Two-dimensional Echocardiography and Infarct Size: Relationship of Regional Wall Motion and Thickening to the Extent of Myocardial Infarction in the Dog

ALAN N. LIEBERMAN, M.D., JAMES L. WEISS, M.D., BODH I. JUGDUTT, M.D., LEWIS C. BECKER, M.D., BERNAHINE H. BULKLEY, M.D., JOHN G. GARRISON, PH.D., GROVER M. Hutchins, M.D., CLAYTON A. KALLMAN, Sc.M., and MYRON L. WEISFELDT, M.D.

SUMMARY To study endocardial wall motion and thickness as indexes of infarction, we used two-dimensional echocardiography to examine regional percentages of systolic wall thickening (%EM) and endocardial motion (%EM) in infarcted canine hearts. Thirteen dogs were studied 48 hours after occlusion of the circumflex or left anterior descending coronary artery. Two-dimensional echocardiographic cross sections obtained every 16 msec at 1-cm intervals from apex to base in an open-chest, anesthetized preparation were analyzed with a computer-aided contouring system for quantification of segmental %EM and %EM at 16 equally spaced points per slice. Slices corresponding to each two-dimensional echocardiographic cross section were examined pathologically for evidence of infarction.

Comparing histologically infarcted with distant normal zones in each slice, %EM and %EM both yielded clear separation with little overlap (−12.5% infarcted vs 37.4% normal for thickness; −11.3 vs 25.7% for motion, p < 0.001 for both). Endocardial motion was less precise than thickening, however, in distinguishing infarct from either distant normal zones or zones directly adjacent to infarct. Although wall thickening was useful in separating out true subendocardial infarct, change in systolic thickening was not accurate in detecting the transmural extent of infarction. In 827 individual two-dimensional echocardiographic segments with varying degrees of transmural involvement, segments with 1–20% extent of transmural infarction showed reduced thickening compared with noninfarcted segments (39.9 vs 15.2%, p < 0.001), whereas myocardial segments with 21–100% transmural infarction showed systolic thinning (−8.9 to −13.3%). There was no significant augmentation in the severity of systolic thinning as the extent of transmural infarction increased from 21% to 100%.

We conclude that: (1) Wall motion abnormalities are less precise than thickening in discriminating between infarcted and noninfarcted zones and could lead to overestimation of infarct size. (2) There is an abrupt deterioration in systolic thickening in segments containing more than 20% transmural extent of infarction. (3) There is no significant augmentation in the degree of systolic thinning as the transmural extent of infarct increases from 21% to 100%. This “threshold” phenomenon may therefore preclude accurate estimation of infarct size by two-dimensional echocardiography. (4) Evidence of any systolic thickening indicates less than 20% transmural extent of infarction.

THE MECHANICAL sequelae of coronary artery occlusion have been recognized since Tennant and Wiggers first described the regional systolic bulging produced by coronary ligation.1 Subsequently, abnormalities in segmental wall function have become the hallmark of coronary artery disease.2, 3 Small regions of ischemic dysfunction have been studied by various techniques,4–10 including M-mode echocardiography.4–10 Abnormalities in wall motion11, 12 as well as systolic wall thickening13–18 have been related to diminished coronary perfusion. However, the limited field of view traversed by the one-dimensional ultrasonic beam makes it difficult to use the M-mode technique to delineate accurately the extent of myocardial infarction in the intact animal. The advent of real-time two-dimensional echocardiography has significantly increased the portion of the left ventricle that can be visualized, and is the only readily available noninvasive technique that allows quantitative analysis of wall thickening around the entire left ventricular circumference.19 Studies in animals19–21 and in man22–28 suggest that the extent of two-dimensional echocardiographic wall motion abnormality exceeds the pathologic infarct size, though the reason is unclear. This echocardiographic overestimation of infarct size may be attributed to adjacent local ischemia, small islands of infarct, or myocardial dysfunction due to mechanical tethering in the zone adjacent to the infarct.28

Previous studies have shown that wall thickening and fiber shortening are closely correlated4, 13 and that systolic thickening may provide more information than changes in epicardial segment length in detecting
infarction. To assess this, we studied regional systolic thickening and endocardial motion in the intact, infarcted canine heart. Using phased-array two-dimensional echocardiography and a computerized contouring system for quantitative analysis of regional wall motion and thickening, we compared regional abnormalities in mechanical function with tissue histology. The ability of two-dimensional echocardiography to distinguish infarcted from noninfarcted myocardium, to determine the meaning of functional abnormalities in the zone directly adjacent to infarct, and to delineate transmural extent of infarcted myocardium was studied as an initial approach to the use of this technique in quantifying infarct size.

Methods

Experimental Animal Preparation

Fifteen mongrel dogs with an average weight of 20 kg (range 17–22 kg) were instrumented under pentobarbital anesthesia with a left lateral thoracotomy. A plastic snare was placed around the left circumflex artery just distal to the first marginal branch in seven dogs and around the left anterior descending artery distal to the first diagonal branch in six dogs. Two other dogs were sham-operated controls. Plastic catheters in the external jugular vein, external carotid artery and left atrium were brought out the back of the neck through a subcutaneous tunnel. All dogs were treated with penicillin (1 million units) and streptomycin (1 g) given intramuscularly after surgery, and the tubes were flushed daily with 1000 U of heparin.

Approximately 10 days later, the dogs were placed in a specially designed sling and sedated with morphine. After adequate sedation, the dogs were premedicated with lidocaine (1 mg/kg) and 5 minutes later the snare was pulled to occlude the coronary artery acutely and permanently. Two days later the dogs were anesthetized with chloralose and a median sternotomy was performed. The pericardium was opened and the heart was supported in a pericardial sling for echocardiographic study. After the echocardiographic study, the dogs were sacrificed with a lethal dose of anesthetic and the hearts were removed, washed free of blood and weighed. The ventricular cavities were packed with gauze and the hearts were fixed in 20% formalin. Each heart was cut in transverse rings from apex to base at 1-cm intervals corresponding to the cross-sectional planes of the echocardiographic images.

The rings of the left ventricle were then freed of the right ventricle, fatty and valvular tissue and weighed. Outlines of the ring and infarct, as seen by the naked eye, were traced using a transparent plastic sheet and verified by a second independent observer. The tracings were aligned using the two papillary muscles, the septal wall and the anterior and posterior junctions of the right and left ventricles. From each ring, samples for histologic verification were taken from the center and margins of the infarct and adjoining non-necrotic tissue.

Echocardiographic Technique

With the heart supported in a pericardial sling, serial cross-sectional views were obtained using a Varian V-3000 ultrasonograph and a 2.25-MHz transducer placed on the epicardium. To offset the transducer from the epicardial surface and minimize mechanical interference with cardiac motion, a castor-oil-filled stand-off device with a polyurethane membrane 10 mils thick was attached to the transducer head (fig. 1). Four calibrated steel rods were firmly secured to the corners of the surgical table. The transducer was supported by a universal joint on a steel rod suspended from a calibrated cross bar attached to the apparatus. A tri-coordinate system of calibration allowed accurate distance measurement and transducer location. With this technique, three to five echocardiographic cross-sectional views per heart were obtained at 1-cm intervals from apex to base, to be compared with the corresponding pathologic slices.

The echocardiographic images were stored on 1-inch videotape (60 fields/sec, International Video Corp.). For evaluation of the echocardiographic data, we used a previously described contouring system. With this system, individual video frames of the cross-sectional image are projected on a high-resolution x,y,z oscilloscope screen using a video disc (VAS). The computer superimposes two sets of 16 points equally spaced in angle around the image, and the reader places the points to fit the endocardial and epicardial margins of the image. A best-fit contour for each two sets of points is selected by the computer, using a spline-fitting technique. With this process, the contour will intersect each of the 16 points and maximize the radius of curvature. Each of the endocardial and epicardial points is repositioned every 16 or 32 msec from end-diastole to the next end-diastole.

![Figure 1. Two-dimensional echocardiographic technique in the open-chested anesthetized dog. With the heart supported in a pericardial sling, serial cross-sectional views are made from the epicardium. A castor-oil-filled stand-off device with a polyurethane membrane is attached to the transducer head to offset it from the epicardial surface and minimize cardiac distortion. A tri-coordinate system of calibrated steel rods allows accurate distance measurement and transducer location. Echocardiographic cross-sectional views are taken at 1-cm intervals from apex to base, to be compared with corresponding pathologic slices.](https://circ.ahajournals.org/content/63/4/740/F1.large.jpg)
beginning and ending with the simultaneously recorded first deflection of the QRS complex. This produces 10–20 fields of data per beat per slice, and one beat is analyzed for every cross-sectional view per heart. This process allows each echocardiographic image to be divided into 16 equally spaced myocardial segments, and indexes of myocardial function are obtained for each segment. Figure 2 illustrates the principles of the contouring system.

Two echocardiographic indexes of myocardial wall function were analyzed for each of the 16 radial points.

Regional percentage of systolic thinning (\%Th) was calculated as:

$$\frac{Th_{ES} - Th_{ED}}{Th_{ED}} \times 100$$

where \(Th_{ES}\) is the thickness of the myocardial segment at end-systole and \(Th_{ED}\) is the thickness of the segment at end-diastole (in cm). Negative values indicate systolic wall thinning.

The regional percentage of radial endocardial motion toward center of area fixed at end-diastole (\%EM) was calculated as:

$$\frac{R_{ED} - R_{ES}}{R_{ED}} \times 100$$

where \(R_{ED}\) is the end-diastolic segmental endocardial radius and \(R_{ES}\) is the end-systolic segmental endocardial radius (in cm). Negative values indicate systolic bulging (dyskinesis).

Analysis of Data

To ensure the most accurate superimposition of the echocardiographic image with the corresponding pathologic ventricular ring, the following system was used. The first appearance of the ventricular cavity at the apex of the heart was identified as the initial landmark. Starting at this level, echocardiographic images were obtained at 1-cm intervals to the base of the heart. The ventricle was later sliced at 1-cm intervals beginning at the same landmark. Anatomic luminal areas were planimetered and matched with diastolic echocardiographic luminal areas to further verify the proper echocardiographic-morphologic correlation. With the aid of the reference coordinate system, we could then superimpose the 16 radial echocardiographic segments in their proper anatomic positions over the tracing of the corresponding pathological specimen. A radial grid system comprising 16 major segments identical in location to those segments analyzed by the computer was inscribed on transparent plastic and placed over the stationary echocardiographic image displayed on the video disc. Four landmarks were chosen for identification from the echo image: the midpoints of the anterior and posterior papillary muscles and the anterior and posterior junctions of the right and left ventricles. In each echocardiographic image, each visible landmark was assigned a numerical radial location by two independent observers corresponding to its intersection with one of 128 possible circumferential points on the grid.* The grid was then placed over the tracing of the ventricular ring. This process allowed us to locate each of the 16 radial echocardiographic segments on the left ventricular circumference and thereby correlate echocardiographic function with underlying tissue morphology. In 90% of the cross-sectional echocardiographic images, two to four of these landmarks were available for the aligning process. When more than one landmark was used, each of the echocardiographic landmarks in the slice had to correspond accurately to its anatomic location in the pathologic specimen for that image to be used for analysis.

The reproducibility of results using the contouring system has been reported.** There was no significant

---

*To test reproducibility of landmark localization only, the computer produced 128 equally spaced points around the left ventricular circumference, not 16.
intra-reader variation for segment length or myocardial thickness, or inter-reader variation for segment length. Although the differences for inter-reader observations for myocardial thicknesses were statistically significant ($p < 0.006$), the percentage difference between readers was small (5%). To assess the reproducibility of the alignment process, which requires accurate location of the echocardiographic landmarks described, two independent observers aligned 23 landmarks in 10 different echocardiographic images to test interobserver and intraobserver variability (table 1). By analysis of variance, there was no significant intraobserver (observation separated by 6 months) or interobserver variability.

Correlating the echocardiographic and morphologic data for each myocardial slice, we identified three categories: (1) *infarct*: the endocardial-epicardial pair of contour points transects a portion of myocardium that contains grossly visible infarct, whether subendocardial or transmural; (2) *adjacent normal myocardium*: the radial echocardiographic contour points transsect myocardium adjacent (within 1 cm) to infarct but without grossly visible infarct present; and (3) *distant normal myocardium*: the contour points transsect myocardium not adjacent to infarct and more than 1 cm from the infarct border.

Infarct weights varied from 2.0–26.5 g (average 13.4) per dog. The average percentage of infarct per ring (by weight) was $16.5 \pm 13.4\%$ (SD) (range 0–47.7%). The extent of infarcted tissue in any radial echocardiographic segment was calculated as a percentage by dividing the linear transmural extent of the infarcted tissue by the total thickness of the ventricular wall at that point. Gross pathologic examination was done in every case verified by microscopic examination of sections stained with hematoxylin and eosin. Using these values we studied the relationship of the percentage of systolic thickening to the percentage of infarct thickness for each radial segment.

### Statistical Evaluation

To test the null hypothesis that there is no difference in systolic wall thickening or motion between tissue that was infarcted, adjacent to infarction, and distant normal, separate two-way analyses of variance were performed using a general linear model for the dependent variables of thickening and motion. The independent factors were tissue morphology and dog. Comparison of the variability accounted for by these measurements allows assessment of the precision of echocardiographic wall thickening and thickening in distinguishing between these tissue types, while testing and adjusting for dog-to-dog variability. To test the null hypothesis that there is no significant relationship between the extent of infarcted tissue in a segment and its systolic thickening, a one-way analysis of variance with contrasts was performed between myocardial segments grouped according to extent of infarct and systolic thickening. Extent of infarct was grouped by 20% increments.

### Results

#### Control Dogs

In the two dogs subjected to sham operations with instrumentation and procedures identical to the experimental preparations except that no coronary ligation was performed, pathologic examinations verified the absence of infarction, either grossly or microscopically. Echocardiographic study showed homogeneous systolic thickening, with mean values of 34% and 36%, respectively, for the two dogs. There was no evidence of akinesis or systolic bulging, and mean values for the percentage of radial endocardial motion (%EM) in the control dogs were 23% and 21%, respectively.

#### Regional Endocardial Motion as a Function of Tissue Histology and Location

We first determined the accuracy of %EM in identifying the regional infarct. An index was determined by averaging the echocardiographic data from all segments of each anatomic type within each ventricular ring, grouped according to anatomic location, i.e., within, adjacent to or distant from infarction. As can be seen in figure 3, %EM distinguished between normal, adjacent, and infarcted tissue. The mean %EM was 25.7% for distant normal zones, 4.5% for areas adjacent to infarct, and −11.3% for infarcted areas (overall SD 11.5%). By analysis of variance, these differences between groups were highly significant ($p < 0.001$). The k-ratio multiple comparisons test showed the least percentage difference in %EM required to be significant at the $p < 0.01$ level when comparing pairs of the three tissue groups was 5.73–6.00%. The observed mean differences were 15.76–36.98%.

### Regional Thickening as a Function of Tissue Histology and Location

Correlating %Th with morphology (fig. 4), a similar but even clearer separation between normal, adjacent and infarcted tissue was obtained: 37.37%, 14.45% and −12.57%, respectively (overall SD 11.95%), and the separation was highly significant ($p << 0.001$, analysis of variance). The k-ratio multiple comparisons test showed statistically significant mean differences in %Th between all pairs of the three groups ($p << 0.01$). The range of differences required for significance at

### Table 1. Reproducibility of Landmark Localization by Two-dimensional Echocardiographic Contouring System

<table>
<thead>
<tr>
<th>Observers</th>
<th>se of measurement†</th>
<th>$F$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between</td>
<td>3.5</td>
<td>0.63</td>
<td>NS</td>
</tr>
<tr>
<td>Within</td>
<td>4.4</td>
<td>—</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Two-way analysis of variance. Two independent observers aligned 23 landmarks from 10 stop-frame echocardiographic images.
†Percent of left ventricular circumference (equivalent to standard deviation of differences).
this level was 5.92–6.23%, and the observed mean differences were 22.92–49.95%.

Comparison of Regional Endocardial Motion and Percentage Thickening

The above data suggested that both %Th and %EM could separate infarcted, adjacent and distant normal zones, but that %EM was less precise than %Th. To examine this further, we compared the accuracy of %Th and %EM by assessing the proportion of variability in %Th, as opposed to %EM, accounted for by tissue morphology and dog-to-dog variability as independent variables. Tissue morphology accounted for a greater proportion of the variability in %Th (70.66%) than did %EM (55.57%). In addition, undesirable dog-to-dog variability was considerably more important in accounting for differences in %EM (16.69%) than in %Th (8.72%). For these reasons, %Th appears to be the better discriminator between normal, adjacent and infarcted tissue, and more accurately separates anatomic sites according to wall function than does %EM. There is little overlap in %Th between normal and infarcted tissue (fig. 4). Only three of 41 infarcted zones thicken (to a maximum of 9%); the rest reveal systolic thinning of varying degrees.

Relationship of Segmental Percent Systolic Thickening to Percent Infarct Thickness

To assess the value of %Th in determining the extent of transmural involvement of the infarct, we plotted segmental %Th against the percentage of infarct thickness in 20% increments (fig. 5). A threshold effect is evident: by one-way analysis of variance with contrasts, infarct-free segments show statistically greater systolic thickening than segments with small amounts of infarction (1–20% thickness). Similar analysis shows that segments containing more than 20% of transmural infarct thin during systole. Beyond this degree of infarct thickness (i.e., 21–100%), segments manifest similar degrees of systolic thinning (F = 1.33, p = 0.27). Thus, there is no gradual decrement in %Th from normal regions to zones containing transmural infarction, but rather, an abrupt deterioration in systolic function when more than 20% of the transmural thickness of a segment is infarcted. This threshold effect would obviate absolute infarct size determination with this technique.

Infarct Content of Adjacent Zones

The zones adjacent to infarcted regions contained no infarcted tissue by gross examination. Never-
thickening probably cannot be used to quantify the absolute mass of infarcted tissue. However, evidence of any systolic thickening indicates that the region is devoid of transmural infarction. Specifically, the transmural extent of infarction in these segments is not more than 20%, and most often 0. If it can be shown in man that the presence of systolic thickening excludes significant transmural infarction, this technique would have significant clinical potential for the identification of noninfarcted myocardium.

The function of zones immediately adjacent to infarcted regions is an issue of current great interest. Recent studies by Jugdutt et al. have on three-dimensional mapping of myocardial infarction show that grossly normal-appearing myocardium within 5 mm of the border of an infarct may contain up to 10% infarct in the form of interdigitating islands of necrotic tissue. Our results were similar: 0–8% infarct was present within 5 mm from the infarct border, diminishing to histologically absent infarct at distances greater than 1 cm.
Abnormalities of function in zones adjacent to infarct have been described in echocardiographic and cineangio graphic studies. As an explanation for the functional depression of normally perfused myocardium adjacent to ischemic myocardium, Wyatt et al. postulated that ischemic muscle in parallel to nonischemic muscle might function as a parallel resistance and transmit to adjacent normal muscle some of its own contractile properties. In the present study we found reductions in adjacent zone thickening and endocardial motion that were intermediate between distant normal and infarcted regions. The depression of mechanical performance in muscle adjacent to infarct may be related to the tethering effects described above, but the precise role that small amounts of necrotic tissue may play in the functional abnormalities of this zone is unclear. Another explanation for the reduced function of the adjacent tissue is ischemia, as the tissue was within the vascular "risk region."

The present study was designed to idealize experimental conditions as much as possible. The use of an open-chest preparation and our transducer support apparatus allowed acquisition of uniformly high-quality echocardiograms of the entire left ventricular circumference. In addition, the use of an animal model with a single coronary lesion, as opposed to the characteristically diffuse coronary disease of man, helped simplify interpretation.

Despite our attempt to optimize experimental conditions, this study does have limitations. Our data were obtained from 48-hour-old infarctions, and extrapolation of our results to more recent infarcts is not yet justified. The limits of resolution of the ultrasonic technique we used must also be recognized. The quantification of regional wall thickening was made possible only by use of a computerized contouring system. It appears that the use of such a system, which is not commercially available, is necessary to quantify large numbers of segments in the intact heart. Nonetheless, the reproducibility of data using the contouring system is good.

Because two-dimensional echocardiography can usually visualize a large portion of the left ventricle at any moment, it seems well suited to the study of the relation of wall motion and thickening to regional morphologic changes. We have shown that echocardiographically measured changes in systolic thickening separate infarcted from noninfarcted tissue. The extent of myocardial dysfunction exceeds the boundaries of the infarcted tissue itself to include that immediately adjacent to infarct. Likewise, the threshold phenomenon, which results in all degrees of transmural infarct greater than 20% producing like amounts of systolic thinning, limits the use of two-dimensional echocardiography in quantifying infarct size. Conversely, data show that the presence of any systolic thickening is indicative of less than 20% transmural extent of infarction. Further studies are needed to evaluate the functional capacity of ischemic tissue within the distribution of the occluded coronary bed and to evaluate therapeutic interventions intended to reduce infarct size.

References

5. Goldstein S, de Jong JW: Changes in left ventricular wall dimensions during regional myocardial ischemia. Am J Cardiol 34: 56, 1974
22. Charuzi Y, Davidson RM, Barret MJ, Swan HJC: Segmental wall motion in acute myocardial infarction determined by wide-angle two-dimensional echocardiography. (abstr) Clin...
Two-dimensional echocardiography and infarct size: relationship of regional wall motion and thickening to the extent of myocardial infarction in the dog.
A N Lieberman, J L Weiss, B I Jugdutt, L C Becker, B H Bulkley, J G Garrison, G M Hutchins, C A Kallman and M L Weisfeldt