Ultrasonic Tissue Characterization Predicts Myocardial Viability in Early Stage of Reperfused Acute Myocardial Infarction

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Background—The aim of the present study was to characterize temporal changes in cyclic variation of ultrasonic integrated backscatter (IBS), which reflects intrinsic contractile performance, in patients with reperfused acute myocardial infarction (AMI) and to elucidate the clinical value of tissue characterization in predicting myocardial viability.

Methods and Results—We recorded short-axis IBS images before and 3, 7, and 21 days after reperfusion in 26 patients with AMI and obtained the cyclic variation of IBS in the normal and infarct zones. When cyclic variation showed synchrony and asynchrony, we expressed its magnitude as positive and negative values, respectively, called the phase-corrected magnitude. We also measured average wall motion score (dyskinesis, 4; normal, 0) of the infarct segments. The phase-corrected magnitude was lower in the infarct zone than in the normal zone before reperfusion (0.3 ± 2.5 versus 5.2 ± 1.7 dB, P < .05). At day 3, the phase-corrected magnitude increased by 2.1 ± 2.6 dB despite no improvement in wall motion. Improvement in wall motion was observed only at day 21. The patients with the phase-corrected magnitude of ≥2.0 dB at day 3 showed significantly lower wall motion score at day 21 than did the other patients (1.7 ± 0.6 versus 2.4 ± 0.5, P < .01).

Conclusions—In patients with AMI, cyclic variation of IBS is blunted during ischemia but recovers much faster after reperfusion than the improvement in wall motion. The greater phase-corrected magnitude at day 3 may be a predictor of better functional improvement. (Circulation. 1998;97:356-362.)

Key Words: myocardial infarction ■ echocardiography ■ reperfusion ■ myocardial contraction ■ ultrasonics

One of major problems facing modern cardiology involves the evaluation of myocardial viability within a region of acute ischemic injury. This issue is particularly important in the era of rapid interventional treatment for AMI. Methods based on wall motion analysis fail to differentiate viable tissue from irreversibly damaged myocardium until and unless wall motion improves.1-4 Assessment of regional myocardial perfusion with myocardial contrast echocardiography or assessment of wall motion response to dobutamine stress is another promising approach for evaluating myocardial viability.5,7 However, these approaches are performed in only a small number of acute patients because of technical limitations.

Ultrasonic tissue characterization with IBS offers a promising method for the assessment of myocardial contractile performance independent of wall motion.8-17 Normal myocardium exhibits cardiac cycle-dependent variation of IBS that reflects the intramural contractile performance. In animals, the cyclic variation of IBS is blunted promptly by ischemia and is augmented after reperfusion.18-22 The recovery of wall motion lags behind the recovery of the cyclic variation after brief periods of myocardial ischemia. In patients with reperfused AMI, Milunski et al23 documented that the obvious recovery of cyclic variation of IBS is observed a mean of 7 days after coronary reperfusion regardless of minimal improvement in wall motion. Therefore, the analysis of cyclic variation of IBS may have a potential to detect the viable myocardium early after reperfusion.

In this study, we characterized the temporal changes in cyclic variation of IBS at days 1, 3, 7, and 21 of reperfusion in patients with AMI. We compared these changes with the temporal recovery of regional wall motion to elucidate whether we can predict the functional recovery in individual patient with ultrasonic tissue characterization in the early stage of AMI.

Methods

Study Population

The study group included 26 consecutive patients with AMI who underwent successful coronary angioplasty within 24 hours after symptom onset. Eligible criteria were (1) no prior myocardial infarction, (2) totally or subtotally occluded infarct-related artery (Thrombolysis in Myocardial Infarction grade 0 or 1) at initial coronary angiography, (3) the postprocedural stenosis of <50%, (4) no ischemic
event during follow-up, (5) patent infarct-related artery 1 month later, and (6) adequate echocardiographic image quality. The diagnosis of AMI was made on the basis of ischemic pain of ≥30 minutes’ duration, ST-segment elevation of ≥1 mm in two or more contiguous ECG leads, and an increase in creatine kinase of more than three times the normal value. β-Blockers and calcium channel blockers were administered at the discretion of the attending physician. No patients were being treated with the positive inotropic agents. One of the investigators obtained informed consent from each patient. The study protocol was approved by the hospital ethics committee.

Acoustic Densitometry
We used a special software package (Acoustic Densitometry) developed by Hewlett-Packard incorporated into a commercially available echocardiograph (SONOS 1500). This system is capable of providing either conventional echocardiographic images or two-dimensional images in which gray level is displayed proportional to IBS amplitude. Sixty frames from consecutive cardiac cycles (30 frames/s) are displayed after scan conversion and are stored on the optical disk. The system has a unique feature by which the transmit power, log compression, and time-gain compensation values are displayed on the screen and are stored with the images, which allows an operator to adjust the system to the same values at any follow-up examination. The dynamic range of the IBS processor is 40 dB.

Protocol
We routinely performed multiple-plane echocardiographic examination in the coronary care unit before catheterization to establish the diagnosis; this took a mean of 10 minutes. We used a sector scanner equipped with acoustic densitometry (carrier frequency, 2.5 or 3.75 MHz). Each patient rested in a left decubitus position and breathed in a relaxed manner. We recorded two-dimensional echocardiographic images on 1.25-cm S-VHS videotape. Then, we depicted two-dimensional IBS images of the short-axis plane at the level of the papillary muscles and transferred the sequential 60 images (2 seconds) onto the 600-megabyte optical disk. This procedure took <2 minutes. We repeated the multipane two-dimensional echocardiographic examination and the recording of IBS images at 3, 7, and 21 days after the onset of AMI. The transmit power, compression setting, and individual values of time gain compensation were kept constant at each IBS study in individual patients.

Data Analysis
We analyzed the digitally acquired images with the acoustic densitometry package to construct time-intensity waveforms of the IBS. We divided the short-axis image of the left ventricle into eight segments. We defined the segment at risk as the segment showing asynergy at baseline study. To do this, we divided the left ventricle into 17 segments (8 segments on each short-axis slice at the levels of the mitral valve and midpapillary muscle, and apical segment on the apical long-axis view).5 The same observers scored at the center of the segments at risk and in the remote normal region.

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Reproducibility of Data
We determined intraobserver and interobserver variabilities of measuring the magnitude and normalized delay value of cyclic variation of IBS by measuring the two variables in 10 randomly selected records twice by the same observer and by two independent observers, respectively. Intraobserver and interobserver variabilities of the magnitude of IBS were 4.2±4.0% and 5.1±4.2% (absolute difference), respectively. Intraobserver and interobserver variabilities of normalized delay values were 4.2±3.2% and 4.7±2.4% (absolute difference), respectively.

Statistics
All data are expressed as mean±SD. Multiple comparisons were made with a one-way ANOVA, and individual data were compared with the use of Scheffe’s F test for factor analysis. Statistical analysis of temporal changes in certain variables was computed with ANOVA and Scheffe’s F test for repeated measures. Differences were considered significant at P<.05.

Results
Patient Characteristics
Among the 26 patients (mean age, 59±12 years; age range, 36 to 77 years), 23 patients (81%) were male and 3 patients were female (Table). All patients had one-vessel disease. Anterior, inferior, and posterior myocardial infarction was found in 16, 7, and 3 patients, respectively. The mean time from the asymptomatic onset to coronary reperfusion was 6.5±4.6 hours. The peak creatine kinase level was 3052±2050 IU/L. Twenty-three patients (92%) subsequently developed Q-wave infarction, and the other 3 manifested non-Q-wave infarction.

Cyclic Variation of IBS Before Reperfusion
Cyclic variation of IBS was present in all 26 normal regions and averaged 5.2±1.7 dB in magnitude. The average normalized

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Selected Abbreviations and Acronyms

AMI = acute myocardial infarction
IBS = integrated backscatter
ROC = receiver operating characteristic

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time delay of cyclic variation was 0.95 ± 0.19 (Figs 1 and 2). In the short-axis image, the center of all infarct segments showed akinesia at baseline study. The magnitude of cyclic variation in the infarct segments decreased significantly to 1.9 ± 1.7 dB (P<0.05). No cyclic variation was detectable in 7 of 26 infarct segments. Even when these 7 regions were excluded from the average, the magnitude of cyclic variation was still lower than normal values, averaging 2.5 ± 1.5 dB. Normalized time delay of cyclic variation was measurable in 16 infarct segments, and the value was significantly longer than that in the normal zone.

Clinical Characteristics and IBS Data for 26 Study Patients

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CV indicates cyclic variation; delay, delay of cyclic variation; A, anterior wall; I, inferior wall; and P, posterior wall.

Figure 1. Cyclic variation of IBS in the normal posterior wall (left) and infarct anterior wall (right) in a patient with anterior wall myocardial infarction. Cyclic variation in the normal posterior wall shows synchronous contraction, but it shows an asynchronous pattern in the infarct anterior wall. The magnitude is significantly lower in the infarct zone than in the normal zone.

Figure 2. Normalized time delay (left), magnitude (middle), and phase-corrected magnitude (right) of cyclic variation of IBS at baseline in the normal and infarct zones. Normalized time delay was significantly greater and magnitude and phase-corrected magnitude were significantly lower in the infarct zone than in the normal zone. Values are expressed as mean ± SD. *P<0.05, †P<0.01.
Normalized delay value was $1.25 \pm 0.49$, $P<0.05$. Normalized delay value was $>1.2$ in 7 patients, indicating asynchronous contraction or passive stretching. Thus, the phase-corrected magnitude was significantly lower in the infarct regions than in the normal regions ($0.3 \pm 2.5$ versus $5.2 \pm 1.7$, $P<0.05$).

**Temporal Changes in Cyclic Variation and Wall Motion After Reperfusion**

Cyclic variation of IBS was present in 23 of 26 infarct segments at 3 days later (Figs 3 and 4). Cyclic variation was detectable at this phase in 7 patients in whom no cyclic variation was detectable at baseline. The number of patients showing asynchronous contraction decreased from 7 to 3 at day 3 (Table). As a whole, there was no significant changes in the magnitude of cyclic variation in the infarct region from baseline to the second study, and it was still lower than that in the remote normal region ($2.6 \pm 2.0$ versus $5.2 \pm 1.4$ dB, $P<0.05$). The normalized time delay value slightly decreased to $1.10 \pm 0.38$ at day 3, but it was still higher than that in the normal zone ($1.10 \pm 0.38$ versus $0.93 \pm 0.15$, $P<0.05$). Phase-corrected magnitude of cyclic variation significantly increased from baseline to day 3 ($0.3 \pm 2.5$ versus $2.1 \pm 2.6$ dB, $P<0.05$) (Fig 4). However, there was no significant improvement in wall motion in the center of the infarct segment. The phase-corrected magnitude increased to $3.0 \pm 3.6$ at day 7, but it did not show a significant increase after that. In contrast, wall motion score significantly decreased only at day 21 (day 1 versus day 21, $3.0 \pm 0.0$ versus $2.4 \pm 0.8$, $P<0.05$).

**Prediction of Wall Motion Improvement From Phase-Corrected Magnitude**

We assessed the potential of the phase-corrected magnitude for predicting functional improvement in the infarct segments (Figs 5 and 6). Using an ROC curve, we examined the sensitivity and specificity of various cutoff points of phase-corrected magnitude at day 3 for predicting viable myocardium. The ROC curve is a plot of sensitivity against 1-specificity as the positive/negative cutoff point is varied. Definition of viable myocardium was wall motion score index of $\leq 2$, in the convalescent stage. Based on this curve configuration, we considered the optimal cutoff point to predict viable myocardium appears to lie around the phase-corrected magnitude of $2$ dB, which is a median value of this magnitude at day 3.

The patients were divided into two groups according to this value for phase-corrected magnitude: those with the phase-corrected magnitude of $\geq 2.0$ dB were considered group A (14 patients), and those with the phase-corrected magnitude of...
Discussion

Before coronary reperfusion, the cyclic variation of IBS in the infarct zone is markedly blunted and even shows asynchronous waveform in patients with AMI. The phase-corrected magnitude of cyclic variation significantly increased despite the minimal improvement in wall motion 3 days after reperfusion. It progressively increased until day 7. An improvement in wall motion, however, was found only at day 21; therefore, an increase in the phase-corrected magnitude precedes an improvement of wall motion. In addition, our data indicated that the greater values for the phase-corrected magnitude at day 3 are associated with the better functional improvement of the postischemic myocardium. Thus, the ultrasonic tissue characterization can provide a useful measure of intramural contractile function, relatively independently of wall motion, and may permit the prediction of wall motion recovery in very early stage of reperfused AMI.

Cyclic Variation of IBS in Infarct Segment

Several experimental and clinical studies have documented that the cyclic variation of IBS is promptly blunted and often shows substantial time delay compared with left ventricular systole, which implies asynchrony, during myocardial ischemia. In patients with AMI, we also observed the marked reduction in the magnitude of cyclic variation and the significant increase in the time delay in the infarct segment before reperfusion. The pattern of cyclic variation, however, varies among patients. Cyclic variation was not detectable in 7 of 26 patients. Apparent asynchronous contraction was observed in 7 patients (27%). In 5 patients (patients 1, 7, 23, 25, and 26), the absolute magnitude of cyclic variation was comparable to or greater than that in the normal segment, but their pattern appears to be a mirror image of normal cyclic variation pattern. This asynchronous pattern of cyclic variation may be caused by stretching or passive distention of ischemic myocardium during systole. Although wall motion of the infarct zone was evaluated as akinisia before reperfusion, the intramyocardial contraction pattern varies among patients and the analysis of IBS is useful to assess the pathophysiology of the wall motion abnormalities.

Several mechanisms are postulated to explain the cyclic variation of IBS: (1) changes in acoustic impedance, which is related to passive elastance; (2) changes in fiber orientation or shape from diastole to systole; and (3) changes in elastic modules during sarcomere shortening. In open-chest dogs, Wickline et al showed that cyclic variation of IBS in the myocardium parallels contractile performance. However, wall thickening is not linearly related to the magnitude of the cyclic variation in dogs with acute coronary occlusion followed by reperfusion. Although influenced by wall thickening, cyclic variation of IBS appears to reflect the intramural contractile performance rather than geometric phenomenon.

Mechanisms responsible for the temporal delay of cyclic variation of IBS are also unclear. In open-chest dogs, Brown et al documented postystolic shortening and thickening of myocardium during coronary ligation. Early diastolic or postystolic events may be related to persisting contraction or delayed relaxation within the ischemic myocardium and perhaps to effects of stretching or passive distention, although it is hard to differentiate these events. Thus, the delayed cyclic variation that we observed may reflect postystolic events and ultimately provide an approach for their detection and quantification. Because these events are considered to be unfavorable to global left ventricular contraction, we expressed the corrected magnitude of cyclic variation as a negative value if the cyclic variation exhibited asynchronous contraction.

Effect of Reperfusion

In animals, the reduced magnitude of cyclic variation of IBS during ischemia gradually increased after coronary reperfusion. Milunski et al documented that partial recovery of cyclic variation, which included an increase in the magnitude of cyclic variation and a decrease in the normalized time delay, was observed at a mean of 7 days after reperfusion in patients with AMI despite minimal recovery of wall motion. In this study, we investigated the temporal changes in the cyclic variation 3 days after reperfusion. The results are a little different from their results because temporal changes in cyclic variation varied among patients with the pattern of cyclic variation of IBS at baseline. An increase in the magnitude of cyclic variation was observed 3 days after reperfusion in 15 of 19 patients showing synchronous or no detectable cyclic variation at baseline study, but the other 4 patients showed a decrease in the magnitude. In these 4 patients, the contribution of progressive myocardial damage after reperfusion was speculative. The patients showing the asynchronous pattern of cyclic variation at baseline represented a decrease in the absolute magnitude, and thus coronary reperfusion does not always lead to a increase in the phase-corrected magnitude of cyclic variation. In the majority of these patients, however, the normalized delay decreased to the normal range, and the corrected magnitude increased 3 days after reperfusion. These data imply that reperfusion usually augments the cyclic variation in case of synchronous contraction and diminishes the delayed relaxation or passive stretch in cases of asynchronous segmental contraction, resulting in an increase in the corrected magnitude as early as 3 days after reperfusion. At this phase, however, no substantial improvement in the segmental motion was detectable in the center of myocardial infarction.

Milunski et al observed the temporal changes in wall motion and cyclic variation of IBS in the infarct zone until a mean of 7 days after reperfusion. However, the temporal changes in the phase-corrected magnitude of the cyclic variation until the convalescent stage of AMI and their relation to the recovery of wall motion remain unknown. Our data demonstrated that the phase-corrected magnitude increased...
until day 7 but did not exhibit a significant changes at day 21. On the other hand, we observed substantial improvement in wall motion of the infarct segment only at day 21. At day 21, the majority of the infarct segment (88%) exhibited a synchronous contraction pattern. This finding clearly demonstrated that the improvement in wall motion lags behind the recovery of cyclic variation of IBS and is in agreement with the results of an experimental study that used a model of modest ischemic injury ("stunned" myocardium).

Although the recovery of the cyclic variation of IBS may be accomplished within 7 days after reperfusion, the improvement in wall motion requires ≥21 days. This early recovery of cyclic variation of IBS that we observed is consistent with the hypothesis that ultrasonic tissue characterization provides a useful measure of regional intramural contractile function, relatively independent of wall motion. The delay of wall motion recovery may be attributed to several causes. First, the recovery of intramural contraction would be heterogeneous early after reperfusion. Even though some fraction of the infarct segment exhibits synchronous intramural contraction, the wall motion might not improve if the other fractions show delayed contraction or passive stretch. Second, the increased afterload imposed on the injured but functional myocardium by neighboring normal segments could constrain improvement of wall motion despite the salvage of the tissue. Only after residual contractile function has improved possibly with an increase in the number of actively contracting myocardium, fiber shortening and regional wall motion improve. Finally, myocardial ischemia promptly breaks the intracellular structures that mediate between sarcomere shortening and myocardial contraction.34 The recovery of this intracellular structure requires several days. In such instances, the augmented sarcomere shortening, which produces cyclic variation, does not necessarily result in improvement in wall motion.

Magnitude of Cyclic Variation and Myocardial Viability
Recovery of cyclic variation of IBS is achieved much sooner than the recovery of wall motion, but it the predictive value of the ultrasonic tissue characterization for assessing the recovery of wall motion in individual patients has been unknown. In this study, we divided the study patients into two groups on the basis of the values for phase-corrected magnitude 3 days after reperfusion. We used the median value for phase-corrected magnitude at day 3 (ie, 2.0 dB). The ROC curve analysis documented that this value seems to be an optimal cutoff value for predicting functional improvement of infarct zone. In fact, the functional improvement was significantly better in patients with the phase-corrected magnitude of ≥2.0 dB than in those with the lower values. In view of our results, the phase-corrected magnitude may reflect the intramural contractile performance, which should be related to the amount of stunned myocardium. If the phase-corrected magnitude shows the higher values after ischemic injury despite the minimal improvement in wall motion, we can predict the better final functional improvement. This estimation is quite important for the decision of the clinical strategy because the functional improvement significantly varies among patients despite achievement of coronary recanalization in the early stage of AMI and because the amount of viable myocardium determines the final functional outcomes and patients’ prognosis.

Study Limitations
Cyclic variation of IBS is dependent on the angle between fiber orientation and ultrasonic beam, called anisotropy.24,25 Time delay also varies systematically with fiber orientation. Data in this study were obtained exclusively from the anteroseptum and inferior and posterior regions in the parasternal short-axis views, in which myocardial fiber of these segments is oriented nearly perpendicular to the ultrasound beam, thereby avoiding problems with anisotropy as much as possible. In addition, the analysis is largely dependent on the image quality.

One of the disadvantages of IBS imaging in its current form is that there is a relatively narrow dynamic range before which system saturation occurs. However, the problem regarding narrow dynamic range can be minimized by reducing the transmit power. Another disadvantage of IBS imaging in its current form is a significant degradation in spatial resolution compared with conventional two-dimensional echocardiography.

The IBS signal is influenced by gain setting. We set the time-gain control to the identical value in each patient, and only total gain was controlled to clearly depict the IBS image. The difference in total gain should not influence the magnitude of the cyclic variation of IBS.

Clinical Implications
Detection of regional wall motion abnormalities through conventional two-dimensional echocardiography facilitates the localization of the injured or infarct segments. Its use, however, may not delineate the overall extent of myocardial salvage early after reperfusion until and unless the recovery of wall motion has occurred. Our results documented that an increase in the phase-corrected magnitude precedes the improvement in wall motion in patients with reperfused AMI. Such information cannot be obtained through qualitative or quantitative analysis of wall motion alone. Clinically, the analysis of the cyclic variation of IBS may allow the rapid assessment of regional myocardial viability despite no or minimal improvement in wall motion.

Myocardial contrast echocardiography or dobutamine stress echocardiography is another method by which to assess myocardial viability in the early stage of AMI.26,27 Because of technical limitations, these methods cannot be applied to all acute patients. Compared with these methods, ultrasonic tissue characterization is simple; therefore, ultrasonic tissue characterization should be a new diagnostic modality for evaluating myocardial viability at the bedside in patients with AMI.

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Tissue Characterization in AMI


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