Detection of Acute Myocardial Infarction in Closed-Chest Dogs by Analysis of Regional Two-Dimensional Echocardiographic Gray-Level Distributions


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SUMMARY. We hypothesized that acute myocardial infarction could be detected in standard two-dimensional echocardiograms of closed-chest dogs by evaluating regional echo amplitude distributions using computerized image analysis. We tested this hypothesis by performing standard, 2.4 MHz two-dimensional echoes before and 2 days after circumflex coronary occlusion in seven closed-chest dogs. Control and infarcted regions of interest were studied in digitized stop-frame images. Average gray level was calculated for each region of interest, and the shape of the gray-level distribution was analyzed by calculation of skewness and kurtosis and by qualitative features of shape. Average gray level increased significantly from the pre- to postocclusion images in the infarcted regions (16.7 ± 4.2 vs. 32.4 ± 4.4 units, P < 0.01), but not in the control regions (17.4 ± 4 vs. 22.3 ± 5.5, P = NS). Average gray level could not distinguish between infarcted and normal regions within the postocclusion images (36 ± 5.2 vs. 33.6 ± 5.8, P = NS). Three independent observers qualitatively evaluated histogram shape and correctly identified 7/7 MI regions (100% sensitivity) and 14/20 normal regions (70% specificity). Quantitatively, infarct regions exhibited a significant decrease in kurtosis (2.8 ± 0.9 to 0.44 ± 0.5, P < 0.01); the normal regions showed no significant change in kurtosis from pre- to postocclusion images (7.1 ± 4.0 vs. 5.2 ± 2.9, P = NS). Within postocclusion images, infarcted regions displayed a significantly lower kurtosis than did normal regions (0.27 ± .47 vs. 2.5 ± 1.0, P < .01). We conclude that acute myocardial infarction may be detected in closed-chest dogs by analyzing regional echo amplitude data from standard two-dimensional echocardiograms (Circ Res 52: 36-44, 1983)

Echocardiography has been used to identify and localize regions of myocardial infarction by detection of local left ventricular contraction abnormalities. Decreased regional endocardial motion displayed on M-mode and two-dimensional (2D) echo implies the presence of ischemia or infarction (Stefan and Bing, 1972; Kerber and Abboud, 1973; Corya et al., 1975; Meerbaum et al., 1977; Heger et al., 1980; Lieberman et al., 1981; Weiss et al., 1981). Similarly, abnormal wall dynamics, thickening and thinning, is an accepted echocardiographic marker of ischemic or infarcted tissue (Corya et al., 1977; Pandian et al., 1980; Lieberman et al., 1981). Abnormalities of wall motion and thickening, however, are indirect measures, and cannot distinguish acute ischemia from acute infarction or scar, all of which may produce similar abnormalities of regional left ventricular contraction.

Another, fundamentally different, approach to the ultrasonic detection of infarcted myocardium is the analysis of regional acoustic properties—that is, the interactions between ultrasound and the myocardium.

Alterations of acoustic impedance (Namery and Lele, 1972) and attenuation (Miller et al., 1976; Mimb et al., 1977) have been demonstrated in acutely infarcted myocardium. Ultrasound is also reflected or backscattered abnormally by infarcted myocardium (Mimb et al., 1980; Mimb et al., 1981). Several approaches have been used to identify and localize this abnormal ultrasound backscattering. Chronically infarcted myocardium has occasionally been identified by an increased apparent brightness of echoes returning from the scarred region as displayed on M-mode echocardiograms (Rasmussen et al., 1978). A recent experimental approach has confirmed changes in the brightness of chronically infarcted myocardium as displayed in two-dimensional echocardiograms (Moynihan et al., 1980). Other investigators have attempted to detect acute myocardial infarction by quantitative analysis of backscattering from cardiac muscle (Mimb et al., 1980, 1981). In general, the preliminary quantitative data have been acquired in vitro or in open-chest animal models, utilizing broadband transducers. These approaches are therefore not consonant with the usual instrument constraints of clinical echocardiographic imaging in closed-chest subjects, in which relatively narrowband transducers of lower operating frequency were used.
echocardiographic laboratory 48 hours postocclusion. At ventricular ectopic beats. The dogs were returned to the tored and lidocaine given intravenously as necessary for grams were performed and papillary muscle level short-axis occluded the circumflex coronary artery by tightening the transducer. Surface electrocardiograms were moni-
ted and lidocaine given intravenously as necessary for ventricular ectopic beats. The dogs were returned to the echocardiographic laboratory 48 hours postocclusion. At that time, another two-dimensional echocardiogram was recorded. After the second echocardiogram, the dogs were anesthetized with sodium pentobarbital, killed with intravenous potassium chloride, and the heart was removed for examination.

Image Processing and Analysis
Photographic negatives of echocardiographic stop-frames were developed with sodium sulfite. These negatives then were placed on a light table and digitized, using a Hamamatsu video camera interfaced to a PDP 11/34 computer and to a Ramtek image display system. The data were digitized into a 256 X 256 matrix with 8-bit (256) gray level resolution. Pre- and postocclusion image pairs were digitized on the same day under identical conditions of illumination.

Circular regions of interest were chosen in four areas of the cross-sectional echocardiographic image (Fig. 1): the mid- to posterior ventricular septum and anterolateral ventricular wall were chosen as control regions, presumably remote from the distribution of the occluded artery. The posterior left ventricular wall was chosen as a region in the distribution of the occluded artery. A region of interest was also placed in the ventricular cavity as a control for system noise and to correct for variations in background gray level due to photographic processing variability. All myocardial regions of interest were placed entirely within the wall area, avoiding the specular reflections from the endocardium and epicardium. Regions of interest of similar size and location were chosen in the pre- and postocclusion short-axis papillary muscle level images for each dog.

Gray Level Histogram Analysis
The distribution of gray levels present in each region of interest was displayed as a gray level histogram, showing the frequency of occurrence of each gray level within that region (Fig. 2). Fifty-six gray level histograms were generated: 4 regions of each of seven dogs, before and 2 days after coronary artery occlusion.

The average gray level in each region was calculated. The shape of the gray level distribution was also evaluated in two ways: (1) independent observers qualitatively assessed changes in histogram shape before and after coronary occlusion, and (2) a quantitative analysis of the shape of the distribution was performed, using skewness and kurtosis.

Qualitative Analyses
Three independent observers participated in a training session during which they were shown several examples of gray level histograms from control and infarcted regions. General characteristics of normal and abnormal histograms

Experimental Protocol
The studies were performed 7-10 days after recovery from thoracotomy. After treatment with intravenous morphine sulfate (10 mg), control two-dimensional echocardiograms were performed and papillary muscle level short-axis images recorded as described above. We then permanently occluded the circumflex coronary artery by tightening the implanted snare. Surface electrocardiograms were monitored and lidocaine given intravenously as necessary for ventricular ectopic beats. The dogs were returned to the echocardiographic laboratory 48 hours postocclusion. At that time, another two-dimensional echocardiogram was recorded. After the second echocardiogram, the dogs were

Methods
Animal Preparation
Seven adult mongrel dogs were studied. The dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), and ventilated with a Harvard respirator. A left thoracotomy was performed through the 4th intercostal space. A 1-0 silk snare was placed around the circumflex coronary artery, distal to the first or second marginal branch. This snare was tunneled subcutaneously and attached to skin buttons at the back. The thoracic incisions were closed using sterile technique, and the dogs were allowed to recover from the operation.

Echocardiographic Technique
Echocardiograms were performed with the dog lying in a right lateral decubitus position on a table (Wyatt et al., 1979). Echocardiograms were obtained through a cut-out on the table with the transducer applied from below to the right parasternal area near the point of maximal impulse. The transducer was angulated so as to obtain a short-axis view of the left ventricle at papillary muscle level. The studies were done using a Toshiba SSH-10A Sonolayergraph, a 2.4 MHz, phased-array, real-time ultrasound system. The image processing and display adjustments on the 2D echo machine were manipulated to produce a control image which displayed all regions of the myocardium at approximately equal brightness to the observer performing the echocardiogram. Note then was made of these machine parameter settings in order to keep them constant from control to postocclusion echocardiograms in a given dog. These parameters included brightness and contrast settings of the display oscilloscope, coarse and fine overall gain controls, time-gain compensation controls, and system dynamic range and echo enhance controls. We used a digital freeze-frame device to obtain stop-frame images at end-diastole and end-systole. The images were photographed from the primary oscilloscope using Polaroid 665 film (positive/negative 75 ASA), with a shutter f-stop of 4.5 and a 5-second exposure time. Real-time echocardiograms were also recorded on standard videotape.

FIGURE 1. Regions of interest chosen in the cross-sectional echocardiographic images: the posterior left ventricular wall (3) was chosen as a region in the distribution of the occluded artery; the ventricular septum (1) and anterolateral wall (4) were chosen as control regions, remote from the distribution of the occluded artery. A region of interest was also placed in the ventricular cavity (2) to correct for system noise and background variations.
were discussed (see Results) (Fig. 2). After the training session, the observers were shown pairs of histograms. Each pair consisted of histograms generated before and after occlusion for the same region of myocardium (e.g., a region of interest within the lateral wall before and after coronary occlusion). For each pair of histograms, the observers were asked to assess whether the shape of the gray level histogram had changed noticeably from pre- to the postocclusion study. An abnormal histogram in a postocclusion study was one which deviated from the skewed appearance of the control histogram (Fig. 2). The 28 pairs of histograms were presented in random order; each observer’s assessment was made independently, and each was unaware of the pathological findings in the regions which they were assessing. The observers were also unaware of which histogram was assembled from the pre- and which was from the postocclusion data.

Quantitative Analyses

The quantitative analysis of histogram shape was performed by calculating the skewness and kurtosis of each distribution: skewness to measure the asymmetry of the shape of the distribution and kurtosis to measure the “peakedness” of the distribution relative to the length and size of its tails (Fig. 3). These parameters were calculated by means of the standard SAS statistical program; specific algorithms are listed in the appendix (SAS Users Guide, 1979; Snedecor and Cochran, 1967).

Pathological Examination

After sacrifice, the dogs’ hearts were removed and fixed in a 10% buffered formalin solution. Transverse sections of the heart were cut at approximately 1-cm intervals, parallel to the plane of the atrioventricular groove. The section which approximated the mid-papillary muscle level was chosen for comparison with the echocardiographic data. The hearts were examined grossly for evidence of myocardial infarction; necrosis was confirmed histologically, using standard preparation of tissue sections stained with hematoxylin and eosin (Bloor, 1978).

![Figure 2: Gray-level histograms from infarcted and control myocardial regions, before and 2 days after coronary occlusion. Panel A: Histograms from a control (anterolateral wall) region. The shape of the gray-level histogram (i.e., the echo amplitude distribution) did not substantially change between the two studies. Panel B: Histograms from an infarcted (posterior wall) region. A change in the gray-level distribution is seen in the postocclusion image, with a relatively higher frequency of higher gray levels.]

![Figure 3: Kurtosis calculations were used to analyze histogram shapes quantitatively. A normal distribution is termed mesokurtotic. Increased kurtosis values signify increased peakedness of the distribution (leptokurtotic). Decreased kurtosis values signify flattening and broadening of the distribution (platykurtotic).]
Data Analysis

Average Gray Levels

The average gray level in each cavity region was subtracted from the average gray level in each tissue region of the same digitized image, in order to partially correct for background gray level differences between images. The average gray level (after background subtraction) in each region before coronary occlusion was compared to the average gray level in the same region 2 days after occlusion. The significance of differences between the gray level of a region before and after occlusion was calculated by paired t-test. In order to analyze for regional differences in gray level within the postocclusion images, we compared the average gray level in each infarcted (septal or posterior wall) region to that in the opposite (anterolateral) wall region. The significance of differences was calculated using a paired t-test.

Qualitative Histogram Shape Analysis

Each observer's assessment of the shape of the 28 histogram pairs was compared to the pathological examination of the heart. The pathological evaluation was used to define a given region as a true positive (infarcted) or a true negative (not infarcted). Observers considered a histogram pair positive if a noticeable difference was apparent between the shapes of the pre- and postocclusion distributions. Sensitivity and specificity were calculated as follows:

Sensitivity = true positives/(true positives + false negatives)
Specificity = true negatives/(true negatives + false positives)

Average sensitivity and specificity were calculated for the three observers. A majority decision was also derived for each region: a region was considered normal or abnormal based on the responses of at least two of three observers. Sensitivity and specificity were calculated from the majority data. Interobserver discordance was also calculated.

Quantitative Histogram Shape Analysis

Skewness and kurtosis were calculated for each region of interest using the SAS program (see Appendix). Values of these parameters calculated for each region pre- vs. postocclusion were compared, and the significance of differences noted was evaluated using the Friedman rank test. To evaluate regional differences in histogram shape within the postocclusion images, skewness and kurtosis of each infarcted region (posterior wall or ventricular septum) were compared to the values of the opposite (anterolateral) wall region. The significance of differences was evaluated by Friedman rank test.

Results

Pathological Examinations

At postmortem examination, 48 hours after coronary occlusion, five of the seven hearts showed evidence of myocardial infarction. The infarction involved the posterior wall in all five hearts and extended to the posterior ventricular septum in three. This septal extension of the infarction involved the region of interest placed in the mid- to posterior septum in these echocardiographic images. Therefore, eight infarcted regions were present, with 20 control regions (including the ventricular cavity).

Average Regional Gray Levels

No regional increase in brightness or change in echo pattern was apparent in the postocclusion images when evaluated visually. Average gray level (background corrected) was calculated for each tissue region of interest in pre- and postocclusion images. Radii of the regions varied from 5 to 10 pixels, yielding region areas of approximately 80 to 300 pixels. In the postocclusion image of one dog (#6), the ventricular septal region had to be excluded from analysis due to an image artifact.

The mean gray level did not vary significantly among regions within the preocclusion images (21.3 ± 5.4 for anterolateral wall; 13.9 ± 4.7 for posterior wall; 16.2 ± 5.3 for ventricular septum; P = NS by analysis of variance). Figure 4A shows the comparison of average regional gray level pre- and postocclusion, for infarct and normal regions. The infarct regions exhibited a significant increase in average gray level (16.7 ± 4.2 vs. 32.4 ± 4.4 units, P < 0.01). The control regions showed no significant change in gray level (17.4 ± 4

![Figure 4A](http://circres.ahajournals.org/)

*Figure 4A. Average gray level in control and infarct regions. Panel A: Average gray levels are shown for infarct and control regions before and after coronary artery occlusion. A significant increase in average gray level was found in infarcted regions but not in control regions.*
TABLE 1
Accuracy of Qualitative Assessment of Histogram Shape

<table>
<thead>
<tr>
<th>Observers</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100(7/7)</td>
<td>65(13/20)</td>
</tr>
<tr>
<td>B</td>
<td>100(7/7)</td>
<td>80(16/20)</td>
</tr>
<tr>
<td>C</td>
<td>71(5/7)</td>
<td>65(13/20)</td>
</tr>
<tr>
<td>Averages</td>
<td>90 (6.3/7)</td>
<td>70 (14/20)</td>
</tr>
<tr>
<td>Majority</td>
<td>100(7/7)</td>
<td>70 (14/20)</td>
</tr>
</tbody>
</table>

vs. 22.3 ± 5.5, \( P = NS \)). Figure 4B shows the comparison of average gray levels of infarcted and normal regions within the postocclusion images; no statistically significant difference was found (36 ± 5.2 vs. 33.6 ± 5.8, \( P = NS \)).

Gray-Level Histogram (Distribution) Shape

Representative gray-level distributions are shown in Figure 2. The histograms in Figure 2A are derived from a (normal) lateral wall region of interest. A high number of relatively low gray levels is seen, with a rapid, smooth fall-off in the frequency of higher gray levels. The shape of the postocclusion histogram (i.e., the gray-level distribution) appears similar to that of the preocclusion histogram.

Figure 2B shows a pair of gray-level histograms from an infarcted region; a change in the shape of the distribution from the preocclusion to the postocclusion histogram is evident. An increased frequency of higher gray levels is seen in the postocclusion histogram. The appearance of higher gray levels after infarction was a typical finding.

Qualitative Histogram Shape Analysis

The overall results of the three observers' qualitative assessment of the pairs of gray-level histograms is shown in Table 1. The sensitivity of the observers’ assessment of gray-level histograms was 100% (7 of 7 infarcted regions correctly identified) for two of the observers, and 71% (5 of 7) for the third observer. The specificity ranged from 65% (13 of 20 control regions correctly identified) to 80% (16 of 20). The average sensitivity was 90% and specificity 70%. Based on majority scores (i.e., the decision of two out of three observers) the sensitivity was 100% and the specificity 70%. Interobserver disagreement occurred in 8 of 27 (30%) regions; all three observers agreed in 19 of 27 (70%) regions.

Quantitative Histogram Shape Analysis

Skewness and kurtosis values for all regions of interest are shown in Tables 2 through 7. The values of skewness were not significantly different for infarcted vs. normal regions. However, the values of kurtosis proved to be reliable descriptors of the characteristic change in gray-level distribution after infarction. Figure 5A shows the comparison of kurtosis values of infarcted and normal regions, pre- and postocclusion. Analysis of infarct regions revealed a significant decrease in kurtosis, signifying the change to a flatter, less peaked distribution (from 2.8 ± 0.9 to 0.44 ± 0.5, \( P < 0.01 \)). For normal regions, the analysis showed no significant change in kurtosis from pre- to postocclusion images (7.1 ± 4.0 vs. 5.2 ± 2.9, \( P = NS \)). Figure 5B shows the comparison of kurtosis of infarcted and normal regions within postocclusion images. Infarcted regions exhibited a significantly lower kurtosis than did normal regions (0.27 ± 0.47 vs. 2.5 ± 1.0, \( P < 0.01 \)).

Discussion

The major finding of our investigation was that 2-day-old myocardial infarction could be detected and localized by an analysis of gray-level histograms obtained from conventional two-dimensional echocardiograms performed in closed-chest dogs. Specifically, the gray-level (echo amplitude) distributions of infarcted myocardial regions were characteristic: a
relatively higher frequency of occurrence of higher gray levels was found compared to the gray-level distributions of normal myocardium. This produced a broadening and flattening of the gray-level histograms of infarct regions which was reliably detectable compared to the gray-level distributions of normal myocardium. This produced a broadening and flattening of the gray-level histograms of normal myocardium. Therefore, in clinical use, since an immediate preinfarction image would rarely be available, analysis of histogram shape might be a potential approach to distinguish normal from infarcted myocardium, whereas mean gray level would not. Our discussion will concern four questions relevant to these findings: (1) What are the physical/anatomic bases of the alterations in gray-level distributions found in our study? (2) What factors contribute to the failure of average gray level to distinguish between normal and infarcted myocardium? (3) How do our data compare with previous attempts to identify myocardial infarction by altered acoustic properties of tissue? (4) What are the implications of this approach?

Biological Basis of Altered Acoustic Properties

The appearance of bright echoes from large, smooth (specular) interfaces in the heart or other organs is usually explained as due to an acoustic impedance mismatch. This explanation assumes a large, smooth interface between two relatively homogeneous media of differing characteristic acoustic impedance (White, 1976). The mechanism of ultrasound backscattering from tissue regions not containing these large, specular interfaces is less well understood. Several models have been proposed to explain tissue scattering, including the presence of many microscopic, randomly distributed scatterers placed within a relatively homogeneous medium (Joynt, 1970). In the case of the heart, these scatterers might include cell-to-cell interfaces, intercellular connective tissue, or subcellular organelles. The presence of relatively large vascular structures (large compared to the wavelength) within the tissue might also contribute an angle-dependent specular component to cardiac tissue scattering. In an attempt to delineate the precise biochemical or anatomic basis for myocardial backscatter, Miller and coworkers have performed a number of studies implicating collagen as an important contributor to scattering (Miller et al., 1976; Mimbs et al., 1977, 1980). Tissue concentration of hydroxyproline correlated highly with attenuation and with backscatter. The amplitude of backscatter was shown to fall in rabbit

### Table 4

<table>
<thead>
<tr>
<th>Dog</th>
<th>Infarct regions</th>
<th>Normal regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.106(PW)</td>
<td>2.434(LW)</td>
</tr>
<tr>
<td>2</td>
<td>1.521(SEP)</td>
<td>2.434(LW)</td>
</tr>
<tr>
<td>4</td>
<td>0.593(PW)</td>
<td>1.781(LW)</td>
</tr>
<tr>
<td>4</td>
<td>1.559(SEP)</td>
<td>1.781(LW)</td>
</tr>
<tr>
<td>5</td>
<td>0.628(PW)</td>
<td>1.427(LW)</td>
</tr>
<tr>
<td>6</td>
<td>0.205(PW)</td>
<td>0.391(LW)</td>
</tr>
<tr>
<td>6</td>
<td>0.389(SEP)</td>
<td>0.391(LW)</td>
</tr>
<tr>
<td>7</td>
<td>0.405(PW)</td>
<td>0.355(LW)</td>
</tr>
</tbody>
</table>

Mean 0.800 ± 0.186 1.374 ± 0.315

PW = posterior wall; LW = lateral wall; SEP = ventricular septum.

### Table 5

<table>
<thead>
<tr>
<th>Dog/region</th>
<th>Preocclusion</th>
<th>Postocclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/PW</td>
<td>5.860</td>
<td>0.671</td>
</tr>
<tr>
<td>2/SEP</td>
<td>3.365</td>
<td>2.514</td>
</tr>
<tr>
<td>4/PW</td>
<td>4.000</td>
<td>-0.619</td>
</tr>
<tr>
<td>4/SEP</td>
<td>5.042</td>
<td>1.639</td>
</tr>
<tr>
<td>5/PW</td>
<td>2.013</td>
<td>0.650</td>
</tr>
<tr>
<td>6/PW</td>
<td>-0.338</td>
<td>-1.148</td>
</tr>
<tr>
<td>7/PW</td>
<td>-0.241</td>
<td>-0.640</td>
</tr>
</tbody>
</table>

Mean 2.817 ± 0.926 0.438 ± 0.503*

PW = posterior wall; SEP = ventricular septum. * P < 0.01 compared to preocclusion images.

### Table 6

<table>
<thead>
<tr>
<th>Dog/region</th>
<th>Preocclusion</th>
<th>Postocclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/PW</td>
<td>15.179</td>
<td>0.945</td>
</tr>
<tr>
<td>1/LW</td>
<td>-1.145</td>
<td>-1.191</td>
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<tr>
<td>1/SEP</td>
<td>-0.845</td>
<td>-0.321</td>
</tr>
<tr>
<td>2/LW</td>
<td>10.020</td>
<td>6.419</td>
</tr>
<tr>
<td>3/PW</td>
<td>7.721</td>
<td>37.624</td>
</tr>
<tr>
<td>3/LW</td>
<td>1.270</td>
<td>11.563</td>
</tr>
<tr>
<td>3/SEP</td>
<td>4.707</td>
<td>5.025</td>
</tr>
<tr>
<td>4/LW</td>
<td>0.697</td>
<td>3.146</td>
</tr>
<tr>
<td>5/LW</td>
<td>2.949</td>
<td>1.925</td>
</tr>
<tr>
<td>5/SEP</td>
<td>52.315</td>
<td>3.664</td>
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<tr>
<td>6/LW</td>
<td>-0.117</td>
<td>-0.459</td>
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<tr>
<td>7/LW</td>
<td>-0.723</td>
<td>-0.518</td>
</tr>
<tr>
<td>7/SEP</td>
<td>0.521</td>
<td>-0.601</td>
</tr>
</tbody>
</table>

Mean 7.119 ± 4.007 5.172 ± 2.885

PW = posterior wall; LW = lateral wall; SEP = ventricular septum.

### Table 7

<table>
<thead>
<tr>
<th>Dog</th>
<th>Infarct regions</th>
<th>Normal regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.671(PW)</td>
<td>6.419(LW)</td>
</tr>
<tr>
<td>2</td>
<td>2.514(SEP)</td>
<td>6.419(LW)</td>
</tr>
<tr>
<td>4</td>
<td>-0.619(PW)</td>
<td>3.146(LW)</td>
</tr>
<tr>
<td>4</td>
<td>1.639(SEP)</td>
<td>3.146(LW)</td>
</tr>
<tr>
<td>5</td>
<td>0.650(PW)</td>
<td>1.935(LW)</td>
</tr>
<tr>
<td>6</td>
<td>-1.148(PW)</td>
<td>-0.459(LW)</td>
</tr>
<tr>
<td>6</td>
<td>-0.892(SEP)</td>
<td>-0.459(LW)</td>
</tr>
<tr>
<td>7</td>
<td>-0.640(PW)</td>
<td>-0.318(LW)</td>
</tr>
</tbody>
</table>

Mean 0.272 ± 0.467* 2.454 ± 1.022

PW = posterior wall; LW = lateral wall; SEP = ventricular septum. * P < 0.01 compared to normal regions.
myocardium after perfusion with collagenase, a procedure which did not change the tissue concentration of hydroxyproline (Mimbs et al., 1980). This suggests that intact collagen may be necessary for increased backscatter in chronic infarction. These workers have also shown alterations in attenuation of ultrasound as soon as 15 minutes after coronary occlusion, long before deposition of collagen occurs (O'Donnell et al., 1979). Edema may be responsible for a change in ultrasound velocity or attenuation at this early stage of acute myocardial infarction (Mimbs et al., 1981).

In our experiments, ultrasound studies were performed 2 days after coronary occlusion, and the histological evaluation showed evidence of acute myocardial necrosis. Therefore, the alteration in backscatter presumably was related to the presence of edema, cellular disorganization, and, possibly, leukocytic infiltration in the area of infarction. Another important contributor to altered echo amplitude data may have been the altered wall dynamics, i.e., abnormal wall thickening or frank wall thinning. Since abnormal regional wall dynamics might affect the relative fiber architecture and myofibrillar spacing, this may be an important source of altered echo amplitude information. The present study did not allow assessment of the relative contribution of these factors.

Analysis of Average Gray Level

Chronic myocardial infarction has been occasionally detected by noting areas of increased brightness on M-mode (Rasmussen et al., 1978) and 2D echocardiograms, and this detection may be enhanced by a pseudocolor display (Moynihan et al., 1980). However, no definite increase in regional echo brightness due to acute infarction has been documented, although a suggestive finding has been presented by vonRamm and Smith (1979). In contrast, Werner and coworkers have reported a zone of sonolucency (decreased brightness) in acute infarction (Werner et al., 1981). We found that average gray level was too variable in normal and infarcted regions to be used as a reliable indicator of acute ischemic injury. These findings suggest that during the acute period of infarction, the complex and somewhat variable structural alterations (edema, cellular infiltration, hemorrhage) produce variable amplitudes of backscatter. Further, technical artifacts may produce significant alterations in mean gray level. First, the presence of relatively large structures (e.g., blood vessels) within tissue regions may engender specular reflections which are probably angle-dependent and which are of larger amplitude than the amplitudes of scattering from other tissues. Therefore, differing transducer angulations may produce alterations in regional backscatter. Second, our experimental design involved the transfer of information through two optical systems (the photographic step and the digitization by video camera). Artifacts or data compression related to these procedures may have altered global and regional gray level values. Third, the current system of receiver gain compensation for attenuation in two-dimensional echocardiographic imaging is a source of artifactual regional gray level variations (Melton and Skorton, 1981). Currently, gain compensation for attenuation is achieved in our system on a range-dependent basis only. That is, signals from regions of the image at a constant distance from the transducer are compensated (amplified) the same amount regardless of line-of-sight and of the actual attenuation due to the different tissues between the transducer and region of interest. Therefore, significant differences in amplitude (or gray level) must be anticipated based on differential attenuation, quite aside from differences which arise because of physical structural differences (Melton and Skorton, 1982).

Comparison with Previous Studies

In an early, in vitro study, Namery and Lele demonstrated a difference between the acoustic impedance of infarcted and normal cardiac tissue (1972).
Gramiak and coworkers (1979) similarly showed differences in the amplitude of returning ultrasound from infarcted compared to normal myocardium in vitro. Mimbs and coworkers (1977) demonstrated two acoustic techniques which detected myocardial ischemia. Their initial studies were performed in vitro (excised pieces of myocardium) and in transmission mode, and identified the frequency dependence of attenuation as a parameter capable of separating normal from ischemic myocardium. This group has also used a measure of integrated backscatter to separate infarcted from normal tissue on the basis of pulse-echo as opposed to transmission mode examination (Mimbs et al., 1980, 1981). These latter studies have identified significant differences in both attenuation and backscatter in infarcted compared to normal myocardium. The investigations were done using broad band transducers, typically with a frequency spectrum from approximately 2 to 10 MHz. A measurable increase in backscatter after infarction was, however, also demonstrated in vitro using 2.25 MHz, a common clinical transducer frequency (Mimbs et al., 1980). All of these studies have indicated an increase in backscatter or in attenuation in infarcted myocardium, consistent with our results. The possible clinical pertinence of these observations is also supported by the occasional direct visualization of scar on routine echocardiograms (Rasmussen et al., 1978).

Therefore, previous work has suggested possible physical bases of increased ultrasound backscatter after infarction, and clinical observations have shown that such differences may occasionally be directly visualized. The present approach consisted of the digital image analysis of two-dimensional echocardiograms to extract information not readily visible in the images obtained. Our study has shown that alterations in acoustic properties of myocardium can be detected in a quantitative manner, using a clinically relevant (i.e., closed-chest) model by an analysis of regional gray-level distributions. Its routine clinical use, however, must await technical improvements aimed at the remaining problems in detecting altered backscatter reliably in intact subjects.

Future Implications

We feel that an important problem must be addressed before the techniques demonstrated in this study, or in the other studies cited, will be closer to being useful on a routine basis. A method is needed for correctly compensating for tissue intervening between the transducer and the region of interest. This intervening tissue will alter our ability to measure and differentiate accurately backscattered ultrasound of normal from infarcted regions of myocardium. Some advances have recently been made toward this goal (Cohen et al., 1981; Melton and Skorton, 1981).

The ability to identify correctly areas of myocardial ischemia or infarction by ultrasound would represent an easily used non-invasive, and non-ionizing method of infarct imaging. This would be of immense value to the clinician caring for patients with myocardial infarction, as well as to investigators studying the pathophysiology of this common condition.

Appendix

Calculations of Skewness and Kurtosis of Gray-Level Histograms

Values for skewness and kurtosis of the gray-level distributions were calculated using the standard SAS statistical software packages. First, a standardized variable, \( Z \), is computed:

\[
Z = \frac{(X - \bar{X})}{S},
\]

where \( \bar{X} = \text{mean of the distribution} \) and \( S = \text{standard deviation of the distribution} \).

The following calculations are then performed:

\[
\text{Skewness} = \frac{N}{(N-1)(N-2)} \sum Z^3
\]

\[
\text{Kurtosis} = \frac{N(N+1)}{(N-1)(N-2)(N-3)} \sum Z^4 - \frac{3(N-1)(N-1)}{(N-2)(N-3)}
\]

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