Myocardial contrast echocardiography is superior to other known modalities for assessing myocardial reperfusion after acute myocardial infarction

K Greaves, S R Dixon, M Fejka, W W O’Neill, S R Redwood, M S Marber, R Senior

Background: Angiographic flow measurements do not define perfusion accurately at a microvascular level, so other techniques which assess flow at a tissue level are to be preferred.

Objectives: To compare intravenous myocardial contrast echocardiography (MCE) with other methods of assessing microvascular reperfusion for their ability to predict left ventricular function at one month after acute myocardial infarction.

Design: 15 patients underwent primary percutaneous coronary angioplasty for acute myocardial infarction, with restoration of TIMI grade 3 flow. Corrected TIMI frame count (cTFC), myocardial blush grade (MBG), and percentage ST segment resolution at 90 and 180 minutes were recorded. Baseline regional wall motion score index (WMSI) and regional contrast score index (RCSI) were obtained 12–24 hours after the procedure, with a final regional WMSI assessment at one month.

Results: Mean (SD) cTFC was 27 (9.4), and ST segment resolution was 69 (22)% at 90 minutes and 77 (20)% at 180 minutes. MBG values were 0 in six patients, 2 in seven, and 3 in seven. Baseline regional WMSI, RCSI, and follow up WMSI were 2.7 (0.71), 1.5 (0.71), and 1.6 (0.73), respectively. The correlation coefficient between RCSI and follow up WMSI was 0.82 (p = 0.0012). Peak CK correlated significantly with follow up WMSI (R = 0.80). None of the other reperfusion assessment techniques correlated significantly with follow up WMSI. Multiple regression analysis showed that a perfused hypokinetic or akinetic segment was 50 times more likely to recover function than a non-perfused segment. MCE predicted segmental myocardial recovery with a sensitivity of 88%, a specificity of 74%, and positive and negative predictive values of 83% and 81%, respectively.

Conclusions: MCE is currently the best and most accurate measure of reperfusion at a microvascular level and an excellent predictor of left ventricular function at one month following acute myocardial infarction.

METHODS

In this study we compared intravenous MCE, using low power real time images, with other modes of microvascular reperfusion assessment for their ability to predict left ventricular function one month after successful primary percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction, resulting in TIMI (thrombolysis in myocardial infarction trial) grade 3 flow.

Abbreviations: cTFC, corrected TIMI frame count; MBG, myocardial blush grade; MCE, myocardial contrast echocardiography; PET, positron emission tomography; PTCA, percutaneous transluminal coronary angioplasty; RCSI, regional contrast score index; TIMI, “thrombolysis in myocardial infarction” trial flow grade; WMSI, wall motion score index
minutes and not responsive to fluids, or less than 100 mm Hg with vasopressors); the requirement for an intra-aortic balloon pump before or during coronary angioplasty; significant left main coronary artery disease (more than 50% diameter stenosis); previous myocardial infarction within one month; pretreatment with a thrombolytic agent; and pregnant women.

The study was approved by the local institutional review board and written informed consent was obtained from each patient before enrolment.

Before catheterisation all patients received low flow nasal oxygen, aspirin 300 mg orally, and heparin 5000 units intravenously. Diagnostic coronary arteriography was performed by the femoral approach according to the Judkins technique, and arteries were visualised in multiple projections. The infarct related artery was identified by the site of the coronary occlusion, by localisation of the ECG findings, or haemodynamically by > 50% diameter coronary stenosis, and by analysis of the wall motion defect by ventriculography. Coronary intervention was undertaken using 7 French or 8 French guide catheters and standard guide wires and balloon catheters. Heparin was given to maintain the activated partial thromboplastin time at more than 250 seconds. Stent deployment and the use of glycoprotein receptor antagonists were permitted at the physician’s discretion.

Blood samples were drawn at baseline and at 4, 8, 12, 16, 24, 36, 48, and 72 hours after angioplasty for creatine kinase estimations.

**Echocardiography**
Echocardiography was done 12–24 hours after reperfusion to assess regional and global left ventricular function using a phased array transducer switched to harmonic mode, with mean transmit and receive frequencies of 1.8 and 3.6 MHz. At one month, patients were recalled for a follow up study to reassess regional and global left ventricular function.

**Myocardial contrast echocardiography**
MCE was done 12–24 hours after reperfusion, using intravenous Optison (Molecular Biosystems, San Diego, California, USA) as the myocardial contrast agent. We used commercially available equipment (Hewlett Packard Sonos 5500, Andover, Massachusetts, USA) for the echocardiographic imaging, with the patient in the left lateral decubitus position. Contrast echocardiography was achieved using low mechanical index real time imaging (power modulation) with a broad band 2.2 MHz phased array (range 1.8–2.4 MHz). Transmitted power was adjusted to produce a mechanical index of 0.1–0.2. Before contrast was injected, a sequence of images was captured. These included three apical views (apical two to three and four chamber views) and two parasternal views (long and short axis views) to allow baseline wall motion assessment. Optison was injected as a slow bolus (0.3 ml) through a peripheral vein, followed by a 10 ml very slow saline flush (over 10 seconds). Image acquisition was initiated just before contrast injection. Manually triggered transient high mechanical index imaging (“flash” imaging) was used at peak contrast intensity to destroy microbubbles within the myocardium, exclude artefacts, and observe myocardial replenishment. MCE image acquisition was obtained for 10–15 beats following flash imaging, in the apical two, three, and four chamber views. All images were stored on optical disk and on super-VHS tape for subsequent analysis.

**Statistical analysis**
Statistical analysis was done using Sigmastat software (SPSS Science, Chicago, Illinois, USA). Results are expressed as mean (SD) or as percentages. Multivariate analysis by multiple linear regression was used to evaluate the independent contribution of age and sex. Sensitivity, specificity, and positive and negative predictive values were evaluated according to standard definitions. The correlation between different groups was assessed using a Pearson product–moment correlation matrix. A probability value of \( p = 0.05 \) was considered significant.

**RESULTS**

**Clinical characteristics**
Patient characteristics are outlined in table 1. In all, 15 patients (eight female, seven male) were treated with primary PTCA for acute myocardial infarction. Their mean age was 62 years. The mean (SD) time from the onset of chest pain to the first balloon inflation was 4.7 (2.3) hours.

**Angiography**
The left anterior descending, right coronary, and circumflex coronary arteries were the infarct related vessels in seven, five, and three patients, respectively. There was complete occlusion of the infarct related artery in nine patients. Two or more vessels were diseased in eight patients. Angioplasty only was carried out in four patients, while the rest had stents. In one patient, a distal left anterior descending coronary artery occlusion (RS) blinded to the clinical information was assessed the second injection of the artery and no PTCA was required. Abciximab was given to six patients and epifibatide to six. The rest received heparin only. All
patients had a TIMI grade 3 flow after the procedure. MBG was normal in seven patients (47%).

**ECG**

ECGs were recorded at 93 (9.8) and 186 (12.2) minutes post-procedure. One patient missed the 90 minute ECG through being en route to the coronary care unit. Lead involvement corresponded to the infarct related artery in all patients. At least 30% resolution occurred in the first 90 minutes in all the patients. Eight patients showed no further change at 180 minutes.

**Creatine kinase**

All patients had a rise in creatine kinase, although the values from one patient were excluded as he required electrical cardioversion for ventricular fibrillatory arrest during cardiac catheterisation.

**Echocardiography**

Baseline echocardiography was carried out 16 (2) hours after angioplasty, and follow up echocardiography took place 29 (4) days after acute myocardial infarction. Thirteen of the 15 patients had an abnormal baseline regional WMSI following PTCA; of these, six (40%) had absent myocardial perfusion on MCE. Of the total of 64 dysfunctional segments on baseline echocardiography, eight could not be analysed by MCE because of artefacts. Of the 56 analysable dysfunctional segments, 55 were akinetic and one hypokinetic. Of the 55 akinetic segments, 30 (55%) showed homogeneous contrast opacification, three showed reduced opacification, and the remaining 22 (40%) showed absent uptake. The one segment with hypokinesia showed normal contrast opacification.

**Follow up echocardiography**

Of the 56 dysfunctional segments, 32 showed improved contractility one month after revascularisation. Of the 32 segments showing recovery of function, MCE (homogeneous or reduced contrast opacification) predicted 28 (88%) that recovered function. Absent contrast opacification correctly predicted 18 (74%) of the 24 segments that did not recover function. Thus the positive and negative predictive values of MCE for recovery of function at one month after revascularisation were 83% and 81%, respectively. There was no significant difference in the accuracy for predicting recovery of function in patients with anterior versus inferior acute myocardial infarction.

**Comparison of MCE with other methods for predicting functional recovery**

Table 2 shows the correlation coefficients between the different methods used to assess reperfusion. There was no significant correlation between baseline regional WMSI and follow up regional WMSI, or any other form of reperfusion assessment. RCSI correlated strongly with the follow up regional WMSI, with an R value of 0.82 (p = 0.001), and also with cardiac enzyme release (R = 0.71; p = 0.01), but not with any of the other assessments of reperfusion. Peak creatine kinase correlated strongly with follow up regional WMSI (R = 0.80; p = 0.002); only ST segment resolution on the 180 minute ECG correlated significantly with peak creatine kinase (R = 0.54; p = 0.01) but not with follow up regional WMSI. The remaining techniques for assessment of reperfusion showed no significant correlation with follow up regional WMSI or between each other.

Table 3 shows the results of logistic regression analysis adjusting for the effects of age and sex. Regional CSI was significantly associated with an improvement in contractility, with an odds ratio indicating that a perfused hypokinetic or akinetic segment is 50 times more likely than a non-perfused segment to recover contractile function. An older age also
appears to be significantly associated with improvement in outcome, but an odds ratio of 1.4 suggests that this is not clinically important.

Figure 1 shows an example of a patient with an anterior acute myocardial infarct demonstrating apico-septal akinesia 12 hours after PTCA. However, MCE showed homogeneous opacification of the septum and apex, suggestive of preserved microvascular perfusion; this predicted recovery of function, shown by follow up echocardiography at one month. Figure 2 is an example of another patient with an anterior acute myocardial infarct with apico-septal akinesia 12 hours after PTCA. MCE showed no opacification of these segments, suggesting lack of microvascular perfusion despite a patent epicardial artery. The follow up echocardiogram did not show recovery of function in the akinetic segments, as predicted by MCE.

DISCUSSION

In this study we have verified that a significant proportion of patients have impaired reperfusion at tissue level following apparently successful primary PTCA (TIMI 3 grade flow). The cause of the “no reflow” or “low reflow” phenomenon following acute myocardial infarction is unclear but several mechanisms have been suggested, including cellular oedema, endothelial damage, and microembolisation by platelets, thrombi, and other tissue debris. We found a significantly higher proportion of patients with reduced or absent tissue perfusion in the context of normal angiographic flow than have been reported elsewhere. The hyperaemic effect that occurs immediately on reperfusion suggests that studies undertaken within 12 hours of treatment could produce an artefactually high level of flow on contrast echocardiography. This would result in an underestimation of the true level of perfusion. Hence Ito and colleagues, who performed MCE immediately after successful reperfusion for acute myocardial infarction, reported a contrast deficit of 25%, whereas Maes and associates, who performed positron emission tomography (PET) within 24 hours of acute myocardial infarction, found that over two thirds of their patients had significant perfusion defects. To overcome this potential problem, we did the contrast study in the 12–24 hour period following PTCA, when the effect was thought to have resolved.

To our knowledge, this report is the first to compare MCE with other techniques of reperfusion assessment and to examine their respective capabilities in predicting long term left ventricular recovery. The rate of ST segment resolution is a simple and well established technique for determining the status of reperfusion. Several large trials have shown its value in predicting outcome in patients with acute myocardial infarction. Schroder and colleagues measured the percentage of ST segment resolution three hours after thrombolysis in 1516 patients with acute myocardial infarction. For complete (> 70%), partial (30–70%), and no ST segment resolution (< 30%) at three hours, the ejection fractions were 60%, 53%, and 49%, respectively, and mortality rates at one month were 2.2%, 3.4%, and 8.6%. In that study, ST segment resolution did not correlate with the follow up regional WMSI but was found

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pearson product–moment correlation matrix of different methods of reperfusion assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MBG</td>
</tr>
<tr>
<td>cfTFC</td>
<td>-0.44</td>
</tr>
<tr>
<td>MBG</td>
<td>0.15</td>
</tr>
<tr>
<td>ECG 90 min</td>
<td>0.44</td>
</tr>
<tr>
<td>ECG 180 min</td>
<td>0.30</td>
</tr>
<tr>
<td>bRWMSI</td>
<td>0.30</td>
</tr>
<tr>
<td>RCSI</td>
<td>0.30</td>
</tr>
<tr>
<td>fRWMSI</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Indices represent R values. *p=0.05; †p=0.001; ‡p=0.01; ¶p=0.002.

bRWMSI, baseline regional wall motion score index; CK, creatine kinase; cfTFC, corrected TIMI frame count; fRWMSI, follow up regional wall motion score index; MBG, myocardial blush grade; RCSI, regional myocardial contrast score index.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multiple logistic regression analysis adjusting for age and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>RCSI</td>
<td>49.6</td>
</tr>
<tr>
<td>Age</td>
<td>1.4</td>
</tr>
<tr>
<td>Sex</td>
<td>1.9</td>
</tr>
</tbody>
</table>

CI, confidence interval; RCSI, regional contrast score index.

Figure 1 (A) Apical four chamber view in systole showing akinetic septum and apex (arrows). (B) Homogeneous contrast opacification of the akinetic segments. (C) Follow up echocardiography at one month, showing recovery of function of these segments (arrows) with reduction of left ventricular end systolic volume.
to correlate with infarct size as determined by the peak rise in creatine kinase.

Neither cTFC nor MBG showed any significant relation with the follow up assessment of regional WMSI in our study. The corrected TIMI frame count method was originally introduced to supersede TIMI flow grading by providing a more accurate quantification of angiographic flow, with minimal interobserver variability and enhanced reproducibility. In a study of 1248 patients with acute myocardial infarction, Gibson and colleagues found that faster (lower) 90 minute cTFCs were related to improved in-hospital and one month clinical outcomes after thrombolytic treatment in both univariate and multivariate models. Similarly, MBG is another method of assessing the degree of no or low reflow following acute myocardial infarction, and its semiquantitative grading system has been shown to be an independent predictor of long term mortality. In one study of 777 patients undergoing primary PTCA for acute myocardial infarction, the investigators found that those with blush grades of 3, 2, and 0/1 had ejection fractions of 50%, 46%, and 39% respectively, and mortality rates of 3%, 6%, and 23%.

Our results show that MCE is far superior to these other forms of reperfusion assessment. In particular, many fewer patients were required to show a significant correlation with left ventricular functional outcome. The most likely explanation for this is that the other methods provide a less accurate representation of tissue viability than MCE and therefore require larger numbers to demonstrate an association with outcome.

Neither coronary blood flow nor MBG assesses myocardial perfusion. Myocardial perfusion can be defined as tissue blood flow at the capillary level. The two components of blood flow, blood volume and velocity, can be assessed by MCE. MCE signal intensity represents relative blood volume, and the number of cardiac cycles required for myocardial contrast replenishment following destruction with a high energy ultrasound pulse represents blood velocity. We have previously shown that MCE done 3–5 days after acute myocardial infarction and thrombolysis is an independent predictor of recovery of function six months after acute myocardial infarction.

Earlier studies with MCE, using both intracoronary and intravenous techniques, similarly predicted recovery of function in the dyssynergic segments following primary coronary interventions. In a series of 39 patients with anterior acute myocardial infarction studied by Ito and colleagues, intracoronary MCE predicted improvement in regional and global left ventricular function if myocardial perfusion was demonstrated following PTCA. However, Bolognese and colleagues observed a lower specificity and positive predictive value for recovery of left ventricular function than we found in our study. This is possibly because they used high mechanical index imaging, which results in an increase in tissue artefact giving rise to a false positive contrast effect. This also explains the lower rate of detection of perfusion defects in patients with inferior acute myocardial infarcts compared with anterior infarcts in a study by Kamp and associates, as tissue signals tend to be stronger in the inferior wall compared with the anterior wall in the apical views. The low mechanical index employed in our study resulted in absence of tissue noise, which translated into improved prediction of inferior acute myocardial infarction.

The prognosis following myocardial infarction is directly related to the amount of myocardial damage sustained. Following acute infarction and revascularisation, infarct related dyssynergic segments may continue to be dysfunctional despite microvascular perfusion. The presence of dysfunctional but perfused myocardium predicts myocardial viability. The identification and quantification of these areas of tissue viability allows clinicians to risk stratify patients and target those likely to benefit from aggressive medical treatment. On the other hand, if no microvascular reflow can be demonstrated treatment to improve microvascular flow may be necessary. Such treatments are being investigated.

Current methods such as PET, nuclear scintigraphy, and dobutamine echocardiography are difficult to employ immediately after acute myocardial infarction as they are cumbersome, expensive, or require specialised licensing, and they are commonly contraindicated on clinical grounds. In contrast, MCE is an accurate, low cost technique which is easily undertaken at the bedside in critically ill patients, using a peripheral venous injection. MCE may also be used to determine the success or failure of thrombolysis at the bedside. Patients who show lack of myocardial perfusion after thrombolysis may benefit from rescue PTCA.

**Study limitations**

Our study is limited by the small number of patients. Demonstration of the relative predictive values of the other techniques would have further validated our results. Our semiquantitative visual analysis of segments shown on MCE could be considered a limitation of the study, and videodensitronic analysis may improve overall accuracy further. We acknowledge that some patients could have had long standing wall motion abnormalities, but by restricting the analyses to segments within the territory of the infarct related artery we...
hoped to minimise this effect. However, the inclusion of previously diseased segments would be more likely to cause an underestimation of the correlation coefficient and predictive values than an overestimation.

Conclusions
MCE is a highly accurate and superior measure of the quality of reperfusion at a microvascular level. As a result it is an excellent predictor of left ventricular recovery after acute myocardial infarction. The technique is easy to use and can accurately identify a high proportion of myocardial segments that will recover function. MCE may have a primary role in assessing the quality of reperfusion following acute myocardial infarction, thus allowing accurate risk stratification.

ACKNOWLEDGEMENT
We thank Elean Sharpe and Sing Kai Lo for technical and statistical assistance.

References


www.heartjnl.com
Myocardial contrast echocardiography is superior to other known modalities for assessing myocardial reperfusion after acute myocardial infarction

K Greaves, S R Dixon, M Fejka, W W O'Neill, S R Redwood, M S Marber and R Senior

Heart 2003 89: 139-144
doi: 10.1136/heart.89.2.139

Updated information and services can be found at:
http://heart.bmj.com/content/89/2/139

These include:

References
This article cites 24 articles, 17 of which you can access for free at:
http://heart.bmj.com/content/89/2/139#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Interventional cardiology (2933)
Clinical diagnostic tests (4779)
Echocardiography (2127)
Acute coronary syndromes (2742)
Drugs: cardiovascular system (8842)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/