Determination of Successful Reperfusion After Thrombolysis for Acute Myocardial Infarction
A Noninvasive Method Using Ultrasonic Tissue Characterization That Can Be Applied Clinically

J.E. Hancock, MB ChB, MRCP, PhD; J.C. Cooke, MB ChB, FRACP; D.T. Chin, MB ChB, MRCP; M.J. Monaghan, PhD

Background—The aim of the present study was to determine the use of cyclic variation in ultrasonic integrated backscatter (IBS), which is reduced in ischemic myocardium, to predict an occluded infarct-related artery (IRA) after thrombolysis for acute myocardial infarction (AMI). This is important, because patency of the IRA 90 minutes after thrombolysis has been shown to predict outcome.

Methods and Results—One hundred thirteen patients with AMI had peak-to-peak cyclic IBS measured in the myocardial territory supplied by their IRA as well as a remote territory with normal function from the parasternal long- or short-axis view. This analysis took 5 to 10 minutes. Wall motion score index was assessed, and coronary angiography, to determine patency of the IRA, was performed in all patients. Cyclic IBS in the IRA territory was much lower in segments supplied by an occluded IRA (3.3 versus 4.6 dB, \( P < 0.00001 \)). Using a difference in cyclic IBS between infarcted and normal segments of 15% (or 1.5 dB) as a cutoff, the sensitivity, specificity, positive and negative predictive values to determine an occluded IRA were 92%, 75%, 81%, and 89%, respectively.

Conclusions—The difference in cyclic IBS between IRA and remote normal segments, which can be analyzed rapidly, can be used to predict patency of the IRA in patients with AMI. This provides a noninvasive method to determine those patients who may require urgent invasive investigation. (Circulation. 2002;105:157-161.)

Key Words: reperfusion ■ thrombolysis ■ myocardial infarction ■ ultrasonics

One of the continued challenges facing cardiology is the assessment of reperfusion in the region of acute ischemic injury after acute myocardial infarction (AMI) treated with thrombolysis. The gold standard for this has been flow in the epicardial vessel at coronary angiography.\(^1\) Thrombolysis in myocardial infarction (TIMI) flow grade in the infarct-related artery (IRA) of 0 to II flow is associated with poor functional recovery of the left ventricle (LV), and TIMI grade III flow is associated with good functional recovery. However, it has been shown that 25% of segments with TIMI III flow in the IRA actually have no reperfusion at microvascular level using intracoronary myocardial contrast echocardiography (MCE).\(^2\) This is referred to as the no reflow phenomenon. Conversely, an occluded epicardial vessel is not always associated with failure of reperfusion if there is collateral flow to the IRA territory. Coronary angiography is invasive and requires cardiac catheterization facilities, which are not available in all institutions.

The ideal technique to evaluate reperfusion at a microvascular level would be one that is easy to perform, can be done at the bedside, can be analyzed quickly, and is sufficiently accurate to allow stratification of patients with AMI into those who have an occluded IRA (or possibly a patent IRA but no reflow) and who require cardiac catheter facilities urgently and those who have a patent IRA (or occluded IRA but collaterals) and will require cardiac catheterization at an interval, if at all. To date, this has not been achieved.

Of the echocardiographic techniques presently available for this assessment, the most promising are intravenous MCE and ultrasonic tissue characterization with integrated backscatter (IBS). So far, intravenous MCE has not been thoroughly quantified in humans, and several technical limitations remain. Additionally, a few patients may have contraindications to ultrasonic contrast agents.

IBS has been more thoroughly investigated. Several studies exist in the setting of AMI\(^3\) that have shown that the cardiac cycle–dependent variation in this parameter is blunted in regions of myocardium supplied by the IRA compared with adjacent normal myocardial segments. There is recovery of cyclic IBS in the IRA territories supplied by a patent IRA but not in those with an occluded IRA at 7 days in the absence of any change in wall motion, suggesting that this may predict...
viability. Takiuchi et al confirmed this, demonstrating that in patients who had an anterior myocardial infarction treated by coronary angioplasty, an increase in cyclic IBS in the IRA territory 3 days after the procedure was not associated with any change in wall motion score, but these patients had a significant improvement in their wall motion score at 21 days. This suggests that cyclic IBS has the potential to detect viable myocardium and predict functional recovery. Animal and in vitro studies support this.

However, most studies to date have involved small patient numbers. There are also some limitations to the use of cyclic IBS acutely. Although the data are easy to collect, analysis is more difficult. Myocardial fiber orientation and depth of field significantly affect the magnitude of the IBS. In the short-axis view, the anterior septum has the highest levels, where the beam is perpendicular to the myocardial fibers. The lateral wall and inferior septum have the lowest levels, where the fiber orientation is parallel to the insonating ultrasound beam. The posterior wall has IBS levels that are lower than the anterior septum because of the increased depth. Thus, the effect of anisotropy must be corrected for. Furthermore, the phase of the peak of cyclic IBS is affected both by orientation of fibers and by damaged myocardium. Therefore, many authors believe that it is necessary to make a correction for phase of the cyclic IBS. Even in subjects with normal myocardium, there are some variations. Studies have shown wide variation in both the magnitude and phase of cyclic IBS between myocardial segments in healthy subjects. So, although measurement of cyclic IBS is useful, the above constraints have meant that data have had to be analyzed and manipulated offline and limited its clinical application in the acute setting.

In the present study, we have measured differences in the magnitude of the cyclic variation in IBS without additional manipulation in patients in the setting of AMI to reduce the analysis time to 5 to 10 minutes. These data are compared with coronary angiographic findings to elucidate whether we could differentiate between patients with patent and occluded IRAs using this method.

Methods
An unselected group of 124 patients admitted with AMI were considered for the study. Eleven patients had to be excluded because of poor echocardiographic windows. The remaining 113 patients were admitted into the study (Table 1). Patients had AMI diagnosed on clinical history and ECG criteria of ST elevation of 1 mm in ≥2 contiguous chest leads or ≥1 mm in ≥2 contiguous limb leads. All patients were treated with thrombolysis or primary angioplasty (18 patients). Patients who were thrombolysed subsequently had coronary angiography so that the coronary anatomy and, in particular, information on the patency of the infarct-related artery (IRA) was known for all patients. The study had local ethical approval.

Data Acquisition
Cyclic IBS was measured in the territory of the IRA as well as a remote territory with normal function. Additionally, images were acquired for analysis of wall motion. This was done before coronary angiography in all cases, but as near as possible to 90 minutes after thrombolysis in the patients who were thrombolysed. All 4 standard, echocardiographic views (parasternal long-axis, parasternal short-axis, apical 4-chamber, and apical 2-chamber) were imaged using an Agilent Technologies Sonos 5500 or 2500 ultrasound system.

### Table 1. Patient Demographic Data

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Occluded IRA (n=60)</th>
<th>Patent IRA (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.7 (32–83)</td>
<td>60.2 (27–84)</td>
<td></td>
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</table>

### Acoustic densitometry (AD) with IBS software was available on both systems. With the ultrasound machine operating in the AD acquisition mode, real-time IBS images were acquired for 60 consecutive frames at a rate of 30 frames per second (2 to 3 cardiac cycles), displayed, stored to magneto-optical disk, and subsequently analyzed. System settings were optimized by adjusting the depth, total gain, and time-gain compensators so that all segments of myocardium were clearly visualized. Imaging was performed using either a 2.5-MHz or an S4 (2- to 4-MHz) transducer.

### Data Analysis
IBS data were analyzed offline for each myocardial region for each subject using the AD analysis package available on the SONOS 5500 imaging system. An elliptical region of interest of 31×31 mm or 41×41 mm was placed in the midmyocardial region in each segment analyzed, positioned to avoid endocardium and epicardium, and tracked manually on a frame-by-frame basis for the entire loop of 60 frames. No attempt was made to differentiate between subendocardial and other myocardial regions within the segment. For each segment, the analysis package provides a mean IBS value in decibels for the entire loop as well as a mean value for each frame. This allows assessment of the magnitude of the cyclic variation, which we have taken as the difference between the average peak and average nadir values of IBS. To avoid the effects of anisotropy as much as possible and to reduce phase correction, only the parasternal views were used for analysis, and region of interests were placed in the anterior septum and posterior, or inferior, wall as perpendicular as possible to the ultrasound beam and directly opposite each other whenever possible.

Wall motion analysis was also performed in each subject for all visible segments in each echocardiographic view. This was done using the standard 16-segment model, as defined by the American Society of Echocardiography, using a visual scoring system where 1 indicates normal or hyperdynamic; 2, hypokinetic; 3, akinetic; and 4, dyskinetic. This analysis was performed by 2 independent observers without knowledge of the coronary angiographic data.

### Statistics
Difference in mean values between infarcted and normal myocardial segments in each imaging mode were analyzed using a Student’s t test. Interobserver reliability was compared using ANOVA. ROC curves were used to determine the optimal cutoff value of difference in cyclic IBS between IRA and normal segments both in decibels and as a percentage for the determination of patency of the IRA. The study was powered to detect a 1-dB difference in cyclic IBS at the 0.05 level. Results were considered significant when the P<0.05.

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Results

Of the 113 patients studied, 60 (53%) had an occluded IRA at angiography. In these patients, the cyclic IBS in the myocardial territory supplied by the IRA was 3.3 ± 1.2 dB, whereas the cyclic IBS in a remote myocardial territory was 6.1 ± 1.2 dB (P < 0.00001). In the 53 patients (47%) who had a patent IRA at angiography, cyclic IBS in the myocardial territory supplied by the IRA was 4.6 ± 1.3 dB compared with 5.8 ± 1.2 dB in a normal myocardial segment (P < 0.00001), Figure 1. The cyclic IBS in the myocardial segments supplied by the IRA was significantly different depending on the patency of the IRA, being much lower in those segments supplied by an occluded IRA (3.3 vs 4.6 dB, P < 0.00001). Cyclic IBS from normal myocardial segments was slightly different depending on patency of the IRA, being lower in normal myocardial segments where the IRA was patent (5.8 vs 6.1 dB, P = 0.05) (Figure 1).

The percentage difference in cyclic IBS between infarcted (IRA) and normal myocardial segments was also significantly different depending on the patency of the IRA, being 9 ± 12% in patients with a patent IRA and 27 ± 10% in patients with an occluded IRA (P < 0.00001) (Figure 2).

The sensitivity, specificity, positive predictive value, and negative predictive value of various differences in cyclic IBS between infarcted and normal myocardial segments is shown in Table 2 for percentage differences and in Table 3 for absolute differences in decibels. The magnitude of cyclic variation in IBS in Figure 1 and Table 3 has been presented in the familiar units of decibels. It must be noted, however, that the ROC analysis results were obtained by first transforming the measurement data from the nonlinear, logarithmic (decibel) domain to the linear domain using the equation $V_d/V_s = 10^{PPI/20}$, where $V_d/V_s$ is the ratio of the average peak voltage at end diastole to the nadir of the voltage at end systole and PPI is the magnitude of the cyclic variation in decibels. The results were then transformed back to the log (decibel) domain by using the inverse transformation $PPI = 20 \times \log(V_d/V_s)$. The ROC curves suggest that the optimal cutoff point to predict occlusion of the IRA is 15% or 1.5 dB (Figure 3).

Wall motion score index (WMSI) for patients with an occluded IRA was 1.84 and 1.67 for patients with a patent IRA (P = 0.001). However, the ROC curve for this data did not show a clear cutoff (Figure 3), so this could not be used accurately to predict an occluded IRA.

Interobserver reliability was 0.86 for cyclic IBS measurements in myocardial segments supplied by the IRA and 0.8 for remote segments with normal function. Intraobserver reliability was 0.95 for cyclic IBS measurements in myocardial segments supplied by the IRA and 0.93 for remote segments with normal function.

Discussion

Previous studies in animals and humans have demonstrated that ischemia causes a reduction in cardiac cycle–dependent

| Difference in IBS, 
| IRA vs Normal, % | Sensitivity, % | Specificity, % | Positive Predictive Value, % | Negative Predictive Value, % |
|------------------|----------------|----------------|-----------------|-----------------------------|-----------------------------|
| 5                | 97             | 28             | 60              | 88                          |
| 10               | 95             | 56             | 70              | 90                          |
| 15               | 92             | 75             | 81              | 89                          |
| 20               | 78             | 83             | 84              | 77                          |
| 25               | 55             | 89             | 85              | 64                          |
| 30               | 38             | 92             | 69              | 57                          |
| 35               | 25             | 94             | 83              | 53                          |

| Difference in IBS, 
<table>
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<th>IRA vs Normal, dB</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
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variation in IBS and that reperfusion can restore the amplitude of this to normal levels.3,8,20 Studies in the setting of myocardial infarction have shown that this parameter can accurately diagnose myocardial infarction3,4 and is capable of identifying stunned as opposed to infarcted myocardium,3,7 particularly when used in conjunction with dobutamine stress testing or thallium scanning.7 However, stress testing can be difficult in the acute setting. Only 2 studies3,5 have made an attempt to correlate the measurement of cyclic IBS from the IRA with coronary angiographic findings. If it were possible to detect failure of reperfusion after thrombolytic therapy using this technique, this would help to determine early after thrombolysis which patients require acute invasive intervention.

In the present study, we have demonstrated that average peak-to-average nadir values of cyclic IBS can be used to determine the patency of the artery supplying an infarcted myocardial segment. Acquisition of the data and measurement of these values, without additional manipulation (eg, phase correction) can be achieved within 10 minutes and often within 5 minutes. A difference in absolute cyclic IBS between the IRA segment and a remote segment with normal function of ≥1.5 dB can predict an occluded IRA with a sensitivity of 88%, a specificity of 77%, a positive predictive value of 81%, and a negative predictive value of 85%.

If these are converted to percentage values, a difference between an IRA segment and a remote segment of ≥15% can predict an occluded IRA with a sensitivity of 92%, a specificity of 75%, a positive predictive value of 81%, and a negative predictive value of 89%. This is comparable with other noninvasive techniques and at least as good as IBS with phase correction reported in previous studies.3,5 In these studies, analysis took a minimum 20 minutes and often 1 hour.3,5

WMSI was found to be significantly different between the 2 groups, being higher in patients with an occluded IRA. This may be because both hyperdynamic and normal myocardial segments were given a score of 1. However, it is clear from the ROC curve that it would not be possible to use WMSI to determine an occluded IRA. This is in keeping with other studies.3,8,17,21

Because it is likely that differences in cyclic IBS actually represent viability and regional contractile performance, in the present study some patients with a patent IRA would have been determined to have an occluded IRA by this method (false-positive), presumably because of the no reflow phenomenon. There were 6 patients who would have fallen into this category. Two of these patients died, and 2 more had no recovery of left ventricular function on long-term follow-up. The remaining 3 did not have follow-up studies. Similarly, some patients with an occluded IRA will have been determined to have a patent IRA (false-negative). This occurred with 5 of the 59 patients in the present study. One might speculate that this was because of collateral flow. However, this was not seen in these 5 patients. Indeed, only 2 patients had retrograde filling of the IRA at angiography. An occluded IRA was predicted by cyclic IBS in these 2 patients. An alternative explanation is that in these patients, the remote normal territory was not, in fact, normal, but supplied by an occluded or significantly stenosed artery. Of the 5 false-negative patients, 2 had single-vessel disease. The remaining 3 had 2-vessel disease, but the diseased vessel supplied the remote normal territory analyzed in only 2 of these. A separate analysis of the subgroup of patients with multivessel disease has not been performed. This is a potential limitation of the study.

Another potential limitation is that no attempt has been made to correct for phase, as many other authors have done. However, as stated previously, the main reason for recording only the average peak to average nadir value of the cyclic IBS was to reduce analysis time to make the technique more clinically useful in the acute situation. Most centers would be able to have an echo machine with IBS software and be in a position to record and analyze these data accurately after some training. However, not all would be in a position to have the necessary computer program or time to perform the more complex data manipulation required for phase correction. Our technique for analysis can be used in a clinical setting to guide management of patients, particularly to determine which patients have failed thrombolysis and require more invasive investigation.

Furthermore, in previous studies with phase correction, segments which were found to have a normalized time delay of >1.2 were considered to be asynchronous, so the peak-to-peak IBS level was multiplied by −1.6 This has the effect of making the cyclic IBS value from the IRA segment even smaller or negative, additionally increasing the difference in cyclic IBS between this segment and the remote segment with normal function. Some authors have reported similar peak-to-peak cyclic IBS measurements from abnormal and normal segments but found that these were completely out of phase with each other.5,10,22 This was not found in our study. Cyclic IBS from normal and abnormal segments was similar when the IRA was patent, so that there was less myocardial damage because reperfusion had been successful. The exception to this was in the 5 false-negative cases discussed above. In those cases, there was no significant difference in phase between the peak value in the IRA territory and remote segments.
Another potential limitation is the fact that only the parasternal views have been used to reduce the effects of phase difference and anisotropy as much as possible. In fact, many other authors have done this, few studying apical views. In all cases in the present study, the segments analyzed all included a segment with abnormal wall motion and a remote segment with normal function, which would have been at the same angle to the insinating beam as the abnormal (IRA) segment. This should reduce the effect of anisotropy as much as possible while still analyzing representative segments.

Another limitation of this study is that we have made no attempt to incorporate a comparison with subjects with normal myocardium. This might have affected our results. However, given the known differences in cyclic IBS in normal myocardium, it is likely that these results, in the setting of AMI, may have reached even greater significance.

Conclusions
Average peak to average nadir measurement of cyclic IBS, which can be performed at the bedside in <10 minutes without additional manipulation, can be used to accurately predict patency of the IRA after reperfusion therapy for AMI. This may help to delineate patients who require immediate invasive investigation, which could help hospitals without invasive facilities on site to stratify their patients with myocardial infarction.

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References
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