Estimation of Myocardial Infarct Size With Ultrasonic Tissue Characterization

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Background. Ultrasonic tissue characterization (UTC) can distinguish normal from infarcted myocardium. Infarcted myocardium shows an increase in integrated backscatter and loss of cardiac cycle-dependent variation in backscatter. The cyclic variation of backscatter is closely related to regional myocardial contractile function; the latter is a marker of myocardial ischemia. The present study was designed to test the hypothesis that intramural cyclic variation of backscatter can map and estimate infarct size.

Methods and Results. Transmural myocardial infarction was produced in 12 anesthetized, open-chest dogs by total occlusion of the left anterior descending coronary artery for 4 hours. A real-time ultrasonic tissue characterization instrument, which graphically displays integrated backscatter Rayleigh 5, cardiac cycle-dependent variation, and patterns of cyclic variation in backscatter, was used to map infarct size and area at risk of infarction. Staining with 2,3,4-triphenyltetrazolium chloride (TTC) and Patent Blue Dye was used to estimate infarct size and the area at risk, respectively. The ratio of infarct size to area at risk of infarction determined with UTC correlated well with that determined with TTC ($r=0.862$, $y=23.7\pm0.792x$). Correlation coefficients for infarct size and area at risk were also good ($r=0.736,y=12.3\pm737x$ for infarct size and $r=0.714,y=5.80\pm1.012x$ for area at risk). However, UTC underestimated both infarct size and area at risk.

Conclusions. Ultrasonic tissue characterization may provide a reliable, noninvasive method to estimate myocardial infarct size. (Circulation 1991;83:1419–1428)

The extent of myocardial necrosis associated with myocardial infarction is of primary importance in determining whether left ventricular dysfunction develops, including the complication of cardiogenic shock or pulmonary edema.1 This observation has led to extensive efforts to develop reliable noninvasive methods for estimating infarct size.1–19 The methods used presently vary from enzymatic measurements to imaging techniques. Each of the currently used methods has certain limitations. Measurement of creatine kinase and the myocardial specific enzyme CK-MB, though sensitive in indicating myocardial necrosis, is not an accurate method for estimating infarct size.20–23 In addition to poor estimation of infarct size, this technique is also time consuming. Estimating infarct size by imaging with $^{99m}$Tc stannous pyrophosphate using single photon emission computed tomography (SPECT) is a sensitive and specific technique.24–27 However, it is difficult to distinguish myocardial uptake from bone uptake and blood pool activity, and serial imaging over 3 to 4 days is not practical. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are more recent, promising techniques for quantification of infarct size.28–31 However, these techniques are expensive and are not widely available. Radionuclide ventriculography32,33 and two-dimensional echocardiography34,35 provide information regarding abnormal segmental wall motion, which is a result of myocardial ischemia and infarction, and indirectly estimate infarct size. Contrast echocardiography with hydrogen peroxide has provided accurate estimation of infarct size in animals.36 However, development of a contrast agent that can be safely used in patients is still awaited.

Ultrasound tissue characterization (UTC) is based on the hypothesis that pathological changes of myocardial structure and function result in alterations of the interaction of ultrasound with tissue.37 It has been previously demonstrated that UTC can distinguish normal from infarcted myocardium.37–40 Infarcted myocardium shows an increase in integrated...
backscatter and a loss of cardiac cycle-dependent variation in backscatter. The cyclic intramural variation of backscatter is closely related to regional myocardial contractile function; the latter is a marker for myocardial ischemia/infarction. The present study was designed to test the hypothesis that cyclic intramural variation of backscatter can map and estimate infarct size.

Methods

General Preparation

Adult mongrel dogs of either sex weighing 15–25 kg were fasted overnight, anesthetized with sodium pentobarbital (25 mg/kg) and sodium barbital (200 mg/kg), and ventilated with room air (1 l/min) enriched with oxygen (0.2–1 l/min). Respiratory rate and tidal volume were adjusted to maintain arterial blood gases within normal physiological limits. Rectal temperature was monitored and maintained at 37.5±1°C by heating pad and servomechanical controller.

Left ventricular and arterial pressures were recorded by a 7F dual pressure transducer-tipped catheter (Millar SPR-277) passed through the left carotid artery into the left ventricle and ascending aorta, respectively. The right femoral vein and left femoral artery were catheterized for drug administration and withdrawal of reference arterial blood samples used in determining myocardial tissue blood flow, respectively. Peak positive dP/dt, an index of left ventricular global contractility, was obtained by electronic differentiation of the left ventricular pressure pulse. A triangular wave signal of known slope was used to calibrate the differentiator. Thoracotomy was performed at the left fifth intercostal space. The lung was retracted and the heart suspended in a pericardial cradle. A 1.0–1.5-cm segment of the left anterior descending coronary artery (LAD) was carefully dissected from surrounding tissue and ligated. The right carotid artery was catheterized with large-bore polyethylene tubing connected to a metal tip for insertion into the LAD to produce a carotid-to-LAD shunt. A cannulating electromagnetic flow probe (Statham 73817) was placed in the circuit to measure coronary blood flow during reperfusion. The flow probe was calibrated with blood at the completion of each experiment. LAD occlusion was produced by occluding the carotid-to-LAD shunt. A catheter was placed in the LAD distal to the occlusion site, and retrograde coronary flow was drained to the atmosphere is an effort to eliminate the majority of coronary collateral blood flow.

Regional myocardial contractile function (segment shortening) was measured in the perfusion territory of the LAD (ischemic), left circumflex coronary artery (normal), and border zone (as defined by UTC) using three pairs of piezoelectric crystals. The crystals were inserted approximately 10–15 mm apart and 7–10 mm deep within the left ventricular wall in a circumferential plane parallel to the expected subendocardial muscle fiber orientation. Subsequently, the crystals were secured with a single suture, and the depth (average, 8.8±1.0 mm) of each was verified at the completion of the experiment. The leads of each crystal were connected to an amplifier that transformed the sound pulse transmitted between the two crystals into an electronic signal proportional to the distance between the crystals. The tracings were monitored on a Soltec oscilloscope (model 520). Diastolic segment length was determined as the distance between the two crystals at the beginning of the rising phase of positive dP/dt (onset of isovolumetric contraction), and systolic segment length was measured at peak negative dP/dt. The diastolic and systolic segment lengths were normalized to a control value of 10 for the initial diastolic segment length by the method of Theroux et al.41 Percent segment shortening (%SS) was calculated from the equation

\[
\%SS = \frac{(DL - SL)}{DL} \times 100
\]

where DL is the diastolic and SL is the systolic segment length. The piezoelectric crystals were disconnected during ultrasonic backscatter data acquisition to avoid any potential interference.

A catheter was placed in the left atrium by way of the atrial appendage for injection of radioactive microspheres. Heart rate was determined from the electrocardiogram (limb lead II). The electrocardiogram, phasic and mean aortic and left ventricular systolic and end diastolic pressures, peak positive dP/dt, phasic and mean coronary blood flow, and regional segment function were continuously recorded on a polygraph (model 7, Grass Instrument Co., Quincy, Mass.).

Infarcted myocardium was identified by the method of Warltier et al.42 Briefly, at the completion of each experiment, Patent Blue Dye was injected into the left atrium while saline was simultaneously injected at arterial pressure into the LAD immediately distal to the site of occlusion. In this manner, this ischemia-reperfused area (area at risk supplied by LAD) remained unstained, and normal myocardium (circumflex territory) was stained dark blue. This unstained area formed the area at risk of infarction. The heart was then electrically fibrillated, immediately removed, and sliced transversely from apex to base in sections approximately 1 cm wide. Myocardium stained blue (normal areas) was separated from the nonstained region (area at risk) in each slice. Samples from the area at risk and normal areas were incubated at 37°C for 15 minutes in 1% 2,3,5-triphenyltetrazolium chloride (TTC) in 0.1-M phosphate buffer. Within the area at risk as determined by a lack of Patent Blue Dye, the TTC stained noninfarcted myocardium with a brick-red color, indicating the presence of dehydrogenase enzymes and leaving infarcted tissue unstained. Thus, the infarct remained as a clearly defined pale zone in each slice. The infarcted region was then separated from the remainder of the area at risk (ischemic but
noninfarcted) and weighed, and infarct size was expressed as a percent of the area at risk.

The distribution of coronary blood flow within left ventricular myocardium was determined by the radioactive microsphere technique. Carbonized plastic microspheres (New England Nuclear, Boston, Mass.) 15±3 μm in diameter labeled with ⁴¹Ce, ⁵¹Cr, ¹⁰³Ru, or ⁹⁵Nb were obtained as 1 mCi nuclide in 5 ml isotonic saline, to which one drop of tween 80 was added to minimize aggregation. The mixture was sonicated (model B3, Branson Ultrasonics Corp., Danbury, Conn.) for at least 5 minutes and agitated before injection in a Vortex mixer (model K-500-2, Scientific Industries, Inc.) for 5 minutes. Approximately 2–4×10⁶ spheres were injected into the left atrium in a total volume of 0.75 l ml per isotope, and each was followed by an 8-ml saline wash. A few seconds before the injection of microspheres, a timed collection of reference flow from the femoral artery was started and maintained at a constant rate (7 ml/min) for 2 minutes with an infusion-withdrawal pump (model 941, Harvard Apparatus, South Natick, Mass.). At the end of each experiment, three to five tissue samples were selected from the central ischemic and normal zones. Each tissue sample was subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal size (0.5–1.0 g). The samples were weighted and placed in plastic scintillation vials; the activity of each isotope was determined at four energy windows in an Auto-gamma spectrometer (Packard 5000 series, Packard Instrument Co., Inc., Meriden, Conn.). Similarly, the activity of each isotope in the tissue sample was also calculated by correcting for energy overlap. Myocardial blood flow (Qm, milliliters per minute per gram) was calculated from the equation

\[ Q_m = Q_r C_m / C_r \]

where Qr is the rate of withdrawal (milliliters per minute) of the reference blood sample, Cr is the true activity (counts per minute) of the reference blood sample, and Cm is the true activity (counts per minute per gram) of the myocardial tissue sample. Myocardial blood flow values of tissue samples from the ischemic and normal areas were pooled for calculation of flow in the subepicardium, midmyocardium, and subendocardium of either region. Transmural myocardial blood flow was the weighted average of flows in the subepicardium, midmyocardium, and subendocardium in ischemic or normal zones.

Ultrasonic Instrumentation and Data Analysis

Ultrasonic backscatter was measured with a research instrument (Marquette Electronics [CTC-II]), a prototype system based on our previous measurement equipment.⁴⁰,⁴³–⁴⁶ The CTC-II consisted of a transmitter-receiver, high-resolution display control panel, and microprocessor circuitry constructed in a mobile cart. The transmitter produced gated carrier bursts (1 μsec) that excited the transducer, which had a calibrated frequency response. The receiver amplified and demodulated the returned echoes for analog-to-digital conversion. The real-time analysis and data-recording procedures were preprogrammed and called up from the control panel so that the microprocessor directed the signal processing, diagnostic display, and data recording on floppy disk.

Myocardial tissue has been shown to backscatter ultrasound with a Rayleigh Spectrum.⁴⁶ Integrated backscatter Rayleigh 5 (IBR5) is an absolute measure of the intensity of this backscattered spectrum at 4 MHz.⁴⁷ The CTC-II was programmed to produce real-time measurements and display IBR5 and a cardiac cycle–dependent variation of IBR5. The displayed information was presented (as in Figure 3) graphically from QRS onset to just 20 msec before the next QRS onset; the data were also archived on a floppy disk for later review. An electrocardiographic module in the CTC-II permitted the microprocessor to synchronize the data analysis with the QRS complex. The transducer was a 6-mm–diameter, unfocused disk with a one-quarter wavelength–matching layer on the radiating face and an impedance-matching transformer connecting it to the electrical transmission line. The transducer’s bandwidth (at the −6-dB point) exceeded the 4.5–6.5-MHz band used and was measured by self-reciprocity calibration methods involving a perfectly reflecting plane as previously described.⁴⁵ The diffraction (or radiation-field response) of the transducer was measured with a suspension of microspheres as a calibration target.⁴⁶

The transducer was fitted with a 2-cm water-filled fixture, closed with a finger cot, and filled with saline. The fixture maintained the transducer approximately 18 mm from the epicardium, which positioned the myocardium at a calibrated portion of the radiation field of the transducer. The IBR5 echoes were produced by the signal processing discussed below and displayed as real-time echoes. While observing the echo patterns on the A-mode display, a range gate denoting the sample volume was positioned within the myocardium. IBR5 backscatter magnitude for echoes in the sample volume was computed in real time and displayed as a time waveform starting with the QRS complex and extending for the entire cardiac cycle (with a resolution of 20 msec).

An extended bandwidth IBR5 echo was produced by rapidly transmitting separate 1-μsec gated carrier bursts at 4.5, 5.5, and 6.5 MHz, respectively (Figure 1[a]). The resulting three-echo patterns (Figure 1[b]) were signal processed by scaling and combining the three echoes by use of mathematical methods previously described.⁴⁶ The three transmissions and their returned echo patterns all occur within a short time (1 msec) so that each represents the same tissue state observed with a unique frequency band. The magnitudes of the three echo signals were separately scaled to adjust for the following attributes: transmitter level, receiver gain, transducer frequency calibration, diffraction calibration, bulk absorption (0.5 dB/cm MHz), and the Rayleigh scattering spectrum (fourth
power of frequency) of the tissue (Figure 1[c]). The corrected echoes resulting from this process possess an absolute magnitude and a perfectly flat frequency content (whitened spectrum) and represent an absolute measure of the backscatter in square centimeters of reflecting material per cubic centimeter of volume.\(^47\) The extended bandwidth IBR5 echoes of Figure 1(c) were formed by aligning the three waveforms in time and adding the squares to produce a composite echo signal having a bandwidth in excess of 2 MHz. The new composite waveform retained the time resolution of the original waveforms (1 µsec) arising from the gated carrier transmissions. The IBR5 echoes could then be averaged within the designated sample volume, with the average forming the magnitude of the IBR5 for that 20-msec interval (Figure 1[d]). Each 20-msec sample was associated with its time from QRS within a heart beat to form a waveform starting at the QRS (Figure 1[f]). The heart interval display was formed in real time by averaging the waveforms from the last eight beats (Figure 1[e]). The real-time heart interval display was presented on the display screen in decibels versus time from the detected QRS time. The CTC-II stored the heart interval display raw data together with various other settings (e.g., transmission level) on a floppy disk for further processing and review.

An IBM-compatible computer was used to calculate the Fourier coefficient of amplitude modulation (FAM) by correlating the IBR5 of the cardiac cycle display with the sine wave whose period matched the cardiac cycle (i.e., the fundamental Fourier component). This Fourier component was the sine wave that best matched the amplitude modulation in both magnitude excursions and the phase relative to the cardiac cycle. The FAM used was twice the magnitude of the Fourier coefficient and represented the peak-to-peak excursion of the backscatter. The phase of the FAM relative to the cardiac cycle, expressed as the percent of the cardiac cycle at which the sinusoid passed from negative to positive, was also determined. In previous work from this laboratory, it was demonstrated that the normal heart presents backscatter that is weak (negative part of sine wave) in systole and strong (positive part of sine wave) in diastole, with the transition near the 50% point of a cardiac cycle.\(^46\)

**Experimental Design**

After completion of surgery and a 30-minute equilibration period, the first injection of radioactive microspheres was administered, and control mea-

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**FIGURE 1.** System diagram of echocardiographic measurements. Separate transmissions are performed at three frequencies (a). This results in three separate echo patterns within 1 millisecond (b). The three echoes are signal processed to form the extended bandwidth IBR5 echo (c). Averaging within sample volume produces one 20-msec value of the IBR5 waveform (d). Heart interval display is an average over last 8 beats with the QRS detection as an alignment (e, f).
FIGURE 2. Panel A: Diagrammatic representation of frontal view of left ventricle showing ultrasonic mapping of infarcted (dark-shaded), border (light-shaded), and normal (unshaded) regions with corresponding graph of cyclic variation in backscatter. Light- and dark-shaded regions together represent area at risk of infarction. Panel B: Diagrammatic representation of thickness of left ventricular anterior wall. Ultrasonic gate (arrows indicate thickness) was positioned between endocardium and epicardium.

measurements of IBR5, FAM, and patterns of cyclic variation were obtained from circumflex and LAD perfusion territories. A 4-hour total LAD occlusion was then produced by occlusion of a carotid-to-LAD shunt. To ensure transmural infarction, retrograde coronary flow in the LAD was diverted from the distal bed. Each dog was heparinized with 4,000 units to prevent clotting, and all blood removed by the retrograde flow collection was returned by way of the femoral vein catheter. The second and third radioactive microspheres were administered at 12 minutes and 4 hours after the onset of coronary occlusion. After 4 hours of LAD occlusion the LAD perfusion territory was reperfused, and after 30 minutes the fourth radioactive microsphere was administered. The normal, border, and infarcted zones were mapped with the transducer placed directly on the cardiac surface.

Figures 2A and 2B are diagrammatic representations of ultrasonic mapping of left ventricular surface and wall thickness. The transducer was placed on the surface of the heart in the normal region. While observing the echo patterns on A-mode display, a range gate denoting the sample volume was positioned in the myocardium as previously reported.40

FIGURE 3. Panel A: Real-time graphic display of cardiac cycle-dependent variation in IBR5 from normal myocardium. Point 0 on the horizontal axis corresponds to R wave of electrocardiogram. Note that IBR5 is weak during systole and strong during diastole. Heart rate is 150 beats/min. Panel B: Real-time graphic display of cardiac cycle-dependent variation in IBR5 from infarcted myocardium. Note complete reversal of cardiac cycle-dependent variation, which is strong during systole and weak during diastole. Heart rate is 154 beats/min. Panel C: Real-time graphic display of cardiac cycle-dependent variation in border zone myocardium. Note blunting of cardiac cycle-dependent variation, which is flat throughout cardiac cycle. Heart rate is 155 beats/min.
Specular epicardial and endocardial echos were excluded. The transducer was systematically moved inch by inch from normal to infarcted myocardium. While observing IBR5 in real time. Normal, border, and infarcted regions thus identified were directly marked on the surface with ink and wall thickness noted. As shown in Figures 2A and 2B, the area at risk was formed by a combination of border (light regions) and infarcted (dark region) myocardium. After the heart was removed from the chest, these regions were traced on an acetate overlay. The area at risk and area of infarction were determined by planimetry with a commercially available analysis system (Nova Microsonics, Indianapolis, Ind.). The volumes of infarcted region and area at risk of infarction were estimated by multiplying planimetered area wall thickness. Weight in grams was determined by multiplying volume by 1.05, specific gravity of myocardium for comparison with weight determined with TTC staining.

Regions were defined as normal if the cardiac cycle-dependent variations were strongest during diastole and weakest during systole (Figure 3A), infarcted if a complete reversal in cyclic variation (weak during diastole and strong during systole) occurred (Figure 3B), and border if a blunting in cyclic variation was present (Figure 3C). This estimate was then compared with the absolute mass of infarcted tissue as determined by TTC staining or mass of infarct expressed as a percent of the area at risk with Pearson's linear regression analysis. The UTC area at risk was similarly computed from the traced infarct and border zones. Data for regional blood flow, segment shortening, and IBR5 were analyzed by Student's paired t test.

**Results**

Hemodynamic data are summarized in Table 1 and did not change significantly during occlusion and reperfusion. Correlation between the percent of the mass infarct and area at risk of infarct as determined by UTC and TTC staining is illustrated in Figure 4A. There was an excellent correlation between the two methods (r=0.862, y=23.7+0.792). Correlation between absolute infarct weight determined by UTC and TTC (Figure 4B) was also good (r=0.736, y=12.3+0.737x). UTC consistently underestimated the absolute infarct size of these small areas. For the areas at risk as determined by UTC and TTC, the correlation coefficient was 0.714, with y=5.80+1.012x (Figure 4C). UTC was consistent with TTC for these larger areas.

Data of regional blood flow in normal (left circumflex-perfused), infarcted (LAD-perfused), and border regions are summarized in Table 2. Blood flow to the infarcted region was significantly reduced compared with the control region during occlusion and reperfusion. Diversion of retrograde collateral flow produced uniform transmural myocardial perfusion of less than 0.10 ml/min per gram, ensuring production of a transmural infarct. The transmural flow in the border region was 0.35±0.04 ml/min per gram after 4 hours of occlusion. After 30 minutes of reperfusion, the flow within the ischemic but noninfarcted (border) zone returned to control level, but the infarcted zone demonstrated the “no reflow” phenomenon (i.e., flow remained significantly depressed).

The normal regions showed segment shortening (16±3%). The infarcted regions consistently showed systolic bulging (~8±2%) and the border zones either systolic bulging or lack of segment shortening (~5±5%). Mean IBR5 was significantly higher in the infarcted zone than in the normal region (~44±1.5 dB versus ~49±1.0 dB, respectively; p<0.01). IBR5 in the border zone was normal (~47±1.0 dB). FAM was 6±1.8 dB in the normal zone, 2.4±1.0 dB in the border zone (p<0.01), and ~5.2±1.2 dB in the infarcted zone, with a complete phase reversal (Table 3).

**Discussion**

The ideal method for estimating myocardial infarct size should be noninvasive, accurate, and easily used

**Table 1. Hemodynamic Data**

<table>
<thead>
<tr>
<th></th>
<th>Before occlusion</th>
<th>4 hours after occlusion</th>
<th>30 minutes after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>152±5</td>
<td>155±6</td>
<td>150±8</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>120±5</td>
<td>113±6</td>
<td>115±9</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>81±5</td>
<td>80±6</td>
<td>87±6</td>
</tr>
</tbody>
</table>

**Table 2. Regional Myocardial Blood Flow (ml/min per gram) Data**

<table>
<thead>
<tr>
<th>Area</th>
<th>Before occlusion</th>
<th>4 hours after occlusion</th>
<th>30 minutes after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal zone</td>
<td>1.09±0.08</td>
<td>1.20±0.14</td>
<td>1.03±0.17</td>
</tr>
<tr>
<td>Border zone</td>
<td>0.97±0.08</td>
<td>0.35±0.04*†</td>
<td>0.91±0.13</td>
</tr>
<tr>
<td>Infarcted zone</td>
<td>0.95±0.12</td>
<td>0.06±0.03*‡</td>
<td>0.16±0.18*††</td>
</tr>
</tbody>
</table>

*All values expressed as mean±SEM.
†p<0.05 significantly different from before-occlusion value.
‡p<0.05 significantly different from respective normal zone.
§p<0.05 significantly different from respective ischemic zone.
Blue Dye for estimating area at risk of developing an infarct have been documented as quite accurate.\textsuperscript{42} The most probable reason for underestimation of infarct size is the relatively small size of the infarct (e.g., 2 cm across) relative to the spatial resolution of our 6-mm–diameter transducer. If the boundary of a 2-cm infarct is displaced by only 3 mm, the resulting estimate will report 75% of the actual area. This would mean that the transducer had to consistently be 3 mm, or half of its diameter, into the periphery of the infarct before proper detection occurred. Moreover, UTC revealed no bias when performed on the relatively larger areas at risk. A real-time imaging ultrasound system should overcome this problem. By experimental design, most of the infarcts were localized to the anterior wall of the left ventricle; however, in some cases where the septum was involved, data from the anterior wall were used. This is another likely cause of underestimation of infarct size. Histochemical staining techniques such as TTC depend on reduction of colorless tetrzolium salt by dehydrogenase enzymes to brightly colored brick-red compounds. It is possible that hemorrhage into the infarct may also affect staining of tissue with TTC. However, tetrzolium stains have been validated by comparison with other techniques.\textsuperscript{42,48,49} Ultrasonic mapping of normal, border, and infarcted regions was based entirely on cyclic variation in backscatter because integrated backscatter could not distinguish infarcted from moderately ischemic myocardium. These observations are similar to those of Milunski et al.\textsuperscript{50,51} who also used cyclic variation and not integrated backscatter to identify stunned but viable myocardium.

Myocardial tissue characterization can not only distinguish normal from acutely ischemic myocardium\textsuperscript{52,53} but can accurately reflect the severity of ischemic injury. Wickline et al.\textsuperscript{53} observed that phase-weighted amplitude modulation of cyclic variation in backscatter could differentiate reversible from irreversible ischemic myocardial injury. In our study, real-time graphic display of cardiac cycle–dependent variation relative to the R wave of the electrocardiogram incorporated amplitude and phase of cyclic variation, which corresponds to the phase-weighted amplitude modulation of Wickline et al. In this study, we postulated that phase and amplitude of cyclic variation will distinguish normal, moderately ischemic, and infarcted regions of myocardium. This was corroborated by the degree of reduction in transmural blood flow in the border and infarcted zones (Table 2). Blood flow in the border zone was significantly higher than that in the infarcted zone. A histological examination of the border and infarcted regions was not performed in the study, and one can speculate from regional blood flow and ultrasound data that the border zone was not as severely ischemic as the infarcted zone.

The literature offers conflicting views on the presence of border zones. Marcus et al.\textsuperscript{54} found no evidence for a geometrically well defined border zone.
of moderately ischemic myocardium surrounding and separating severely ischemic myocardium from normal tissue after 5 minutes of coronary occlusion. In the dog heart, Hirzel et al. found a sharp demarcation between normal tissue and that in which creatine phosphokinase depletion was complete. Barlow et al. found a border zone that appeared as a patchwork of ischemic and normally perfused tissues sharing sharp interfaces. Cox et al. found a border zone surrounding severely ischemic tissue; damage in this border zone was confined to mitrochondrial swelling. Hearse et al. concluded from their findings that the border zone probably consisted of homogenously damaged cells in which the damage was less severe than in the central ischemic zone. We cannot say with certainty whether the zone of intermediate changes shown by UTC represents a true border zone or a mix of normal and infarcted tissue.

Recent studies have shown the variability of infarct size in canine myocardium after sustained coronary occlusion at similar anatomic sites. The area at risk of infarction may be different depending on heart size, coronary anatomy, and development of coronary collateral circulation. Lowe et al. and Judgutt et al. have shown that the amount of infarction is closely related to the size of the occluded bed. They have suggested that the area at risk and the size of the infarct related to this parameter should be measured in each experiment. We measured area at risk of infarction with Patent Blue Dye and size of infarct with TTC. Both of these techniques have been previously validated in our laboratory.

Recent studies have used a two-dimensional tissue characterization imaging system through the intact chest wall in animals and patients to detect stunned myocardium. Real-time tissue characterization has also been used to detect remote myocardial infarction. In this study, data from open-chest dogs not only require validation in patients but also comparison with conventional wall motion abnormalities to determine if UTC provides additional information. Further studies are needed to validate those observations in closed-chest animals and patients, with a real-time imaging system thus obviating the epicardial surface mapping. In summary, UTC offers an accurate, noninvasive method for estimation of infarct size that should be helpful in assessing therapeutic interventions directed toward infarct reduction.

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