Two-dimensional Echocardiography in Experimental Coronary Stenosis

I. Sensitivity and Specificity in Detecting Transient Myocardial Dyskinesis: Comparison with Sonomicrometers

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SUMMARY The purpose of this study was to assess the sensitivity and specificity of two-dimensional echocardiography in detecting ischemia-induced transient myocardial dyskinesis. We prepared an open-chest dog model of severe coronary stenosis (90% reduction of circumflex coronary artery diameter) and induced ischemia by acutely raising myocardial oxygen requirements with i.v. isoproterenol and acute aortic constriction. The changes observed with echocardiography were compared with those obtained by intramyocardial sonomicrometers placed side by side or in an endocardial-epicardial orientation. Ischemia was defined as systolic wall expansion or thinning on sonomicrometers and two-dimensional echocardiography. We found complete agreement between sonomicrometers and two-dimensional echocardiography in all control tracings and after ischemia was induced; whenever dyskinesis occurred it was seen by both techniques. Although there was qualitative agreement between echocardiographic and sonomicrometric techniques, there were quantitative differences in the assessment of wall thickening. Such differences may be related to malalignment of the sonomicrometers, echocardiographic resolution limitations or other technical factors. We conclude that two-dimensional echocardiography is a sensitive and specific technique for detecting transient myocardial ischemia, and therefore should be useful for demonstrating exercise-induced ischemia in patients with coronary artery disease.

TWO-DIMENSIONAL echocardiography can demonstrate resting cardiac wall motion abnormalities after clinical and experimental myocardial infarction. However, coronary artery disease in the absence of myocardial infarction may not be associated with resting abnormalities. Instead, contraction abnormalities may occur only transiently, such as during stress-induced ischemia. Whether two-dimensional echocardiography is sensitive and specific in demonstrating contraction abnormalities during transient ischemia has not been established.

The goal of this investigation was to determine the sensitivity and specificity of two-dimensional echocardiography in detecting transient ischemia in coronary stenosis. Therefore, we compared the ability of two-dimensional echocardiography to detect ischemia-induced contraction abnormalities with an independent standard, ultrasonic sonomicrometers, in a canine model of severe coronary stenosis.

Methods

Model of Coronary Stenosis

Ten dogs that weighed 20–35 kg were anesthetized with i.v. chloralose (100 mg/kg) and urethane (1000 mg/kg) and the carotid arteries were ligated. The left subclavian artery was catheterized with a 10-mm balloon-tipped catheter. The balloon tip was positioned in the left circumflex artery, and intracoronary injection of heparin (4000 units) was performed 15 minutes before coronary artery occlusion.

Coronary artery occlusion was performed by balloon inflation for 15 minutes, followed by balloon deflation for 3 minutes. The coronary occlusion was repeated three times, with each balloon inflation lasting 15 minutes. After each balloon inflation, the dog was allowed to stabilize for 15 minutes before the next balloon inflation. During the stabilization period, the dog was maintained on a respirator with a 50% oxygen mixture.

After the third balloon inflation, the dog was allowed to stabilize for 30 minutes. During this period, the dog was maintained on a respirator with a 50% oxygen mixture.

After the stabilization period, the dog was allowed to stabilize for 15 minutes. During this period, the dog was maintained on a respirator with a 50% oxygen mixture.

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mg/kg), intubated with a cuffed endotracheal tube and ventilated with a Harvard respirator using room air and supplemental oxygen. Arterial blood gases were checked frequently and maintained in the physiologic range by adjusting respirator rate and tidal volume and by administering i.v. sodium bicarbonate. The chest was opened by a left thoracotomy, the left circumflex coronary artery was dissected free and a snugly fitting electromagnetic flow probe (Statham) was placed around it. Polyurethane catheters were placed in the aorta, femoral artery and inferior vena cava for pressure measurement and drug infusion. A silk snare was placed around the circumflex coronary artery proximal to the electromagnetic flow probe. Severe coronary stenosis was produced by the method of Folts et al. This method uses coronary constricting devices constructed of Lexan, a physiologically inert plastic. The constrictors are cylinders 3 mm long and have a v-shaped opening to one side. For the constrictor to be placed on a coronary artery, the vessel is dissected free from the epicardial surface. The tips of snap-ring pliers are inserted into the two holes in the constrictor and spread apart to open the “v” so that the vessel can be slipped into the constricting cylinder in a manner similar to the placement of an electromagnetic flow probe on a vessel. When released, the “v” closes, the cylinder completely encircles the blood vessel and a fixed area of stenosis results. Various degrees of coronary stenosis can be produced by using cylinders of different sizes. Folts et al. demonstrated that a cylinder causing a reduction in coronary artery diameter of approximately 70% abolished reactive hyperemia after a 20-second coronary occlusion. Reduction of the resting coronary blood flow to half was taken to indicate more severe coronary stenosis, approximately 90% reduction in coronary artery diameter. Using this relationship, we produced a 90% coronary stenosis in each dog.

Two-dimensional Echocardiographic Examination

After the constricting cylinder was placed on the circumflex coronary artery, the dogs were turned and a midsternal thoracotomy was performed. A two-dimensional echocardiographic transducer was placed directly on the pericardium overlying the right ventricle. The transducer was fixed to a rigid bar to minimize transmitted motion and the transducer orientation was adjusted to obtain an optimal two-dimensional short-axis image of the left ventricle at the papillary muscle level. Once fixed, the transducer was not moved during the interventions designed to induce ischemia.

Two-dimensional echocardiographic studies were performed using a Toshiba SSH-10A sonolayergraph. The imaging system was a 32-element, 2.4-MHz transducer array with a phased-array electronic beam steering through an 80° sector. Images were recorded on a videotape recorder for later slow-motion and stop-frame analysis. To analyze the images, endocardial and epicardial outlines of the left ventricle were traced on an acetate overlay at end-diastole (peak of the R wave of the ECG) and end-systole (smallest ventricular cavity) using real-time and slow-motion playback to identify borders. To ensure reproducibility, we arbitrarily selected the inner border of all echo interfaces for tracing.

With the junction of the right ventricular posterior wall endocardium and the interventricular septum as a landmark, a line was drawn to the farthest point on the opposite left ventricular epicardium; this line was a minor axis that divided the left ventricular short-axis section into two approximately equal halves (fig. 1). The midpoint of this line was identified, and with that as the center of the image, the whole ventricular short-axis cross section was divided into 12 segments by radii drawn 30° apart. Each region in the 30° sector contains a segment of left ventricular cavity and left ventricular myocardium. This process was performed on an end-diastolic image and then repeated at end-systole. The percent systolic thickening of the wall along each myocardial radius was calculated as

\[
\frac{\text{end-systolic thickness} - \text{end-diastolic thickness}}{\text{end-diastolic thickness}} \times 100.
\]

The percent thickening was calculated in all myocardial radii, and specific attention was given to the risk area. The risk area was defined as myocardial segments that showed wall thinning during an initial 20–30-second circumflex occlusion. Systolic wall thinning (negative thickening) never occurs in normal myocardium and indicates myocardial ischemia.

Sonomicrometers

We used sonomicrometers as an independent standard with which to compare echocardiograms. Pairs of miniature (2-mm diameter) 5-MHz ultrasonic crystals were implanted in the posterior left ventricular wall in the circumflex distribution, either side by side or in an endocardial-epicardial orientation as described by Sayama et al. When ultrasonic crystals are implanted side by side, they register segment length; in a transmural orientation, they register wall thickness (fig. 2). We used both orientations in this study. A 20–30-second circumflex coronary occlusion was performed to demonstrate dyskinesis and to verify that the sonomicrometers were in the ischemic area (fig. 3). The percent segment length shortening (\%ΔL) was calculated as

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

The percent wall thickening (\%ΔT) was calculated as

\[
\frac{\text{end-systolic thickness} - \text{end-diastolic thickness}}{\text{end-diastolic thickness}} \times 100.
\]

Systolic wall thinning is indicated by a negative \%ΔT and systolic expansion or bulging is indicated by a negative \%ΔL; either indicates ischemia. At the end of the experiment, the heart was dissected to verify the location and orientation of the crystals.

To induce ischemia in this model of severe coronary stenosis, we used i.v. isoproterenol (5–10 μg/min) to
increase the heart rate and contractility, and acute constriction of the proximal descending thoracic aorta to elevate the aortic pressure.

Experimental Protocol
In five of the 10 dogs, the sonomicrometer crystals were placed side by side; in the other five dogs, the crystals were placed in an endocardial-epicardial orientation. Two-dimensional echocardiographic and sonomicrometric recordings were first obtained in the control state with no coronary stenosis; recordings were continued during a 30-second complete circumflex occlusion to be sure that the sonomicrometer crystals were placed in the circumflex zone and demonstrated dyskinesis. After at least 15 minutes of recovery, the two-dimensional echocardiographic and sonomicrometric recordings were repeated during a 90% coronary stenosis and then again when isoproterenol and acute aortic constriction were simultaneously superimposed on 90% coronary stenosis to produce transient ischemia. We attempted to raise the heart rate by 15% with isoproterenol and the systolic blood pressure by about 10 mm Hg with aortic constriction. During each state of the experimental protocol, a representative cardiac cycle was chosen for echocardiographic tracing and analysis. All echocardiographic tracings were done by one observer; the sonomicrometric data were analyzed independently by another observer.

Data Analysis
The interventions were compared using analysis of variance to detect significant differences in the overall comparisons. Specific intergroup differences were assessed for significance using Duncan’s multiple-range test. All results are expressed as mean ± sd.

Results
Echocardiography
In the control state with no coronary stenosis, the mean percent thickening of the risk segments was 36%; all segments continued to show thickening despite severe coronary stenosis (90% reduction in vessel diameter). There was echocardiographic systolic thinning during the initial brief total circumflex occlusion; a similar degree of thinning was induced by superimposing isoproterenol and aortic constriction on severe coronary stenosis (table 1, fig. 4).

Sonomicrometers
The ultrasonic crystals showed normal segment shortening or thickening in the control state and during 90% coronary stenosis. Systolic expansion or thinning was evident during total circumflex occlusion and during isoproterenol infusion and aortic constriction added to 90% coronary stenosis.

Figure 5 shows the two-dimensional echocardiographic and sonomicrometric data. Since the response to ischemia of the two groups of dogs with side-by-side and transmural sonomicrometers were similar, we combined the data and compared them with the two-dimensional echocardiographic data. In all dogs, two-dimensional echocardiography showed normal wall thickening when sonomicrometers registered normal wall dynamics. Systolic thinning shown by two-dimensional echocardiography always corresponded to bulging or thinning shown by sonomicrometers. There was complete correspondence between both tech-

FIGURE 1. The method of regional thickening analysis. The short-axis image of the ventricle is divided into 12 equal segments by radii drawn 30° apart. The percent systolic thickening of the wall along each radius is calculated as indicated. Systolic thinning occurred during ischemia.

FIGURE 2. Schematic representation of intramyocardial sonomicrometer placement, indicating the two orientations used in this study.
The effect of acute ischemia on sonomicrometer-registered wall contraction. Coronary occlusion (arrow) is followed immediately by systolic thinning in the sonomicrometers placed in endocardial-epicardial orientation to measure wall thickness, and by systolic bulging in the sonomicrometers placed side by side to measure segment length. Ao = aortic.

Table 1. Effect of Circumflex Occlusion and Isoproterenol and Aortic Constriction on Two-Dimensional Echocardiographic Wall Thickening in Severe Coronary Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Brief Cx occlusion</th>
<th>90% CS</th>
<th>90% CS + AC</th>
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</thead>
<tbody>
<tr>
<td>% thickening by 2-D echo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(risk segments)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>36 ± 15</td>
<td>-21*</td>
<td>37** -21**</td>
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<tr>
<td>% thickening by</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>sonomicrometers</td>
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<td></td>
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<tr>
<td>Mean ± SD</td>
<td>12 ± 1.5</td>
<td>-6*</td>
<td>9** -12**</td>
</tr>
<tr>
<td>% shortening by</td>
<td></td>
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<tr>
<td>sonomicrometers</td>
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<tr>
<td>Mean ± SD</td>
<td>12 ± 6.3</td>
<td>-5*</td>
<td>8** -6***</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>164 ± 29</td>
<td>156</td>
<td>133*+155†</td>
</tr>
<tr>
<td>Aortic systolic</td>
<td></td>
<td></td>
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<tr>
<td>pressure (mm Hg)</td>
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<tr>
<td>Mean ± SD</td>
<td>123 ± 17</td>
<td>115</td>
<td>111 118</td>
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<tr>
<td>Aortic diastolic</td>
<td></td>
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<tr>
<td>pressure (mm Hg)</td>
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<tr>
<td>Mean ± SD</td>
<td>93 ± 15</td>
<td>86</td>
<td>76§ 75§</td>
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<tr>
<td>Rate-pressure product</td>
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<td></td>
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<tr>
<td>Mean ± SD</td>
<td>20068 ± 3366</td>
<td>17921</td>
<td>14870§ 19502†</td>
</tr>
</tbody>
</table>

*p < 0.01 vs control.
†p < 0.01 vs 90% CS.
‡p < 0.05 vs 90% CS.
§p < 0.05 vs control.
¶p < 0.05 vs brief Cx occlusion.
**p < 0.01 vs brief Cx occlusion.

Abbreviations: CS = coronary stenosis; Iso = isoproterenol; Cx = circumflex coronary artery; AC = aortic constriction; 2-D echo = two-dimensional echocardiography.

Discussion

The major finding of this study is that two-dimensional echocardiography, when compared to an independent standard, intramyocardial sonomicrometry, is a sensitive and specific method for detecting ischemia-induced transient myocardial dyskinesis.

Since the original studies of Tennant and Wiggers,17 the rapid appearance of myocardial contraction abnormalities during myocardial ischemia has been well recognized. Transient myocardial dyskinesis is a marker of ischemia, and it would be clinically useful if it could be reliably and easily demonstrated. Two-dimensional echocardiography, with its unique ability to demonstrate rapid changes in wall thickness, should be suitable for this purpose. This study was undertaken to compare the sensitivity and specificity of two-dimensional echocardiography in demonstrating transient ischemia dyskinesis with intramyocardial sonomicrometry.

Numerous studies have established the capacity of sonomicrometers to reliably and accurately measure regional myocardial function in experimental models of myocardial ischemia. Theroux et al.18 and Heyndrickx et al.19 implanted pairs of crystals in a subendocardial side-by-side orientation (segment length gauge) to demonstrate systolic expansion after coronary occlusion. Ross and Franklin20 placed sonomicrometers in a transmural orientation (one subendocardial, one subepicardial) to register dynamic wall thickness, and found that regional changes in systolic thickening closely paralleled the shortening characteristics of subendocardial segments. Regional contractile abnormalities demonstrated with sonomicrometers are a more sensitive indicator of ischemia than ECG ST-segment changes.21

The sonomicrometer technique has also been used to demonstrate myocardial ischemia induced by exercise and atrial pacing in a dog model of coronary steno-
graphic studies showed an average wall thickening of 36–47%, similar to our findings.

Other investigators using sonomicrometry in open-chest dogs have also shown lesser degrees of systolic wall thickening. One source of these quantitative discrepancies might be lateral movement (shearing) of the two ultrasonic crystals with relation to each other during systole. Studies by Feigl and Fry and Fenton et al. suggested that such shearing did occur. However, Osakada et al. evaluated the error caused by such shearing motion of the epicardial and endocardial wall surfaces, and concluded that the average estimated error of systolic wall thickening caused by this phenomenon was only about 2%. Another source of error in the sonomicrometer measurement might be malalignment of the crystals during implantation; even slight errors in alignment cause underestimation of the systolic motion because the diagonal, or off-axis, distance would be perpendicular to the direction of motion or thickening and would change little during systole. Yet another source of error might be local myocardial damage incurred in inserting the sonomicrometers, which would result in a reduced local contractility. Further sources of quantitative discrepancy may be related to difficulties in exact measurement of wall thickness by echocardiography. The best resolution of the two-dimensional echocardiographic technique is 1–2 mm in the axial orientation. Some of the regions we analyzed were located laterally, where the resolution is poorer. Additionally, echo drop-out on still-frames of the videotape images may have added to inaccuracies in the tracings.

Considerable interest exists in the clinical use of echocardiography to monitor global and regional left ventricular performance during exercise. M-mode echocardiographic recordings can be obtained in normal subjects and angina patients despite vigorous levels of exercise. Two-dimensional echocardiograms revealed that the wall thickness at end-diastole was not significantly different between the control and ischemic groups (Figure 5). However, the region-by-region analysis revealed that the systolic thickening varied significantly among the groups. The control group showed a significant increase in wall thickening from baseline to peak exercise, which was not observed in the ischemic group. These findings suggest that two-dimensional echocardiography is a valuable tool for assessing regional wall motion and thickness during exercise.
raphy has been used by DeMaria et al.\textsuperscript{32} and by Adams et al.\textsuperscript{33} to evaluate responses to isometric stress. Wann et al.\textsuperscript{34} showed that two-dimensional echocardiographic exercise studies can be successfully performed in patients with coronary disease. These clinical studies have assumed that echocardiography can register transient dyskinesis during stress-induced myocardial ischemia. The present study, by acutely raising myocardial oxygen requirements in a setting of severe coronary stenosis, simulates the acute hemodynamic effects of dynamic exercise in patients. The excellent qualitative relationship between two-dimensional echocardiography and sonomicrometry in detecting myocardial ischemia provides experimental support for clinical stress echocardiography.

Acknowledgment

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