<td>5</td>
<td>19</td>
<td>9</td>
<td>Normal</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>13±4</td>
<td>35±19</td>
<td></td>
</tr>
<tr>
<td>Long-axis study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Reduced</td>
<td>Severely reduced</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>Normal</td>
<td>None</td>
</tr>
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<td>5</td>
<td>16</td>
<td>Normal</td>
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</tr>
<tr>
<td>6</td>
<td>25</td>
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<td>5</td>
<td>Reduced</td>
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</tr>
<tr>
<td>8</td>
<td>18</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>16±9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LVSP, left ventricular systolic pressure.
There is little evidence for a zone of intermediate blood flow surrounding the ischemic area. Perfusion may be intermediate in the tissue samples at the lateral margins of the ischemic area because this tissue contains the interdigitation peninsulas of the ischemic and normally perfused myocardium that characterize the ischemic/nonischemic interface.\textsuperscript{29-33} In our study, the perfused-to-nonperfused interface that was detected with MCE also showed these interdigitation peninsulas. However, the extent of FBZ was obviously larger than that of the peninsulas except for one patient in whom intermediate perfusion was an important cause of FBZ. This finding strongly supports the mechanical phenomenon theory. Likewise, the boundary of biochemical abnormalities is also abrupt,\textsuperscript{34-36} reinforcing the view that nonischemic dysfunction is not caused by relative ischemia in the area corresponding to FBZ.

The mechanical alternatives proposed to explain nonischemic dysfunction include tethering\textsuperscript{7,8,11} and stress concentration\textsuperscript{27,28} at the ischemic margin. In the absence of a rigorous definition, the concept of tethering cannot be readily tested or distinguished from mechanical explanations such as stress concentration. Because the distribution of stress concentration\textsuperscript{27} appears to correspond well to the distribution of wall thickening impairment, Gallagher's\textsuperscript{5,13} view of elevated stress at the ischemic/nonischemic interface remains the most likely possibility. However, additional investigation is required to substantiate its role in the phenomenon of nonischemic dysfunction.

Limitations

Although the position of the transducer was not changed in our study, the endocardial edges of the normally perfused area in the control study and those during balloon inflation may have been at the different positions because of changes in left ventricular geometry. However, a change in position was not felt to be significant in this study because of the short duration of coronary occlusion and because we excluded patients with severely depressed ventricular function from investigation.

In contrast to the animal studies, we assessed contractile dysfunction by analyzing the wall motion rather than wall thickening. It is considered that wall motion abnormalities are more extensive than wall thickening abnormalities. However, FBZ cannot be fully explained solely by the difference between the extent of the abnormalities in wall motion and wall thickening.

Clinical Implications

Cardiac performance is an important determinant of the prognosis of patients with ischemic heart diseases. It is assessed in the clinical setting by determining the extent of the myocardial perfusion abnormality. Information on the precise area of myocardial ischemia would help in determining the treatment strategy. When an abnormal contractile area determined by echocardiography or left ventriculography is used to assess the malperfused area, one should remember the possibility of underestimating the extent of the viable myocardium.

In this study, the FBZ was evaluated during acute and transient ischemia. It is important to measure the risk area particularly in the evaluation of reperfusion therapy. The risk area should be determined with perfusion images, because we found an overestimation of the use of wall motion abnormality. The use of \textsuperscript{99m}Tc-Sestamibi has recently been found useful in estimating the risk area in both animal models and clinical studies.\textsuperscript{37-39} The risk area or the infarct area can be measured only by myocardial perfusion imaging methods.

Conclusions

Areas of nonischemic contractile dysfunction exist in human hearts. Their size is so large that we should not ignore them when using an abnormality in wall motion to assess a perfusion abnormality.

Acknowledgments

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References


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