Ultrasonic Tissue Characterization With Integrated Backscatter

Acute Myocardial Ischemia, Reperfusion, and Stunned Myocardium in Patients

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We have previously shown in studies of experimental animals that myocardium exhibits a cardiac cycle-dependent variation of integrated backscatter that reflects regional myocardial contractile performance and that is blunted promptly after arterial occlusion and recovers after reperfusion. To define the clinical utility of ultrasonic tissue characterization with integrated backscatter for detection of acute myocardial infarction and reperfusion, 21 patients (14 men and seven women) were studied in the cardiac care unit within the first 24 hours (mean time, 11.3 hours; range, 3.5–23.8 hours) after the onset of symptoms indicative of acute myocardial infarction with conventional two-dimensional and M-mode echocardiography and with analysis of integrated backscatter. The magnitude of cyclic variation of integrated backscatter was measured from several sites within acute infarct regions and normal regions remote from the infarct zone for each patient. The average magnitude of cyclic variation among all patients (n=21) was 4.8±0.5 dB in normal regions compared with 0.8±0.3 dB in infarct regions (p<0.05) within the first 24 hours after the onset of symptoms. Among the patients who had two studies, 15 (mean, 7.1 days; range, 2–31 days for second study) underwent coronary arteriography to define vessel patency. In patients with vessels with documented patency (n=10), the magnitude of cyclic variation in infarct regions increased over time from 1.3±0.6 to 2.5±0.5 dB from the initial to final study (p<0.05). Patients with occluded infarct-related arteries (n=5) exhibited no significant recovery of cyclic variation (0.3±0.3–0.6±0.3 dB). A blinded analysis of standard two-dimensional echocardiographic images revealed no significant recovery of wall thickening in either group over the same time intervals. Ultrasonic tissue characterization promptly detects acute myocardial infarction and may delineate potential beneficial effects of coronary artery reperfusion manifest by restoration of cyclic variation of integrated backscatter in the presence of severe wall motion abnormalities. (Circulation 1989;80:491–503)

Ultrasonic tissue characterization provides a novel approach for defining the physical state of cardiac muscle tissue that complements assessment of ventricular wall motion and chamber dimensions by conventional two-dimensional echocardiography.1–3 The hypothesis underlying its use is that pathologic changes of myocardial structure and function result in alterations in the fundamental physical properties of tissue that can be quantified with indexes dependent on frequency-dependent ultrasonic attenuation and backscatter. We and others have demonstrated that ultrasonic backscatter can characterize structural and functional alterations associated with myocardial ischemic injury and necrosis in both experimental animals and patients.4–18 We have shown that physiologic contraction and relaxation of myocardium are paralleled by a cardiac cycle-dependent variation of integrated backscatter that reflects...
regional, intramural myocardial contractile performance.\textsuperscript{19,20} Characterization of myocardial ultrasonic properties has permitted quantitative delineation of the effects of duration of ischemia and subsequent reperfusion on the time course of recovery of regional intramural contractile function in hearts of experimental animals.\textsuperscript{13,17,18} Recently, this approach has been implemented in a real-time two-dimensional echocardiographic format and validated in clinical studies of patients with idiopathic cardiomyopathy and remote myocardial infarction who manifest blunted cardiac cycle–dependent variation of backscatter in diseased myocardium.\textsuperscript{14,15}

Ultrasonic tissue characterization offers promise for quantitative assessment of regional myocardial contractile performance that is not dependent on conventional analysis of wall motion per se.\textsuperscript{21} We have shown in studies of dogs that the magnitude of cyclic variation of integrated backscatter in myocardium in vivo bears a complex, nonlinear relation to wall thickening.\textsuperscript{17} In dogs with reversible ischemic injury (stunned myocardium), wall motion may not recover for an extended interval after the onset of reperfusion, despite restoration of blood flow to viable and ultimately functional tissue.\textsuperscript{22–28} In contrast, cyclic variation of integrated backscatter appears to recover much faster than wall thickening in reversibly injured myocardium.\textsuperscript{18} Early detection of potential tissue viability despite severe wall motion abnormalities in patients could provide important diagnostic and prognostic criteria useful for rapid assessment of the clinical impact of prompt recanalization of occluded coronary arteries.

Our study was designed to determine whether ultrasonic tissue characterization permits rapid identification of acute myocardial infarction in patients and whether early effects of reperfusion are reflected by augmentation of the magnitude of cardiac-cycle dependent variation of integrated backscatter. Accordingly, in patients with acute myocardial infarction, we measured the magnitude of cyclic variation of integrated backscatter in regions of acute infarction and regions remote from the infarct zone with a novel, combined two-dimensional and M-mode data-acquisition and M-mode analysis system. We hypothesized that ultrasonic tissue characterization would provide sensitive differentiation of normal from acutely infarcted myocardium and that early, potentially salutary effects of coronary artery recanalization could be detected.

**Methods**

**Patients**

Twenty-one patients (14 men and seven women) admitted to the Cardiac Care Unit of Barnes Hospital at the Washington University Medical Center were studied within 24 hours of the onset of symptoms of acute myocardial infarction (AMI). All had a clinical history consistent with AMI, ST-segment elevation in two or more contiguous electrocardiographic leads on a standard 12-lead tracing, elevation of plasma creatine kinase–MB isoenzyme activity, and adequate two-dimensional and M-mode echocardiographic images. Patients unable to provide informed consent or those on mechanical ventilators were excluded. The clinical characteristics of patients studied are shown in Table 1. Some (16) were treated within 4 hours of the onset of chest pain with intravenous recombinant tissue-type plasminogen activator (rt-PA) as part of the multcenter Thrombolysis in Myocardial Infarction (TIMI) trial at the Washington University Medical Center, and one patient was treated within 4 hours with intravenous streptokinase. One (patient 7) was not given a thrombolytic agent but underwent acute percutaneous transluminal coronary angioplasty (PTCA). Among all patients, 18 underwent a second study during the initial hospitalization or shortly after discharge, and 15 underwent coronary arteriography (patients 1–15; Table 1). Results from this group (patients 1–15) were used to quantify changes in the magnitude of cardiac cycle–dependent variation of integrated backscatter over time, for sequential analysis of wall motion, and for the measurement of the delay of cyclic variation of integrated backscatter. Patients with patent infarct-related vessels had TIMI grade 2 or 3 flow on angiography. Patients receiving thrombolytic agents (rt-PA or streptokinase) or PTCA were also given aspirin and briefly received intravenous heparin. \textsuperscript{β} Blockers and calcium channel blockers were administered at the discretion of the attending physician. No patients were being treated with agents with positive inotropic effects. All patients provided written informed consent for a protocol that had been approved by the Human Studies Committee of the Washington University School of Medicine.

**Ultrasonic Tissue Characterization Data Acquisition and Analysis System**

We have previously described a two-dimensional ultrasonic tissue characterization system that provides high-speed data acquisition but requires offline data analysis.\textsuperscript{14,29} Much of the front-end signal processing is the same as for conventional two-dimensional imaging. Briefly, signals from each transducer element of the phased array are amplified, mixed to an intermediate frequency (IF), phase shifted, delayed, and summed with signals from all other elements. The summed analog IF signal then is digitized with six-bit resolution (or 64 A/D steps) and sent to either the standard video processing path or a special integrated backscatter processor before scan conversion. The backscatter processor uses digital hardware to integrate the digitized IF signal with a time constant of integration of 3.2 $\mu$s and produces a real-time signal that is proportional to the logarithm of integrated backscatter along each image line. The dynamic range of the integrated backscatter processor is approximately 30 dB. The digitized integrated backscatter signal is
reconverted to analog format and displayed in real time as a two-dimensional gray scale video image with five-bit resolution (32 gray levels per pixel). A subset of the integrated backscatter image data with six-bit resolution can be transferred to a hard disk via a high-speed custom-designed interface by identifying an area of interest within the displayed two-dimensional sector and then recording 90–110 consecutive frames. Figure 1A shows a representative image obtained with this method. An electrocardiographic signal from a modified chest lead is multiplexed with the image data and recorded as well. The system was used to measure cyclic variation in seven of the patients. The remaining patients were studied with a novel M-mode-based analysis procedure that permitted immediate analysis of integrated backscatter data at the bedside without the need for data archiving and off-line analysis.

The M-mode acquisition and analysis system used was modified from the same commercially available phased-array two-dimensional imaging system capable of both real-time conventional and integrated backscatter imaging. M-mode integrated backscatter imaging was selectable through custom-designed software added to the system that permitted on-line analysis of integrated backscatter. Integrated backscatter signal processing along each M-mode image line is the same as that for the two-dimensional system. M-mode integrated backscatter signals with six-bit resolution were displayed in real-time on the video screen with five-bit resolution (32 gray levels per pixel). Single M-mode frames of integrated backscatter images were recorded simultaneously with an electrocardiographic trace (modified chest lead) at a sweep speed of 50 mm/sec, frozen on the imager’s video screen, and analyzed immediately to provide a measurement of cyclic variation. A square analysis cell that encompassed approximately 100 pixels was placed in a midmyocardial region and could be adjusted to fit within the boundaries of the myocardial wall at end diastole, avoiding the epicardial and endocardial specular echoes. The analysis cell was then moved across the displayed M-mode backscatter image (frozen image on the video screen) within the myocardial region with the use of a trackball cursor. The dimensions of the analysis cell and its track across the screen were used to select integrated backscatter values stored in the imaging system’s memory (with six-bit resolution) to compute average (spatially averaged) integrated backscatter values for the region of interest. A value for integrated backscatter was computed every 10 msec and displayed immediately in graphic form to produce a plot of cyclic variation of integrated backscatter versus time. Hard copies of the video display images were printed for calculation of the magnitude of cyclic variation. Figures 1B and 1C show representative images obtained by this method from

### Table 1. Patient Characteristics

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rt-PA, recombinant tissue-type plasminogen activator.
*Identified by ECG and echocardiography.
†Acute percutaneous coronary angioplasty before first study.
‡Did not have repeat studies.
normal and infarct regions, respectively. A simultaneous, modified chest lead, electrocardiographic tracing was recorded as well. Images were recorded also on 0.5-in. videotape.

Either 2.5 or 3.5 MHz 64-channel phased-array transducers were used for all studies. Transmit power and time gain compensation (TGC) controls were adjusted to yield optimal integrated backscatter images from each subject. Adjustments were such that the echoes received from each region remained within the dynamic range of the integrated backscatter system. Once the transmit power and TGC controls had been set for each subject, they were not changed during the course of the data acquisition. Because the acquired data represent the relative cyclic variation in the magnitude of integrated backscatter rather than the absolute level of backscatter, it was not necessary to calibrate the instrument in absolute terms as long as the values of integrated backscatter remained within the dynamic range of the integrated backscatter system throughout the cardiac cycle for each patient.

All patients were studied by one of three experienced echocardiographers. For purposes of classification, the locus of myocardial “regions” was defined according to standard two-dimensional echocardiographic criteria. Parasternal long-axis views were used primarily to record data from medial and basal regions of septal and inferoposterior wall segments. Apical two-chamber views were used infrequently to record data from medial and basal inferior wall segments. Multiple sites were imaged within each selected myocardial region, with each sample comprising approximately 90–110 consecutive image frames (about 3–4 seconds) for two-dimensional data (3–5 cardiac cycles) or approximately 4–6 cardiac cycles for M-mode data. The 12-lead electrocardiogram and standard echocardiographic criteria were used to identify regions of acute infarction and regions remote (“normal”)
from the region of injury deemed appropriate for quantification of the cyclic variation of integrated backscatter. The same regions (normal and infarct) imaged during the initial study were imaged during the second study. Reliability of imaging the previously studied regions was ensured by having the same echocardiographer who performed the first study perform the second study. Videotapes of the first study were also available for review to verify the regions studied.

Analysis of the Magnitude of Cyclic Variation

Analysis of two-dimensional image data was performed off-line with displays of consecutive frames of data for single sites as previously described. An intramural analysis cell (approximately 1.4×0.8 cm, shown in Figure 1A) was defined for an end-diastolic frame of an integrated backscatter image data set by outlining a region within the boundaries of endocardial and epicardial specular echoes with an interactive graphics display. The remaining image
frames were displayed consecutively with the analysis cell superimposed on them. The location of the analysis cell was adjusted to maintain the centroid of the analysis cell within the midmyocardial region. The analysis cell delineated a subset of the recorded integrated backscatter image data in each frame (100-200 data points) that was used to compute a spatially averaged value for integrated backscatter within the region imaged. Regions with significant image drop-out or those lacking clear wall margins were not subjected to analysis.

Both the two-dimensional and the M-mode systems yielded plots of cyclic variation of integrated backscatter in combination with companion electrocardiographic tracings. The magnitude of cyclic variation of integrated backscatter was calculated as follows. The Q wave and the terminus of the T wave were chosen as markers for end diastole and end systole, respectively. The difference in the values of integrated backscatter at each of these points in the cardiac cycle defined the magnitude of cyclic variation of integrated backscatter in decibels. The magnitude of cyclic variation of integrated backscatter from each Q-T interval was averaged to yield a mean value for a single myocardial site. Averaged data from several sites within a region were combined to yield an average regional value for the magnitude of cyclic variation for each patient. Isolated sites manifested very delayed or even reversed cyclic variation of integrated backscatter, that is, an increase in backscatter during systole. Although we have previously observed this phenomenon in ischemic myocardium and zones of infarction and described its potential physiologic significance, for the purpose of our study such sites were classified as having no (0 dB) magnitude of cyclic variations.15,17 All values for the magnitude of cardiac–cycle dependent variation of integrated backscatter are reported as regional averages. A second observer reviewed the data in a blinded fashion for calculation of the magnitude of cyclic variation. In no cases were methodologic disparities encountered.

Because the acquisition of integrated backscatter data involved the use of two different methods (two-dimensional and M-mode), four control human subjects were studied, each with both methods, to determine whether values obtained for the magnitude of cyclic variation could be combined. Echocardiographic views used for data acquisition and analysis were the same as those described above. Twenty-three sites were studied with the two-dimensional imaging and analysis system. The average regional magnitude of cyclic variation of integrated backscatter was 6.2±0.5 dB. Seventeen sites from the same regions were studied with the M-mode system; average regional magnitude of cyclic variation of integrated backscatter was 5.8±0.6 dB. Because the two-dimensional analysis system permitted off-line analysis of more than one independent site for each region studied, a greater number of sites was analyzed for the two-dimensional compared with the M-mode system. Data were combined to yield a mean magnitude of cyclic variation for each subject (n=4 for each system). The difference in the mean magnitude of cyclic variation obtained with the two-dimensional method compared with the M-mode analysis method was not significant (p=NS; paired t test).

**Analysis of the Delay of Cyclic Variation**

The time delay of the cyclic variation of integrated backscatter measures the degree of synchrony between the cyclic variation and the electromechanical events of left ventricular systole. We express the time delay in terms of a dimensionless ratio as delay equals time from Q wave to nadir of cyclic variation (msec) divided by Q-T interval (msec).

Plots of the cyclic variation of integrated backscatter with accompanying electrocardiographic traces from each site were used to determine the time interval from the Q wave to the nadir of cyclic variation and the Q-T interval in msec. Values for delay from sites within normal and injured regions were combined to yield a mean delay for normal and injured regions in each patient. Delay was calculated from the same sites as those used for the determination of the magnitude of cyclic variation of integrated backscatter. “Normal” values for delay are typically near 1, indicating synchronization between the cyclic variation of integrated backscatter and left ventricular mechanical systole. Higher values (more than 1) are indicative of asynchronous regional contractile function and have been described by our laboratory in patients with remote myocardial infarction who manifested a mean delay of 1.5 in regions of remote infarction.15 A second observer independently reviewed the calculation of the delay values for consistency in defining the interval from Q wave to nadir of cyclic variation and the Q-T interval and found no methodologic disparities.

**Analysis of Wall Motion**

The two-dimensional echocardiographic images recorded on videotape were reviewed by two experienced echocardiographers who were blinded with respect to the patients’ identities, infarct-related vessels, clinical outcomes, and vessel patencies. Myocardial regions localized as defined by Tajik et al30 were assigned “wall motion scores” as shown in Table 2. The echocardiographers scored all possible regions for each study (i.e., not just those areas interrogated by integrated backscatter imaging) to avoid observer bias. Wall thickening and endocardial motion were the criteria used for assigning a score to a segment. No score was given to regions that could not be clearly defined by conventional two-dimensional echocardiographic imaging or to regions in which wall thickening and endocardial motion were poorly defined. Differences in interpretation were resolved by mutual agreement.
fraction was increased, indicative of myocardial infarction. All but four patients received intravenous thrombolytic agents for treatment of acute myocardial infarction (Table 1).

Of the 15 patients who underwent coronary arteriography and had repeat studies, 10 had angiographic evidence of recanalization of the infarct-related artery and five showed persistent occlusion. The mean time from the onset of symptoms to treatment with a thrombolytic agent or PTCA for the 10 patients with patent infarct-related vessels was 2.98±0.5 hours. In the group with patent infarct-related vessels, nine had been given intravenous thrombolytic agents (eight rt-PA and one streptokinase) and one was treated with no thrombolytic agent but with PTCA. In the group with persistent occlusion, three were given rt-PA and two were given no thrombolytic agent. Patients were grouped after their first tissue characterization study on the basis of results of coronary arteriography.

**Cyclic Variation in Normal Myocardial Regions**

A comparison was made of the average magnitude of cyclic variation of integrated backscatter in normal regions in both intervals in the group of 15 patients with angiographically documented coronary artery anatomy. Average magnitude of cyclic variation in the early interval was 4.3±0.8 and 5.3±1.1 dB in patients with and without patent vessels, respectively. In the second study period, average magnitude of cyclic variation was 4.7±0.5 dB in the patients with patent infarct arteries and 5.8±1.3 dB in the patients with persistent vessel occlusion. There were no significant differences in the magnitude of cyclic variation between groups or between time intervals although the magnitude of cyclic variation in normal regions was modestly greater in both intervals in the patients with persistent occlusion.

**Cyclic Variation in Normal Compared With Infarcted Myocardial Regions**

Figure 2 compares the average magnitude of cyclic variation of integrated backscatter in normal and infarct myocardial regions for all patients. Sixty-one sites remote from the area of acute infarction were studied. The average number of normal sites studied in each patient was 2.9±0.3. The average regional value of the magnitude of cyclic variation of integrated backscatter for all normal regions in this group was 4.8±0.5 dB (95% confidence limits, 3.8–5.8 dB). Sixty-four sites identified as infarct areas were studied with an average of 3.1±0.3 sites studied per patient. Average regional magnitude of cyclic variation for all infarcted regions was 0.8±0.3 dB (95% confidence limits, 0.1–1.4 dB). The difference in magnitude of cyclic variation of integrated backscatter between normal and infarct regions was significant (p<0.05, paired t test) and indicates that the magnitude of cyclic variation of integrated back-

### Table 2. Wall Motion Scoring System

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<th>Score</th>
<th>Description</th>
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<tr>
<td>3</td>
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<tr>
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<td>Mild-to-moderate hypokinesis</td>
</tr>
<tr>
<td>1</td>
<td>Moderate-to-severe hypokinesis</td>
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<tr>
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<td>Akinetic</td>
</tr>
<tr>
<td>−1</td>
<td>Dyskinetic</td>
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</table>

(99% final concordance). Mean wall motion scores were obtained for each region by averaging the scores from each reviewer. Scores for normal and injured regions in each interval represent the averages of pooled data from each region.

**Statistical Analysis**

This study was designed to define the temporal changes in the magnitude of cyclic variation of integrated backscatter and wall motion scores for patients experiencing either transient or persistent coronary occlusion. Although intravenous thrombolytic agents were used in most patients, it was not our purpose to compare the efficacy of rt-PA with streptokinase or to compare the relative merits of inducing vascular patency by pharmacologic or mechanical means (i.e., PTCA). Our objective was to characterize the recovery of regional cyclic variation of integrated backscatter in infarct regions with or without recanalized vessels of supply regardless of the method used to induce patency. We hypothesized that the magnitude of cyclic variation of integrated backscatter would be greater in normal compared with infarct regions in the early interval in all patients. For patients with patent infarct vessels, we hypothesized that the magnitude of cyclic variation in injured but viable regions would improve over time but would not change over time in patients without reperfusion. We hypothesized that in the group with patent arteries, the wall motion scores for infarct regions would improve over time and that they would not be in patients with persistent occlusion. Statistical comparisons used were paired and unpaired two-tailed t tests as indicated in the text. Differences were deemed to be statistically significant for p values of less than 0.05. Values are given as mean±SEM.

**Results**

**Characteristics of Patients Studied**

The average age of the 21 patients was 57.7±2.4 years (53.9±2.8 for men and 65.1±3.1 years for women). Mean time from the onset of symptoms to time of initial study was 11.3 hours (range, 3.5–23.8 hours). In the 15 patients with repeat studies who underwent coronary arteriography, mean time of the second tissue characterization study was 7.1 days (range, 2–31 days) after admission. One patient in this group (2, Table 1) underwent emergency PTCA before his initial study on the day of admission. This patient’s peak total creatine kinase activity was only mildly elevated but the MB isoenzyme
scatter distinguishes normal from injured myocardium within this broad classification.

Figure 3A illustrates the temporal evolution of the magnitude of cyclic variation in infarcted myocardial regions in patients with patent vessels who had follow-up studies and demonstrates significant recovery from an initial value of 1.3±0.6 dB to a final value of 2.5±0.5 dB (p<0.05, paired t test). The patient with the highest values of cyclic variation underwent emergency PTCA before his first study and sustained only “mild” myocardial damage judging from creatine kinase–MB isoenzyme levels. Figure 4A depicts the evolution of the magnitude of cyclic variation in infarcted regions in those patients with persistent occlusion. The magnitude of cyclic variation was 0.3±0.3 dB in the early interval and 0.6±0.3 dB in the late period (p=NS, paired t test). Thus, patients with patent infarct vessels demonstrated substantial recovery of cyclic variation. Those with persistent occlusion continued to have depressed cyclic variation.

The difference in magnitude of cyclic variation of integrated backscatter in infarct regions in the early interval in patients with and without subsequent vascular patency was not statistically significant (p=NS, unpaired t test) but was substantially greater in the group with recanalized infarct-related arteries (1.3±0.6 with and 0.3±0.3 dB without reperfusion). However, in the late study interval, the difference in the magnitude of cyclic variation in infarct regions between the groups was significant (2.5±0.5 with and 0.6±0.3 dB without reperfusion; p<0.05, unpaired t test).

Delay of Cyclic Variation of Integrated Backscatter

The average delay of cyclic variation of integrated backscatter in normal compared with infarct regions for all patients (n=21) studied within the first 24 hours of onset of symptoms of acute myocardial infarction was 1.10±0.04 and 1.71±0.09, respectively. The difference between the values is statistically significant (p<0.05, paired t test) and indicates marked asynchrony of mechanical function in infarct regions.

Table 3 shows the delay values for normal and infarct regions in both early and late intervals for the group of 15 patients with angiographically documented coronary anatomy. In patients with documented vessel patency, the average delay in normal and infarct regions in the early period was 1.17±0.06 and 1.61±0.14, respectively (p<0.05, paired t test), indicating marked regional contractile asynchrony in the infarct zones. There was a significant improvement in delay in the infarct regions over the time intervals studied from 1.61±0.14 in the early period to 1.25±0.07 in the late period (p<0.05, paired t test). In those patients with persistent vessel occlusion, the average delay in normal compared with infarct regions in the early period was 0.94±0.03 and 1.75±0.20 (p<0.05, paired t test). Delay declined with time in the infarct regions in those
patients with persistent vessel occlusion, although the improvement was not significant (1.75±0.20 to 1.35±0.13, early compared with late; p=NS, paired t test). Thus, regional contractile asynchrony diminishes over time in infarct regions in patients with and without patent infarct-related vessels.

**Wall Motion**

Figures 3B and 4B illustrate the recovery of wall motion in patients with patent compared with persistently occluded infarct-related arteries. The total number of regions reviewed was 156. Of these, 58 (out of a possible 59) corresponded to regions (normal and infarcted) in which the magnitude of cyclic variation was measured. These regions (58) were the source for the data used for the statistical analyses. One normal region was omitted from the analysis because there were no corresponding cyclic variation data available.

Figure 3B shows that wall motion is severely blunted in infarct regions in the early period and recovers only slightly by the late interval of study in patients with recanalized vessels. Average wall motion scores did not change from early to late periods for normal regions in this group of patients and were 2.9±0.1 and 2.7±0.2 (p=NS, unpaired t test). Scores for infarct regions increased slightly from 0.75±0.3 to 1.1±0.3 for early and late periods, respectively, but did not differ significantly by paired t test. However, the value for infarct regions in the early period (0.75±0.3; 95% confidence interval, 0.09–1.41) is significantly different from a wall motion score of 0, suggesting that although the region supplied by the initially occluded vessel is severely injured, it retains some of its contractile function and remains at least partially viable. Wall motion scores were significantly greater in normal than in infarct regions in both time periods (p<0.05, unpaired t test).

Figure 4B shows the time course of change for wall motion scores in those patients with persistent occlusion. Wall motion in normal regions was associated with average values of 2.4±0.3 and 2.1±0.2 for the early and late periods, respectively (p=NS, paired t test). Wall motion in the infarct regions was severely blunted in both time periods with average scores of 0.2±0.5 and 0.0±0.0 for the early and late periods, respectively (p=NS, paired t test). Wall motion scores were significantly greater for normal than for infarct regions in both time periods (p<0.05, unpaired t test). Thus, wall motion scores did not improve significantly for patients with either patent or persistently occluded arteries over the intervals studied.

**Discussion**

The results of our study demonstrate that ultrasonic tissue characterization rapidly detects acute myocardial infarction and provides a quantitative estimate of the severity of regional contractile dysfunction reflected by reduced magnitude of cyclic variation of integrated backscatter. Significant recovery of the magnitude of cyclic variation and significant return toward normal values for delay of cyclic variation of integrated backscatter are nota-
ble among patients in whom recanalization is successful despite no significant recovery of wall motion. In contrast, patients without recanalization are characterized by the absence of significant recovery of either magnitude or delay of cyclic variation.

We and others have reported previously that the magnitude of cyclic variation of integrated backscatter defines the severity of ischemic injury after experimentally induced coronary artery occlusion and reperfusion in dogs. After occlusion for only 5 minutes, recovery of cyclic variation is rapid and complete. Occlusion for 20 minutes results in delayed but nearly complete recovery of cyclic variation, while occlusion for 60 minutes results in delayed but incomplete recovery to about 50% of baseline magnitude of cyclic variation within a 3-hour period after reperfusion. Restoration of blood flow after 60 minutes of ischemia did not produce any significant, immediate change in the magnitude of cyclic variation, which suggests that recovery of contractile function rather than the restoration of blood flow per se is responsible for the recovery of the magnitude of cyclic variation. Recently, we have shown in dogs that a brief period (15 minutes) of reversible myocardial ischemic injury followed by reperfusion is characterized by a much more rapid recovery of cyclic variation of integrated backscatter than of wall thickening.

The results of the present investigation extend these observations made previously in studies of laboratory animals to patients subject to myocardial ischemia followed by reperfusion: No immediate recovery of cyclic variation was observed in patients despite restoration of blood flow, but partial recovery of cyclic variation occurred over the ensuing 7 days despite minimal but statistically insignificant recovery of wall motion in reperfused myocardium. The slight improvement in wall motion scores for our patients with patent coronary arteries parallel results found by others, although the semiquantitative method used to determine wall motion scores for our patients may have been somewhat insensitive to small changes in regional contractile performance. We chose this method because it represents a widely used and accepted scoring system available to any echocardiographer.

Because no independent clinically practical method is available for defining the distribution and transmural extent of cell necrosis for comparison with ultrasonic analysis, we cannot be certain that recovery of cyclic variation actually corresponds to salvage of reversibly injured tissue. The wall motion scores for patients with patent arteries, although severely depressed in infarct regions, were significantly different from 0, indicating persistent though depressed contractile function in regions where cyclic variation was measured. Furthermore, cyclic variation recovers in patients with patent vessels in a similar manner to that in dogs subject to transient reversible ischemic injury. Although cyclic variation in patients with patent vessels does not recover to levels seen in the normal regions, the mean value for the magnitude of cyclic variation lies between those values recently reported by our group for normal myocardium and established infarction in humans. We would not anticipate complete recovery of cyclic variation or wall motion in those patients with patent vessels because the prolonged intervals of ischemia before treatment would have produced irreversible as well as reversible injury in the myocardial regions supplied by the infarct-related vessel. While it might be informative to obtain very late follow-up measurements of cyclic variation to permit greater recovery of regional mechanical function, the propensity toward reocclusion after successful thrombolysis or angioplasty would mandate recatheterization to ensure continued vessel patency, a factor that renders late study impractical.

Could the recovery of cyclic variation in those patients with patent infarct-related vessels be a manifestation of restored blood flow? Results of experiments performed in our laboratory and by others indicate that cyclic variation can be measured in isolated superfused contracting muscle tissue in the absence of blood flow. Augmentation of blood flow with adenosine does not influence the magnitude of cyclic variation. Furthermore, in dogs, restoration of blood flow to reversibly injured regions after 1 hour of ischemia does not produce any significant immediate recovery of cyclic variation. Thus, it appears unlikely that the recovery of cyclic variation seen in these patients is due solely to the restoration of blood flow.

The early recovery of cyclic variation of integrated backscatter that we observed is consistent with the hypothesis that ultrasonic tissue characterization can provide a useful measure of regional intramural contractile function, relatively independent of wall motion or wall thickening. We have reported that subepicardial contractile function measured by cyclic variation may persist despite diminished wall thickening after modest ischemic injury in dogs. Previously, we have demonstrated that the overall relation between wall thickening and cyclic variation is nonlinear, indicating that cyclic variation represents a physiologic measurement distinct from wall thickening. These observations are consistent with data from Gallagher et al, who measured regional intramural contractile function during ischemia in dogs with implanted ultrasonic crystals and found that subepicardial contraction was relatively well preserved despite substantially reduced wall thickening. Under physiologic conditions, the subepicardium contributes less to overall wall motion than does the subendocardium. With ischemia, the increased afterload imposed on injured but functional subepicardial segments by neighboring normal segments could constrain any anticipated improvement of wall thickening despite significant salvage of tissue. In addition, epicardial segmental shortening may be constrained, or
"tethered," by akinetic endocardial segments, as suggested by Weintraub et al.\textsuperscript{45} and Gallagher et al.\textsuperscript{46} Only after residual contractile function has improved such that the increased regional afterload is matched would fiber shortening and regional wall motion improve.

Our delay index may represent the extent of asynchrony of segmental shortening as described by Gaasch et al.\textsuperscript{47} and Takayama et al.\textsuperscript{48} Delay values for normal regions in both patient groups are within the range of normal values shown previously by our laboratory.\textsuperscript{49} Delay in injured regions in those patients with recanalized vessels improves toward normal levels over the interval studied. Improvement in left ventricular contractile performance after ischemic injury takes place over a period of weeks to months. This modest improvement in delay may be due to more synchronous systolic shortening occurring in salvaged myocardium.\textsuperscript{47}

The predictive value of the technique developed for delineation of reperfusion and recovery of mechanical function is uncertain for individual patients. The principle objective of the present study was to determine whether the two groups of patients, with and without reperfusion, would manifest different responses for cyclic variation. Because up to 30% of patients with coronary artery recanalization may experience reocclusion (some asymptotically) while in the hospital,\textsuperscript{36,37} an increase in cyclic variation measured in a random patient does not ensure eventual recovery of myocardial function. Indeed, some patients with patent infarct-related vessels after their initial tissue characterization study could develop reocclusion of their vessels before or after the second study resulting in decreased cyclic variation (see Figure 3A). A more elaborate protocol with repeat angiography after the second tissue characterization study would be required to extend these results to individual patients.

Detection of regional wall motion abnormalities by conventional two-dimensional echocardiography may facilitate the localization of injured or infarct segments. However, its use alone may not delineate the overall extent of myocardial salvage early after reperfusion. Tissue characterization appears to depict contractile phenomena throughout the myocardial wall without reliance on endocardial motion.\textsuperscript{17-19,21} Although echocardiographic image quality is influenced by both the operator and the subject, the reproducibility of values of cyclic variation for normal myocardium over time indicates the reliability of the imaging technique used. We observed that both the two-dimensional and M-mode data acquisition techniques yield similar and equally reliable values for cyclic variation.

Most of the ultrasonic data in our study were acquired from parasternal long-axis views. Anisotropic properties of ventricular myocardium may require compensation for images obtained from views that subtend nonperpendicular angles of incidence of the ultrasonic beam relative to the predominant myocardial fiber orientation.\textsuperscript{50,51} Furthermore, the M-mode format for data acquisition and analysis may prove difficult to interpret from approaches such as apical two- or four-chamber views. Extension of the present approach to real-time two-dimensional analysis of cyclic variation should be helpful.

Ultrasonic tissue characterization with integrated backscatter is readily applicable in the critical care setting. The simple method developed to quantify regional ventricular contractile properties after myocardial ischemic injury or infarction may serve as a useful adjunct for noninvasive evaluation of regional contractile performance and for the detection of potentially salutary effects of prompt reperfusion of acutely ischemic myocardium.

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