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Intravenous Myocardial Contrast Echocardiography Predicts Recovery of Dysynergic Myocardium Early After Acute Myocardial Infarction

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OBJECTIVES We aimed to ascertain whether triggered intravenous myocardial contrast echocardiography (MCE) can predict functional recovery in patients with acute myocardial infarction (AMI) and to determine the optimal triggering interval in this setting.

BACKGROUND Detection of myocardial viability early after AMI has both therapeutic and prognostic implications. Myocardial contrast echocardiography using intracoronary injections of contrast can detect viable myocardium, but there is little data on the use of recently developed intravenous MCE techniques for this purpose.

METHODS Ninety-six patients with recent AMI (4.8 ± 1.7 days) underwent echocardiography at baseline and six months later or three months after revascularization to determine regional function (score 1 = normal to 3 = akinetic). Myocardial contrast echocardiography was performed at baseline using intravenous injections of Optison. Triggering intervals of 1:1 (early) and 1:10 (delayed) cardiac cycles were used. Segments were deemed viable if they demonstrated homogeneous contrast opacification.

RESULTS Of 400 akinetic segments at baseline, 109 (27%) improved during the follow-up period, and 375 (94%) were adequately visualized with MCE, of which 59 (16%) were homogeneously opacified by early and 125 (33%) by delayed MCE (negative predictive value for recovery of contractile function 74% and 84%, positive predictive value 29% and 47%, respectively). Independent predictors of functional recovery were delayed MCE (odds ratio [OR]: 4.0, $p < 0.001$), revascularization (OR: 6.0, $p < 0.001$), and log creatine kinase (OR: 0.5, $p = 0.03$). However, the presence or absence of >90% stenosis of the infarct-related artery did not influence the ability of triggered MCE to predict functional recovery.

CONCLUSIONS Intravenous delayed triggered MCE can independently detect myocardial viability early after AMI. (J Am Coll Cardiol 2001;38:19–25) © 2001 by the American College of Cardiology

When regional myocardial blood flow is reduced distal to a coronary stenosis, resting contractile function of the affected myocardium may be down-regulated despite the presence of persisting viability. It has been demonstrated in both in animal models (1) and in patients (2) that myocardial contrast echocardiography (MCE) can detect myocardial viability, and this technique has been correlated with nuclear perfusion (3), dobutamine echocardiography (4) and functional improvement (2,5–9). The advent of intravenous contrast agents has facilitated the more widespread use of this technique. There is, however, little published data on the use of MCE for the assessment of myocardial viability in patients early after acute myocardial infarction (AMI).

Since contrast is destroyed by the ultrasound beam, triggered imaging has been required to visualize the small amounts of contrast present within the myocardium when intravenous administration is used. Triggering allows time for contrast to fill the region of interest before the next imaging pulse and, thus, ameliorates the problems of contrast destruction. However, in areas with low resting blood flow, triggering every cardiac cycle may not allow sufficient time for contrast to fill the region of interest, and longer triggering intervals may be required (10). We aimed to determine whether triggered intravenous MCE can be used clinically to predict functional recovery of dysynergic myocardium early after AMI and to ascertain whether delayed triggering improves myocardial opacification.

METHODS

Stable patients with documented AMI were included in this study. Patients with postinfarct angina, persistent left ventricular (LV) failure and significant ventricular arrhythmias were excluded. All patients gave prior consent, and the study was approved by the local ethical committee. Patients underwent MCE during hospital admission but at least three days after AMI. Patients were then followed up and underwent resting echocardiography six months later or at least three months after revascularization in those who underwent such a procedure, whichever was later.

Echocardiography. Echocardiography was performed by the same sonographer using tissue harmonic imaging with a broad-band transducer (4-2 MHz) (HDI5000, ATL, Bothell, Washington). Standard apical and parasternal views

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Abbreviations and Acronyms

AMI	=	acute myocardial infarction
CI	=	confidence interval
CK	=	creatine kinase
CK-MB	=	creatine kinase isoenzyme
ECG	=	electrocardiogram
IRA	=	infarct-related artery
LV	=	left ventricle or left ventricular
MCE	=	myocardial contrast echocardiography
NPV	=	negative predictive value
OR	=	odds ratio
PPV	=	positive predictive value
PTCA	=	percutaneous transluminal coronary angioplasty

were used. Four representative views were stored using a digital capture system. Images from each echocardiography study in each view were displayed side-by-side for subsequent wall motion analysis. Systolic wall thickening was scored using the American Society of Echocardiography 16-segment LV model by two experienced observers who were blinded to the clinical details of the patients. A three point scale was used to score systolic wall thickening: 1 = normal, 2 = reduced, 3 = absent. Disagreements were resolved by consensus.

MCE. Myocardial contrast echocardiography was performed using pulse inversion harmonic imaging (mechanical index 0.9) after baseline wall motion images had been captured. Slow boluses of 0.3 to 0.7 mls of Optison (Mallinkrodt, St. Louis, Missouri) were injected intravenously followed by a saline flush over 20 s, and single frame images were captured using an electrocardiogram (ECG) trigger set at end-systole. Images were captured every cardiac cycle (early MCE) and then 5 and 10 (delayed MCE) cardiac cycles after each injection of contrast in each of the three standard apical views when attenuation was confined to the left atrium, and, at the same time, a flow of contrast was visible in the right ventricle. The focus was set at the mitral valve level, but, if there was concern about a possible apical defect, the focus was moved up toward the apex. Further injections of contrast were used in nonstandard apical views (e.g., bringing lateral wall into sector field) if required to attempt to overcome localized areas of attenuation. The studies were recorded on videotape and analyzed after the completion of the study. The same 16-segment LV model was used, and MCE was scored semiquantitatively using a three point scale: 1 = homogeneous contrast opacification, 2 = reduced or heterogeneous contrast opacification, 3 = no contrast opacification. Myocardial contrast echocardiography was scored at each triggering interval by two experienced observers who were blinded to the clinical details of the patients and the follow-up echocardiography. A contrast defect index was calculated for each triggering interval by adding the contrast scores of akinetic segments and dividing by the number of akinetic segments.

Only segments that were akinetic at baseline were analyzed. In patients with prior infarction, only the segments related to the area of recent infarction were analyzed. The area of recent infarction was defined based on the admitting ECG. Each segment was divided into one of two groups: viable, if myocardial function recovered during follow-up, or nonviable, if no improvement was seen. The viable group was subdivided into segments that improved spontaneously and those that improved after revascularization. Recovery of function was defined as improvement of an akinetic segment (score = 3) to hypokinesia (score = 2) or normality (score = 1). A segment was defined as viable by contrast echocardiography only if there was homogeneous contrast opacification (score = 1), and a score >1 was considered to represent nonviability. This was determined for both early and delayed MCE. Contrast and follow-up echocardiography results were then compared for each segment to determine the ability of MCE to predict functional recovery early after AMI.

Coronary angiography and revascularization. Coronary angiography was not a requirement for entry into this study, but many patients underwent this procedure on clinical grounds. Coronary angiograms were analyzed by the clinician managing the patient using a visual quantitative scoring system as is standard practice in our institution. The infarct-related area (IRA) was determined using the admission ECG to identify the site of AMI, and the most significant stenosis of an artery supplying that territory was used for analysis. The decision to proceed with coronary revascularization was made on clinical grounds and not based on the results of MCE. At our institution, revascularization is performed for recurrent unstable angina, high-risk exercise ECG, severe three-vessel coronary disease or left main stem disease.

Statistics. All categorical variables are shown as proportions. Continuous variables are shown as mean ± standard deviation except for those that are not normally distributed, which are presented as medians with 95% confidence intervals (CI). The median contrast defect index was calculated for each patient, and the Mann-Whitney *U* test was used to compare those patients who did and those who did not show recovery of function. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for prediction of recovery of function on a segmental basis were determined for both MCE variables. Sensitivities and specificities were compared using McNemar's test. Univariate logistic regression analysis to predict recovery of function on a segmental basis was performed for each categorical and continuous variable. Positively skewed variables were log transformed for further analysis. Multiple logistic regression analysis was then performed including all variables using backwards elimination. For all logistic regression analyses, robust Huber-White estimates of the standard errors of the regression coefficients were calculated, taking into account the fact that segments from the same patient may not be independent. Finally, a single variable

Table 1. Demographics of the Study Cohort and Details of Presenting Myocardial Infarction

Demographics:	
Age (yr)	60 ± 12
Men	68 (71%)
Diabetic	13 (14%)
Hypertension	35 (36%)
Smoker	44 (46%)
Ex-smoker	20 (21%)
Medical history:	
History of IHD	14 (15%)
Previous MI	12 (13%)
CABG	1 (1%)
PTCA	1 (1%)
Acute MI:	
ST-elevation	85 (89%)
Thrombolysis	69 (72%)
Q-waves	63 (66%)
Peak CK (IU/l)	2,066 ± 1,844
Peak CK-MB (IU/l)	176 ± 146
Electrocardiographic infarct site:	
Anterior	41 (43%)
Lateral	5 (5%)
Inferior	47 (49%)
Posterior	3 (3%)

CABG = coronary artery bypass graft; CK = creatine kinase; CK-MB = creatine kinase isoenzyme; IHD = ischemic heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

was generated to represent the three possible combinations of contrast opacification for each segment from early and delayed MCE (no contrast opacification, opacification with delayed MCE only, opacification with early and delayed MCE). Logistic regression was then performed using this as the dependent variable and stenosis severity as the independent variable. A p value of <0.05 was considered significant. All statistical analyses were performed using Stata Version 6.

RESULTS

Patients. Ninety-eight patients were included in the study. Two patients suffered a further AMI before the final echocardiography and were excluded from the analysis as a consequence. Demographic details of the remaining 96 patients are shown in Table 1. Baseline echocardiography and MCE were performed 4.8 ± 1.7 days after the AMI.

Follow-up. Of 96 patients, 27 (28%) underwent revascularization procedures (19 percutaneous transluminal coronary angioplasty [PTCA], 8 coronary artery bypass graft) at a median of 32 (CI: 4 to 335) days after the baseline study. The final follow-up echocardiography was performed at a mean of 147 (CI: 18 to 224) days after revascularization in this group and 179 (CI: 27 to 361) days after the baseline study in the entire cohort.

Echocardiography. Of a total of 1,536 myocardial segments, 421 (27%) were akinetic at baseline. Twenty-one of these segments were excluded on the basis of prior remote infarction, and 109 (27%) of the remaining 400 demonstrated functional improvement during the course of the study. Fifty-three (49%) of the segments that improved occurred in patients who underwent revascularization, while the rest improved spontaneously.

MCE. Adequate MCE was achieved in 1,429 (93%) segments overall and in 375 (94%) of the 400 akinetic segments assessed for the study. Over half of the artefacts preventing assessment of MCE occurred in the basal inferoposterior (26%), lateral wall (7%) and the anterior wall (25%). Of the akinetic segments in which contrast could be adequately assessed, homogeneous contrast opacification was seen in 59 (16%) during early and 125 (33%) during delayed MCE.

The median contrast defect index was significantly higher in segments that did not recover than it was in those that did recover, for both early (1.61 [CI: 1.36 to 1.813] vs. 1.26 [CI: 1.19 to 1.46] $p = 0.04$) and delayed triggering (1.52 [CI: 1.16 to 1.69] vs. 1.13 [CI: 1.04 to 1.25] $p = 0.003$), and the index was significantly ($p < 0.001$) higher at shorter triggering intervals.

The overall PPV of early MCE for the prediction of functional recovery was only 29% with an NPV of 74%. The PPV improved to 47% with delayed MCE, and the NPV increased to 84%. The PPV of delayed MCE for the prediction of functional recovery was higher in patients who were revascularized (78%) than it was in those who were not (34%) (Table 2). The PPV of delayed MCE was similar for inferior (44%) and anterior (51%) AMI, but the NPV was higher in anterior AMI (89% vs. 65%). Figures 1 and 2 show respective examples of recovery of function and failure of functional recovery correctly predicted by delayed MCE.

The univariate predictors of recovery of function were homogeneous opacification by delayed MCE, revascularization, non–Q-wave AMI, logCK and logCK-MB. The chi-square and significance values are shown in Table 3. Creatine kinase and creatine kinase isoenzyme were highly correlated, so only one was included in the regression model at any one time. The independent predictors of functional

Table 2. Comparison of Sensitivities, Specificities, NPVs and PPVs for Prediction of Functional Recovery on a Segmental Basis Using Early and Delayed Myocardial Contrast Echocardiography

	All Patients		Revascularized		Nonrevascularized	
	Early	Delayed	Early	Delayed	Early	Delayed
Sensitivity	17%	59%*	21%	62%*	13%	57%*
Specificity	85%	76%*	89%	85%†	84%	74%*
PPV	29%	47%	63%	78%	16%	34%
NPV	74%	84%	57%	72%	80%	88%

*$p < 0.001$; †p = NS.
NPV = negative predictive value; PPV = positive predictive value.

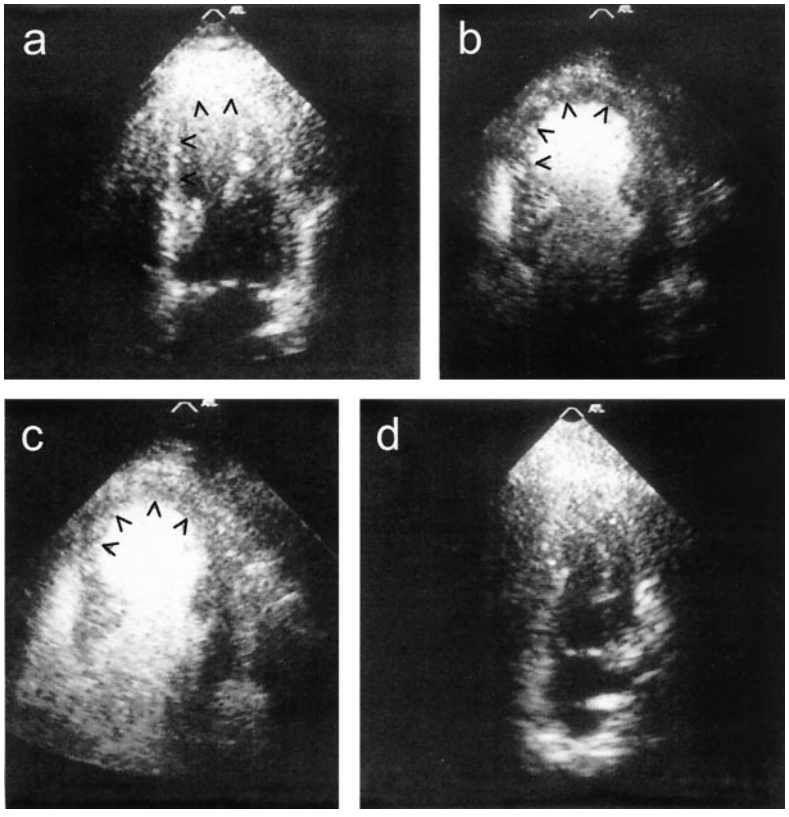

Figure 1. Four-chamber view showing an akinetic septum and apex **(a)** with absent contrast opacification in this region at short triggering intervals **(b)** but homogeneous opacification with delayed triggering **(c)** and normal resting function six months later **(d)**.

recovery were revascularization (odds ratio [OR]: 6.0, 95% CI: 1.8 to 19.9, $p < 0.001$), delayed MCE (OR: 4.0, 95% CI: 1.9 to 8.7, $p < 0.001$) and logCK (OR: 0.5, 95% CI: 0.27 to 0.94, $p = 0.03$).

Coronary angiography. Sixty-six patients (69%) underwent coronary angiography during the follow-up period. Twenty-four patients had occlusion of the IRA, and 25 had a stenosis of at least 90%. Thus, of the patients whose coronary anatomy was known, the majority (74%) had a stenosis of at least 90% in the IRA. However, when entered into the logistic regression model, the degree of stenosis of the IRA was not a significant predictor of recovery of function ($p = 0.9$) or of the relationship between early and delayed MCE ($p = 0.5$).

DISCUSSION

This study demonstrates that intravenous MCE can predict the potential for recovery of myocardial function early after AMI. While hypokinetic myocardium retains some contractile function and, thus, is always viable (and, therefore, was not included in our analysis), akinetic myocardium may be either necrotic or viable. Necrotic myocardium is characterized by loss of membrane integrity, lack of glycolytic or mitochondrial function and absence of contractile potential. These factors can be identified as abnormalities at thallium-201 perfusion imaging, positron emission tomography, technetium-99m perfusion imaging and dobutamine stress echocardiography, respectively. In addition, when tissue becomes necrotic, the local capillary network becomes thrombosed and occluded (11). Viable myocardium, on the other hand, retains all of these functions, which are dependent on the presence of an intact capillary network, but contractile function may be down-regulated in some circumstances. Viable but akinetic myocardium may be subtended by an open artery ("stunned") (12,13) or by a stenotic or occluded artery ("repetitively stunned" or "hibernating"). Stunned myocardium typically occurs in the peri-infarct zone because of an acute reduction in blood flow, which is then partially or completely relieved before necrosis can occur, and thus may be expected to recover spontaneously. However, dysfunctional myocardium may fail to recover despite the absence of necrosis when subjected to persistently reduced flow (hibernating) or recurrent episodes of insufficient flow (repetitively stunned), such as in the presence of a high-grade stenosis or collateral flow in the presence of an occluded vessel. This down-regulation of contractile function will recover only after the restoration of normal blood supply by revascularization. Consequently, the ability to detect dysfunctional, but viable, myocardium after myocardial infarction has important prognostic and therapeutic implications.

Mechanism. Myocardial contrast echocardiography detects contrast microbubbles at the capillary level within the myocardium and, thus, has the potential to assess tissue

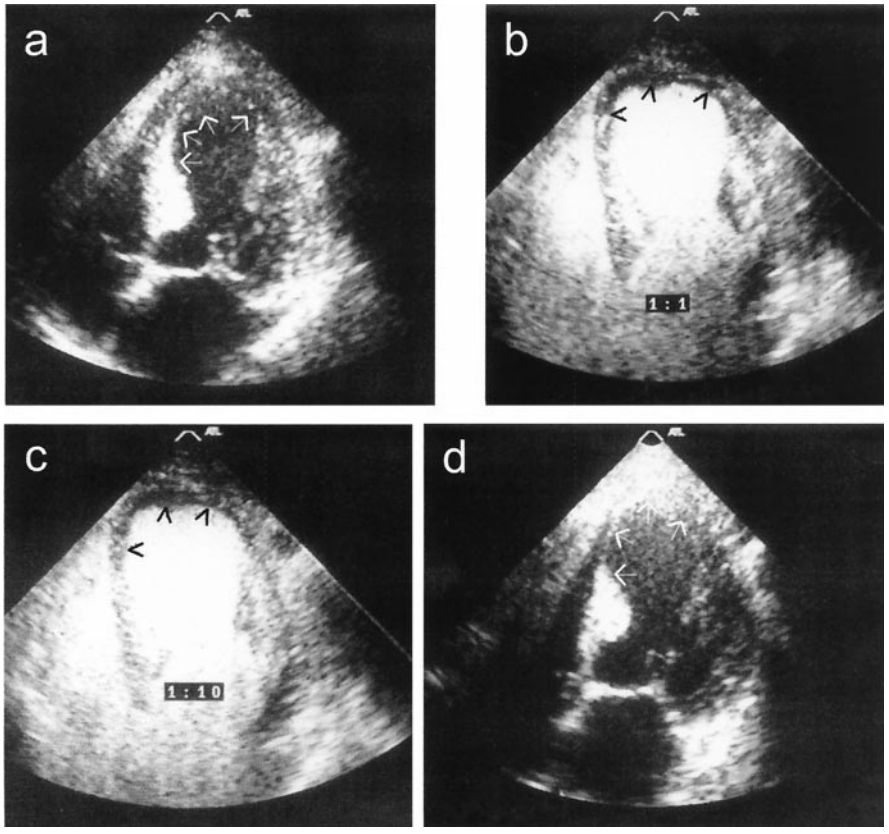

Figure 2. Four-chamber view showing an akinetic septum and apex **(a)** with no contrast opacification in this area with early **(b)** or delayed **(c)** triggered imaging and failure of recovery of systolic function at follow-up **(d)**.

viability (2). However, because the ultrasound beam used to detect the microbubbles also destroys them at normal power outputs (14), the lower the myocardial blood flow the longer the time required to achieve peak video intensity (10). Accordingly, since many patients after AMI have areas of low resting blood flow, the presence of contrast microbubbles, and, thus, viability, might be underestimated if contrast destruction exceeds replenishment. By allowing an increased time interval between imaging pulses, delayed MCE may permit contrast to flow into such poorly perfused areas without destruction and alleviate this problem (15). This study demonstrates that delayed MCE significantly improves the sensitivity for the detection of viability. Furthermore, in this study, delayed MCE independently predicted recovery of myocardial function, while early MCE did not.

Table 3. Chi-Square and Significance Values for Univariate Predictors of Segmental Functional Recovery

	Chi-square	p Value
Age	0.1	>0.1
Gender	0.2	>0.1
Diabetes mellitus	0.0	>0.1
Hypertension	0.8	>0.1
Infarct territory	3.7	0.06
ST-elevation	0.0	>0.1
Thrombolysis	0.8	>0.1
Log (peak creatine kinase)	4.3	0.04
Log (peak CK-MB)	5.6	0.02
Q-wave infarct	5.3	0.02
Early MCE	0.1	>0.1
Delayed MCE	20.2	<0.0001
Revascularization	6.0	0.01

CK-MB = creatine kinase isoenzyme; MCE = myocardial contrast echocardiography.

However, when comparing early MCE with delayed MCE, we were not able to demonstrate that the improved predictive power of delayed MCE was related to the degree of stenosis of the IRA. We believe this is because 74% of patients in this study had IRA stenoses ≥90%, and only three patients had <75% stenoses. Indeed, it is probable that delayed MCE was superior to early MCE in this study specifically because of the high incidence of high-grade stenoses and, thus, the high-frequency of areas of myocardium with impaired resting blood flow. However, further studies of patients with a broader range of IRA stenoses are required to confirm this.

This theory, however, does not explain why some segments with "patent" (<90% stenosis) epicardial vessels showed improved contrast opacification with delayed triggering compared with early triggering. We propose two possible alternative explanations for this finding. In the early days after AMI, it is possible that, despite a patent epicardial vessel, there has been thrombus and plaque embolization to the distal vessels, causing sludging of arterioles and a reduction of microvascular flow ("low reflow") as assessed by

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triggered MCE. Indeed, Brochet et al. (16) reported a group of patients in whom contrast opacification was absent when intracoronary contrast was given immediately after primary PTCA in AMI, but it improved when the study was performed nine days later. In that study, 34% of segments with this improvement in contrast opacification demonstrated functional recovery at six weeks compared with 7% of segments with a sustained contrast defect ("no reflow"). An alternative explanation for the lack of full contrast opacification at 1:1 triggering is that, even with normal flow, there might be insufficient time for contrast to fill the ultrasound beam width.

Clinical implications. The most important clinical implication of these results is that, of all the clinical variables studied, the presence of myocardial viability as detected by delayed MCE was the best predictor of functional recovery. Furthermore, delayed MCE has a high NPV for recovery of function. This correlates well with studies using intracoronary injections of contrast, which have shown that microvascular integrity is a prerequisite for functional recovery (4,5,9,17–20). In particular, the use of delayed MCE further improves the NPV of this technique compared with early MCE. The PPV of delayed MCE for the prediction of functional recovery was, however, less striking. This, too, is in keeping with other studies that have assessed the ability of intracoronary MCE (9) and alternative perfusion imaging modalities to predict functional recovery (8). However, in patients who were revascularized, in whom maximal recovery of hibernating myocardium would be anticipated, the PPV of MCE was much higher (74%) than in patients who did not undergo revascularization (34%), in whom any hibernating myocardium would not be expected to recover. Also, although the majority of functional recovery occurs in the first few weeks after revascularization (9,19), improvement can continue for up to six months or more, particularly in patients with longstanding areas of hibernation (21). For this reason, follow-up scans were performed at least three months after the revascularization procedure was performed. However, it is possible that if additional follow-up had been performed, delayed functional recovery might have been demonstrated, improving the PPV. Another explanation for the lower PPV of contrast echocardiography for detection of functional recovery is the fact that the subendocardium is responsible for 80% of systolic wall thickening (22). Thus, in patients with subendocardial infarction, resting wall thickening may remain absent despite considerable subepicardial viability. On the other hand, these viable areas may still be important for the prevention of adverse remodeling even if they never contribute to resting contractile function (23). In this context, a comparison of MCE with techniques such as radionuclide imaging (positron emission tomography or nuclear perfusion imaging) or gadolinium-enhanced magnetic resonance imaging, which also assess myocardial perfusion, might have resulted in greater agreement.

Comparison with previous studies. Our results complement those of Lepper et al. (24) who demonstrated that MCE using 1:1 triggering has the potential to identify viable myocardium after AMI. This study was performed in patients who had undergone acute PTCA and who, therefore, had patent IRA. It is, thus, likely that blood flow to any viable myocardium would have been normal and, therefore, that 1:1 triggering would be sufficient to demonstrate myocardial perfusion. In our study population, however, thrombolysis was used, with the result that 74% of patients had a severe stenosis (>90%) or occlusion of the IRA, and, therefore, longer triggering intervals were required to achieve adequate assessment of myocardial perfusion.

The assessment of resting perfusion defects using intravenous MCE in patients with prior AMI has been shown to correlate well with regional activity measured using radionuclide imaging (25,26), and other studies have demonstrated the potential of this technique to detect reversible perfusion defects using dobutamine and dipyridamole stress (27).

Study limitations. In this study, only triggering intervals of 1:1, 1:5 and 1:10 were used. It is possible that longer triggering intervals may have further improved the detection of viable myocardium. Also, although a semiquantitative scoring system was used for contrast assessment, this gave only three points on the reperfusion curve, and it meant that we were unable to differentiate between the possibilities of normal flow and small vessel sludging with a patent epicardial vessel. Quantitative analysis of contrast opacification might have improved the separation of groups even further. However, our objective was to determine whether there was any clinical value in the use of unprocessed MCE for the assessment of tissue viability early after AMI. Ideally, for a study of this type, a continuous infusion of contrast should have been used to ensure constant contrast concentrations in the blood throughout each examination. However, we used a slow bolus injection, which was continued until all images had been acquired in that view and, thus, were able to maintain relatively stable contrast concentrations during the image acquisition period. Myocardial contrast echocardiography is prone to artefact and attenuation. This is a particular problem in the basal inferoposterior segments, which may limit the interpretation of MCE in these segments. This is perhaps the reason why we saw a higher false negative rate in patients with inferior AMI. However, as we have demonstrated, these artefacts can often be overcome with attention to detail and the use of nonstandard views.

Conclusions. This study demonstrates that intravenous triggered MCE can be used to assess myocardial viability as early as three days after AMI. Furthermore, using delayed MCE significantly improves the diagnostic power for the prediction of akinetic myocardium that is likely to recover. Specifically, if no contrast is seen in a given segment when delayed MCE is used, it is strongly predictive of a lack of

functional recovery. Thus, MCE can be used for bedside diagnosis of viability of dysfunctional myocardium early after AMI.

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