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REVIEW

Myocardial contrast echocardiography in ST elevation myocardial infarction: ready for prime time?

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Acute myocardial infarction (AMI) continues to be a significant public health problem in industrialized countries and an increasingly significant problem in developing countries. ST elevation myocardial infarctions (STEMI) constitute ~40% of all AMIs with ~670,000 cases yearly in the United States alone. The risk of further cardiac complications such as re-infarction, sudden death, and heart failure for those who survive AMI is substantial. Thus, early assessment and risk stratification during the acute phase of STEMI is important. Furthermore, it is essential to assess the efficacy early after any initial therapeutic intervention, not only to facilitate further management, but also to enable development of new treatment algorithms/approaches to further improve the outcome. The aim of reperfusion therapy in AMI is not only to rapidly restore epicardial coronary blood flow but also to restore perfusion at the microcirculatory level. Myocardial contrast echocardiography (MCE) which utilizes microbubbles can assess myocardial perfusion in real time. Its ability to assess myocardial perfusion and function in one examination allows it to ascertain the extent of myocardial reperfusion achieved in the risk area. Furthermore, in stable patients after AMI, MCE allows assessment of LV function, residual myocardial viability, and ischaemia which are all powerful prognostic markers of outcome. Its portability, rapid acquisition and interpretation of data, and the absence of radiation exposure make it an ideal bedside technique.

Keywords Acute myocardial infarction • STEMI • Myocardial contrast echocardiography • Myocardial perfusion • No-reflow

Introduction

Acute myocardial infarction (AMI) continues to be a significant public health problem in industrialized countries and an increasingly significant problem in developing countries.[1] ST elevation myocardial infarctions (STEMI) constitute ~40% of all AMIs[2] with ~670 000 cases yearly in the United States alone.[2,3] The estimated mortality, although declining, still remains high[4] and the risk of further cardiac complications such as re-infarction, sudden death, and heart failure for those who survive is substantial. Thus, early assessment and risk stratification during the acute phase of STEMI is important. Furthermore, it is essential to assess the efficacy early after any initial therapeutic intervention, not only to facilitate further management, but also to enable development of new treatment algorithms/approaches to further improve the outcome.

The aim of reperfusion therapy in AMI is not only to rapidly restore epicardial coronary blood flow (CBF) but also to restore the perfusion at the microcirculatory level. This leads to maximal myocardial tissue salvage and thereby improves both morbidity and mortality.[5,6] In the immediate aftermath of thrombolysis, it is important to determine whether the infarct-related artery (IRA) is patent, and if so whether successful myocardial reperfusion has been achieved. Addressing these questions expeditiously is important for subsequent treatment strategies, as prompt identification of failure of thrombolytic therapy allows early transfer for

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rescue percutaneous coronary intervention (PCI).[7] Furthermore, even when patency of the IRA is restored, with PCI, one has to determine whether microvascular perfusion has been achieved for risk stratifying patients.[8] Important considerations following thrombolysis include assessment of residual myocardial viability, detection of ischaemia in the IRA territory, and flow-limiting stenosis in a remote coronary artery territory. Ischaemia in myocardium subtended by the IRA, or a remote coronary artery territory, and the extent of residual myocardial viability directly influences decisions for proceeding to coronary arteriography to evaluate revascularization strategy. Correct triaging of patients to revascularization vs. medical therapy has both prognostic and therapeutic implications[7–10] and likely cost benefit.

Methodology for review

All papers reviewed were obtained by performing a PubMed search from web-page http://www.ncbi.nlm.nih.gov/sites/entrez in January 2007. This primary bank of articles used was generated by entering the search item 'myocardial contrast echocardiography' (MCE) in PubMed; this provided a bank of 19 174 articles, this was narrowed down to 14 935 by limiting to those published in English, and then 13 809 by excluding review articles. Further literature searches were performed from January 2007 to July 2007 prior to finalizing the article to include any recently published articles. The different questions we set out to answer were then used to narrow down the list of articles further when writing each section.

Myocardial contrast echocardiography

Myocardial contrast echocardiography is a technique that uses microbubbles during echocardiography. These microbubbles remain exclusively within the intravascular space, and their presence within any myocardial territory denotes the status of microvascular perfusion within that region.[11] The volume of blood present in the entire coronary circulation (arteries, arterioles, capillaries, venules, and veins) is ~12 mL/100 g of cardiac muscle,[12] and approximately one-third of this is present within the myocardium itself and is termed myocardial blood volume (MBV).[12] The predominant (90%) component of MBV resides within the capillaries.[13] Myocardial contrast intensity reflects the concentration of microbubbles within the myocardium. When a steady state of microbubble concentration has been achieved in the myocardium, during a continuous infusion of contrast, the observed signal intensity denotes the capillary blood volume.[13,14] Thus, any alteration in signal intensity in this situation occurs principally because of a change in capillary blood volume. Furthermore, it has been shown that following destruction of microbubbles in the myocardium with high-energy ultrasound, myocardial contrast replenishment, both during low and high power, reflects myocardial blood velocity (β).[14] The product of these two components denotes myocardial blood flow at the tissue level.[14] Thus, MCE can detect capillary blood volume and, by virtue of its temporal resolution, can also assess myocardial blood flow.

During STEMI, the reduction in myocardial blood flow detected by MCE results from reduced microvascular flow as a result of the presence of an occlusive thrombus in an epicardial coronary artery. It has been established that myocyte loss parallels microvasculature loss and[15] thus, a relative reduction of MBV in the setting of STEMI denotes capillary loss and hence myocyte necrosis.

Pathophysiology of ST elevation myocardial infarction and relevance to principles of myocardial contrast echocardiography

The extent of myocardial necrosis following AMI is directly related to (i) the total duration of coronary artery occlusion, (ii) the extent of myocardium subtended by the IRA, and (iii) the quality of collateral circulation. Thus, following AMI, the progression of myocardial necrosis may be halted if the IRA opens either spontaneously, following reperfusion therapy, or if there is sufficient collateral circulation supplying the jeopardized region despite the presence of an occluded artery. Prolonged ischaemia may result in the failure to establish microvascular reperfusion (low reflow or no-reflow state) despite restoration of epicardial coronary patency.[16] The no-reflow state is a marker of myocyte necrosis and hence the lack of residual myocardial viability and persistent myocardial dysfunction.[16] Myocardial dysfunction after reperfusion may also occur as a result of stunning, i.e. necross. Human studies have confirmed that abnormal wall thickening extends beyond the infarction zone, but the ultimate outcome is more closely related to the extent of necrosis than the extent of wall-thickening abnormality.[8] In the immediate reperfusion period, however, coronary hyperaemia may occur and can result in underestimation of myocardial necrosis by any technique that uses intravascular tracers such as MCE.[17] The magnitude and spatial extent of the no-reflow phenomenon varies over time[17] and this dynamic feature of post-ischaemic flow must be taken into account to determine the appropriate timing and interpretation of MCE following AMI.

Application of myocardial contrast echocardiography in acute ST elevation myocardial infarction

Determination of ultimate infarct size at the time of acute myocardial infarction

Patients presenting with on-going chest pain and ST elevation on electrocardiogram (ECG) need emergent reperfusion therapy. However, there are patients who present to the emergency room in whom chest pain has resolved despite persistent ST elevation. Under these circumstances, MCE could be used to help determine the extent of jeopardized myocardium. It has been successfully demonstrated in acute canine models that the size of defect visualized by MCE late after a destruction-replenishment sequence using high-power and incremental-

triggered imaging corresponded to the ultimate infarct size.[18,19] It has also been shown that myocardial blood flow assessed by MCE accurately predicts the collateral blood flow during acute coronary occlusion.[12] Coggins *et al.*[18] showed that perfusion defect size on MCE at $\geq$10.6 s after high-power imaging correlated well with infarct size ($r \geq 0.92$, $P < 0.001$) and that 90% of regions not showing opacification by 10.6 s ultimately showed necrosis. However, it is important to note that while the extent of wall-thickening abnormality immediately after AMI and MCE imaging early after high-power imaging defines risk area, the final infarct size is best demonstrated by MCE as MCE is able to assess collateral blood flow that sustains myocardial viability at the margins of the risk area.[20] Thus, it can be speculated that if the MCE perfusion defect is small because of occlusion of a small artery or presence of good collateral flow, initial treatment could be conservative. However, if the perfusion defect is large, thrombolysis or mechanical reperfusion should be instituted immediately.

Assessment of reperfusion

Following thrombolysis

It has been documented that IRA patency may not be achieved in as many as 40% of patients following thrombolytic therapy.[21] Clinical predictors, such as subsidence of chest pain, resolution of ST elevation, and degree of cardiac enzyme release, for detecting IRA patency immediately after thrombolysis have been shown to have limited accuracy.[22] IRA patency can be determined with MCE based on the physiological considerations described earlier. In the absence of collateral flow, a transmural contrast perfusion defect occurs during acute total coronary artery occlusion. Following successful reperfusion the defect no longer remains transmural. Indeed, the contrast defect is usually smaller than that seen during occlusion because of post-ischaemic hyperaemia, sparing of an epicardial rim of viable tissue, or both, irrespective of presence or absence of infarction.[23] Thus, IRA patency can be determined with MCE by comparing the transmural extent of defects on images collected pre- and post-reperfusion therapy. It has been demonstrated in an animal experimental model that both myocardial risk area and infarct area can be accurately assessed by MCE as early as 60 min following reperfusion.[19] Thus, an approach incorporating real-time assessment of myocardial perfusion early after thrombolysis should lead to timely and appropriate triaging of patients, with only those most likely to benefit from rescue PCI being referred. Recent data from the REACT Trial Investigators[7] demonstrated a 6 month event-free survival rate among patients treated with rescue PCI of 85% compared with 70% among those receiving conservative therapy and 69% among those undergoing repeat thrombolysis. In this study, failed thrombolysis was defined as failure of a 50% reduction in ST elevation on ECG. At least two studies have demonstrated that MCE is superior to ECG criteria for failed reperfusion.[24,25] The ability of MCE to directly assess microvascular integrity and myocardial perfusion should result in improved differentiation between successful and failed myocardial reperfusion early following thrombolysis, rather than using a surrogate marker such as ST segment resolution. However, data using MCE to predict patency of IRA following thrombolysis are lacking and hence the use of MCE in this setting remains speculative.

Following percutaneous coronary intervention

The no-reflow phenomenon

The management of AMI for many years has focused on achieving epicardial artery patency at the site of plaque rupture and occlusive thrombus. Advances in interventional techniques and adjunctive pharmacological treatment have now made it possible to achieve normal (TIMI Grade 3) epicardial flow in ~95% of patients. However, this success has highlighted the limitations of current treatment protocols with respect to the real goal of restoration of myocardial perfusion. As many as 40% of patients do not achieve microvascular blood flow and myocardial perfusion despite restoration of TIMI Grade 3 coronary artery flow.[5,26] The no-reflow phenomenon in myocardial tissue was originally described in a canine model of coronary artery ligation followed by reperfusion.[16] In an experimental study by Kloner *et al.*,[15] electron microscopy revealed microvascular obstruction as a result of endothelial cell blebbing, white cell infiltration and red cell stagnation, and extravascular oedema.[15] This process can be accelerated after reperfusion as a result of injury from oxygen free radicals. In the clinical setting, no-reflow is also caused by microembolism from the occlusive thrombus and plaque dispersion following thrombolysis or PCI and by microvascular spasm following release of vasoactive amines from activated platelets. This phenomenon varies according to plaque and thrombus burden. No-reflow has been shown to be an important predictor of left ventricular (LV) remodelling, LV dysfunction, and major adverse cardiac events.[5,6,27] Ito *et al.*[5] first described the significance of no reflow detected by intracoronary MCE despite successful recanalization with thrombolysis or PCI. In a study of 39 patients presenting with anterior AMI, they found that patients demonstrating no-reflow had significantly lower left ventricular ejection fraction (LVEF) (42.7 ± 8.9 vs. 56.4 ± 13.4, $P < 0.05$) and lower regional wall motion scores ($-3.18 \pm .52$ vs. $-1.87 \pm .85$, $P < 0.005$) at 1 month follow-up. Further intracoronary MCE studies, by the same group, have also shown no-reflow to be a marker of adverse outcome. In a study of 116 patients with first anterior AMI, Ito *et al.*[6] demonstrated that no-reflow, assessed by MCE performed shortly after coronary reflow, predicted development of pericardial effusion ($P = 0.001$), and both early and late CHF ($P = 0.001$ and 0.01, respectively). Also LV end-diastolic volume progressively increased in the convalescent period in patients with MCE determined no-reflow (early vs. late, 145 ± 43 vs. 169 ± 60 mL, $P < 0.001$), whereas it decreased in those with MCE reflow (154 ± 42 vs. 144 ± 44 mL, $P < 0.01$).

Intravenous MCE performed within 24 h of primary PCI has also been shown to predict microvascular reflow.[24] In this study, Greaves *et al.* compared clinical markers (resolution of chest pain and ST segment elevation), coronary angiographic markers (TIMI flow, TIMI frame count, and myocardial blush grade), and MCE to predict recovery of LV function at 1 month following AMI and PCI. MCE was found to be the best predictor of improvement of LV function with sensitivity and specificity of 88 and 74%, respectively. The apparent low specificity for the presence of predicting recovery of resting LV function is not unexpected because, despite the presence of significant myocardial viability, resting LV function may not improve. This is because only the subendocardium (20% of myocardium) which contributes largely to wall

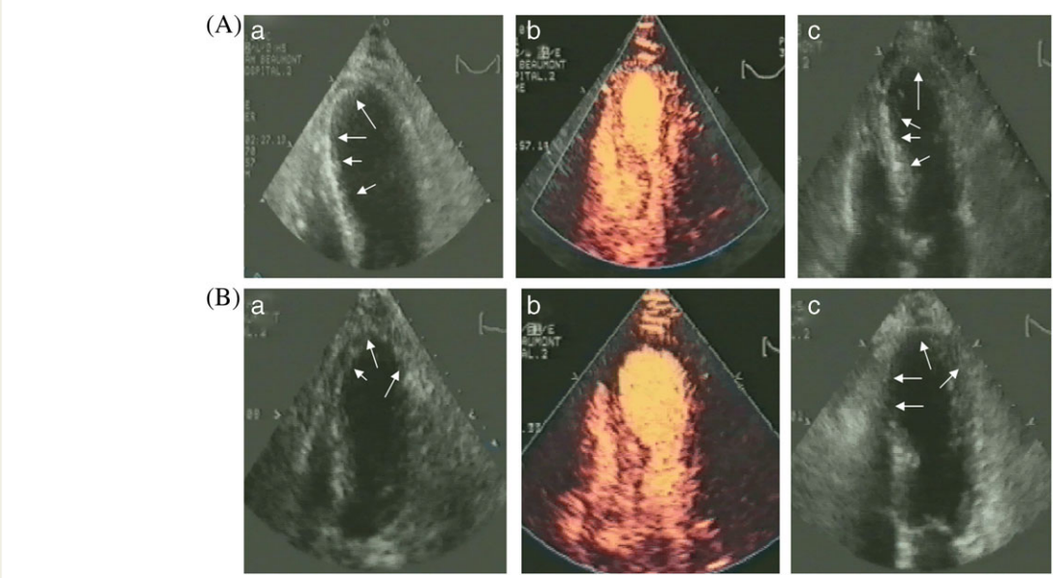

Figure 1 (*A*a) Apical four-chamber view in systole showing akinetic septum and apex (arrows) 12 h after successful PTCA. (*A*b) Homogeneous contrast opacification of the akinetic segments. (*A*c) Follow-up echocardiography at 1 month, showing recovery of function of these segments (arrows) with reduction of left ventricular end-systolic volume. (*B*a) Apical four-chamber view in systole showing akinetic mid septum and apex (arrows) 12 h after successful PTCA. (*B*b) No contrast opacification seen in mid-septum and apex. (Bc) Follow-up echocardiography at 1 month, showing lack of recovery of function of these segments (arrows) with no change in left ventricular end-systolic volume

Table 1 Summary of studies indicating effect of MCE determined reflow vs. no-reflow on LVEF

Authors	Patients (*n*)	Route	Reflow group			No-reflow group		
			LVEF at baseline	LVEF FU	*P*-value	LVEF at baseline	LVEF FU	*P*-value
Ito *et al.*[5]	39	Intracoronary	42 ± 11	56 ± 13	<0.001	35 ± 9	43 ± 9	NS
Sakuma *et al.*[30]	50	Intracoronary	44 ± 9	56 ± 12*	NR	35 ± 18	45 ± 14	NR
Bolognese *et al.*[28]	124	Intracoronary	40 ± 7	51 ± 11	<0.01	33 ± 8	39 ± UN	NS
Porter *et al.*[29]	45	Intravenous	59 ± 10	63 ± 9[a]	NR	55 ± 13	46 ± 5	NR
Ito *et al.*[6]	116	Intracoronary	46 ± 11	57 ± 13	<0.001	38 ± 13	43 ± 12	<0.05
Ito *et al.*[27]	86	Intracoronary	46 ± 13	57 ± 12	<0.001	38 ± 8	40 ± 8	NS

FU, follow-up; LVEF, left ventricular ejection fraction; MCE, myocardial contrast echocardiography; NR, not reported; NS, not significant.
[a]Significantly ($P < 0.05$) better compared with LVEF FU in no-reflow group.

thickening at rest may be infarcted abolishing wall motion despite significant viability which will contribute to contractile reserve and preserved LV remodelling. *Figure 1A*[24] shows an example of a patient with an anterior acute myocardial infarct demonstrating apico-septal akinesia 12 h after PCI. However, MCE shows homogeneous opacification of the septum and apex, suggestive of preserved microvascular perfusion and viability. Follow-up echocardiography at 1 month shows recovery of function, as predicted by MCE. *Figure 1B*[24] is an example of a patient with an anterior AMI with apico-septal akinesia 12 h after successful PTCA. However, MCE shows no opacification of these segments, suggesting absence of microvascular perfusion despite a patent epicardial coronary artery. As predicted by MCE, follow-up echocardiography did not show recovery of function in the akinetic segments. *Table 1* summarizes the studies indicating the effect of MCE-determined reflow vs. no-reflow on LVEF.[5,6,27–30] It has been recently demonstrated that the lack of microvascular perfusion determined by MCE after primary PCI predicted LV remodelling, cardiac death, and heart failure.[8,28] Although trials are lacking demonstrating altered outcome if aggressive pharmaceutical therapy (for LV dysfunction) is instituted early in patients with low tissue perfusion, it will be logical to treat aggressively these patients while patients demonstrating good MCE perfusion may be reassured and discharged early.[31]

Although coronary hyperaemia[23] may occur, there is now an increasing body of published data in which MCE has been used

Table 2 Summary of studies evaluating the efficacy of adjunctive medical therapies for treatment of no-reflow

Authors	Drug	Subjects	*n*	Route	Summary
Iwakura *et al.*[36]	Statins	Human	293	Intracoronary	Patients on chronic statin therapy ($n = 33$) prior to admission with AMI had lower incidence of no-reflow and had better functional recovery.
Micari *et al.*[37]	Adenosine	Human	37	Intravenous	Infarct size as a ratio to the risk area was smaller in those patients treated with adenosine both at early (3–5 days) and late stages (28 days)
Ito *et al.*[34]	Nicorandil	Human	81	Intracoronary	Improvement in regional LV function, wall motion score, and regional wall motion significantly better in nicorandil group
Sakata *et al.*[35]	Nicorandil	Human	20	Not stated	Regional wall motion improved more significantly at 1 month with nicorandil use
Taniyama *et al.*[32]	Verapamil	Human	40	Intracoronary	Verapamil use attenuates microvascular dysfunction and leads to better functional outcome (wall motion score) at 1 month follow-up
Yani *et al.*[38]	Glycoprotein IIb/IIIa inhibitors (GPI)	Animal	40	Intravenous	Tirofiban (GPI) markedly reduced the incidence of myocardial no reflow
Kunichika *et al.*[33]	Glycoprotein IIb/IIIa inhibitors (GPI)	Animal	16	Not stated	Use of GPI improves microvascular flow and reduces infarct area after coronary occlusion/perfusion independent of epicardial flow

Table 3 Accuracy of MCE and CMR to predict Contractile Reserve

Test for contractile reserve	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Normal perfusion on MCE	73	96	89	88	88
Normal reduced perfusion on MCE	82	83	70	90	82
≤25% TEI	60	97	91	83	85
≤50% TEI	67	92	80	85	84
≤75% TEI	79	62	50	86	67

to assess microvascular perfusion and extent of no-reflow early (5–60 min) post-intervention. A clinical study used intracoronary MCE to evaluate the no-reflow phenomenon in 199 patients at a mean of 15 min following primary PCI.[26] No-reflow within the risk area was observed in 79 patients (40%), and the remaining 120 patients were classified as having reflow. The patients with MCE reflow showed lower peak CK values than those with MCE no-reflow ($P < 0.0001$). Further studies[32–38] have assessed the efficacy of adjunctive treatments such as GIIbIIIa inhibitors, adenosine, nicorandil, and verapamil using MCE as early as 5–90 min following PCI (*Table 2*). In these studies, MCE used early following PCI was able to differentiate differing degrees of reflow between subjects receiving adjunctive therapies and those not.

Despite the well-recognized phenomenon of reactive hyperaemia following reperfusion therapy,[23] these studies do indicate that MCE, by virtue of its high spatial and temporal resolution, has an important role in providing information regarding establishment of myocardial perfusion early following PCI.[32–35] Another technique with high transmural resolution, namely magnetic resonance imaging (MRI), may also be used to assess re-flow following AMI. This technique utilizes gadolinium that measures the increased interstitial space associated with myocyte loss because gadolinium is an extravascular, extracellular tracer. The excellent spatial resolution and high-contrast MRI allows accurate assessment of transmural extent of AMI.[39,40] However, in the immediate aftermath of reflow, there will be significant oedema which is likely to indicate apparently larger no-reflow area with gadolinium-enhanced MRI.[40,41] The ideal timing of MRI to assess reflow will be 7–10 days after AMI when oedema has resolved.[40,41] On the other hand, MCE may be performed early after AMI and reperfusion therapy for the assessment of reflow. In a comparative study between MCE and CMR, they were equivalent in predicting contractile reserve when CMR was performed 7–10 days after AMI and reperfusion (*Table 3*).[42]

A tool to assess new adjunctive medical therapies to improve microvascular blood flow following STEMI

Myocardial contrast echocardiography allows real-time assessment of myocardial perfusion, and thus, is an ideal tool enabling accurate assessment of intervention intended to improve microvascular flow. In addition, its portability allows easy integration into the operating theatre and catheter laboratory alike, and the absence of radiation exposure allows frequent and repeated re-assessment in the early post-intervention period.

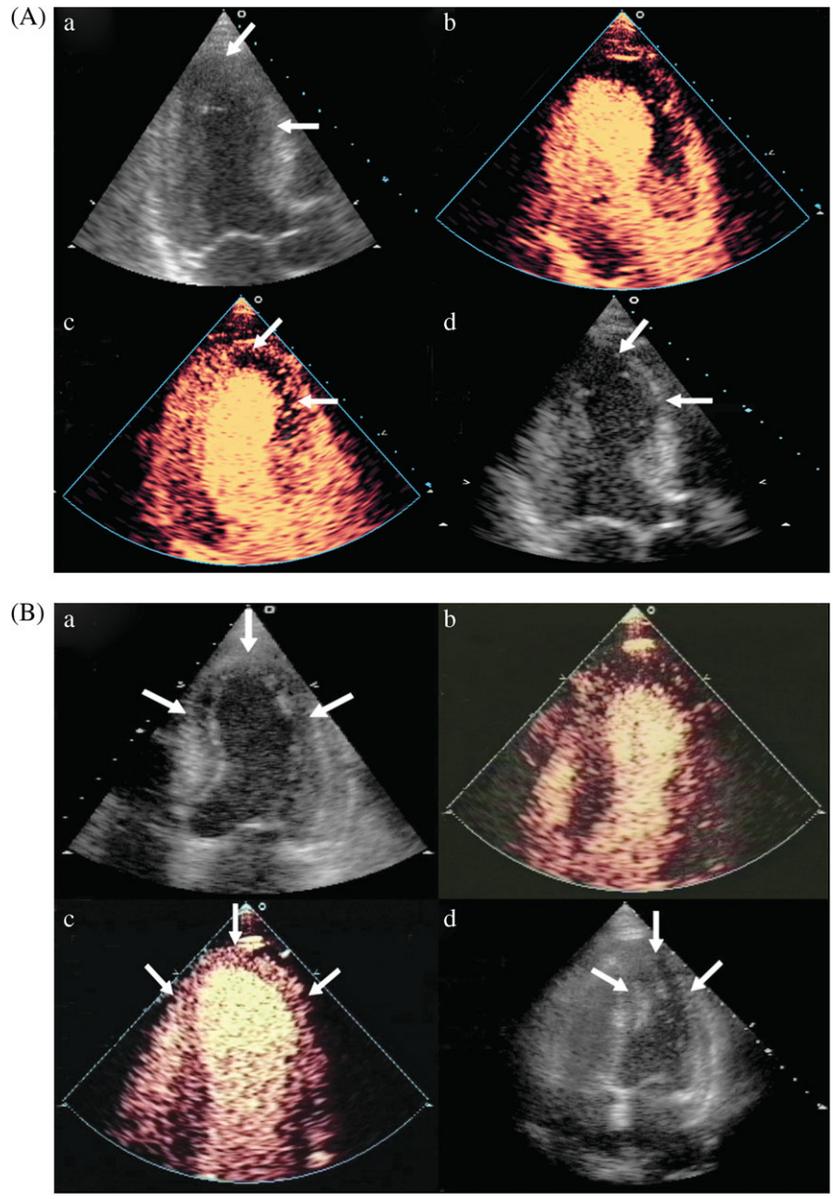

Figure 2 (*A*) End-systolic frames of the apical three-chamber view showing: (*Aa*) akinetic mid-anterior septum and apex *(arrows)*; (*Ab*) complete destruction of myocardial contrast immediately after a high mechanical index pulse on MCE; (*Ac*) lack of contrast opacification of the dysynergic segments, even at 15 cardiac cycles *(arrows)*; (*Ad*) lack of functional recovery at 12 weeks despite revascularization *(arrows)*. (*B*) End-systolic frames of the apical four-chamber view showing: (*Ba*) akinetic mid-septum, apex, and mid-lateral segments *(arrows)*; (*Bb*) complete destruction of myocardial contrast immediately after a high mechanical index pulse on MCE; (*Bc*) homogenous contrast opacification of the dysynergic segments by 15 cardiac cycles *(arrows)*; (*Bd*) functional recovery at 12 weeks after revascularization *(arrows)*

In a recent study, intravenous MCE was used during coronary occlusion and sequentially after reperfusion to assess the effect of intracoronary adenosine on promoting microvascular reflow and reducing infarct size when initiated early in AMI patients undergoing primary PCI.[37] It was found that the adjunctive use of intravenous adenosine after PCI reduced infarct size relative to the risk area early (0.37 ± 0.29 vs. 0.68 ± 0.25, $P < 0.01$) and at 4 weeks (0.34 ± 0.26 vs. 0.60 ± 0.21, $P < 0.01$). MCE has also provided supportive evidence for the potential use of nicorandil and verapamil to promote microvascular reflow and reduce infarct size in AMI patients undergoing PCI.[30,32,33] It has also given valuable insight into the differing mechanisms and sites of action of aspirin and clopidogrel vs. GIIbIIIa inhibitors and why the latter improve outcome when used with PCI.[33] Most recently, in an intracoronary MCE study of 293 patients[36] with reperfused AMI, chronic statin therapy was found to be associated with a lower incidence of

no-reflow than those without (9.1 and 34.6%, $P = 0.003$). However, large multicentre trials especially with GIIbIIIa inhibitors and PCI failed to demonstrate improved microvascular perfusion and this could be related to variability in plaque and thrombus burden in patients.[43] Until such time that adjunctive therapies following primary PCI are shown conclusively to alter outcome in relation to myocardial perfusion, the role of MCE in this scenario will be limited. However, MCE can serve as a tool to help assess/develop new adjunctive therapies to reduce the incidence of no-reflow.

Risk stratification after acute myocardial infarction

The most important determinants of outcome in patients who are clinically stable after AMI are resting LV function,[44] extent and degree of residual myocardial viability, and ischaemia[8–10,31,45] (at the site of AMI or remote territory). MCE is unique in that it can address all the above in a single examination.

Determination of left ventricular function

While LVEF, determined by echocardiography, has been consistently shown to predict outcome accurately after AMI,[44] several studies have shown that contrast-enhanced LVEF determination is more accurate than non-contrast echocardiography.[46] In a recent post-AMI study, by Lim *et al.*,[47] LVEF determined by contrast-enhanced echocardiography with low-power real-time imaging was found to be more accurate compared with unenhanced echocardiography, using CMR as the gold standard. It is important to assess LVEF accurately in this group of patients, not only for correct prognostication, but also for determining suitability for implantation of defibrillator devices. Inaccurate LVEF assessment may result in depriving patients of life-saving measures or expose them to unnecessary expensive and invasive procedures.

Determination of myocardial viability

Experimental studies have shown that MCE can accurately assess infarct size and hence residual myocardial viability after reflow has been established following AMI. In the first clinical study using intracoronary MCE, it was demonstrated that following AMI, normal perfusion in an akinetic segment predicted the recovery of function while absent perfusion resulted in persistent dysfunction.[48] This group established the principle that there is a close association between microvascular and myocellular integrity.[49,50] However, the optimal timing for determining residual myocardial viability after AMI and reperfusion is at least 48 h after AMI. At that time, not only hyperaemic response has abated but also dynamic changes in resting tissue perfusion due to vasospasm, myocardial oedema, and microvascular stunning have subsided. Thus, the extent of no-reflow correlates well with infarct size and hence residual myocardial viability. In a study that examined patients at 24 h and 3–5 days after PCI following AMI, intravenous MCE performed at 3–5 days correlated more strongly with contractile reserve than MCE at 24 h.[51]

As stated previously, the degree and extent of residual myocardial viability depends not only on the duration of IRA occlusion and area at risk but also on the quality of collateral perfusion. Regions supplied by collateral flow predicted by MCE improve function following revascularization even in patients with recent AMI and occluded IRAs.[52,53] As collateral flow is generally less than normal flow, regions with adequate collaterals fill later than normal myocardium during destruction–replenishment MCE. Normal capillary blood flow is 1 mm/s and as ultrasound beam elevation is 5 mm, normal regions fill within 5 s. Regions which do not replenish within 10–15 cardiac cycles have markedly reduced flow and are unlikely to escape necrosis.[48] This has been demonstrated in 20 patients with occluded IRAs, where myocardial segments which did not replenish within 10–15 cardiac cycles following microbubble destruction showed significantly less contractile reserve after revascularization compared with those segments which replenished.[54] *Figure 2A*[54] is an example of a patient with an anterior AMI; MCE shows the absence of contrast opacification of the mid-anterior septum and apex that were dysynergic at baseline. Follow-up echocardiography at 12 weeks failed to show functional recovery despite revascularization. *Figure 2B*[54] is an example of a patient who sustained an antero-lateral AMI; MCE shows homogenous contrast opacification of the dysynergic segments. These segments demonstrated recovery of function 12 weeks after revascularization. Myocardial blood flow was found to be <25% of normal, in segments demonstrating no contractile reserve (*Figure 3*).[54]

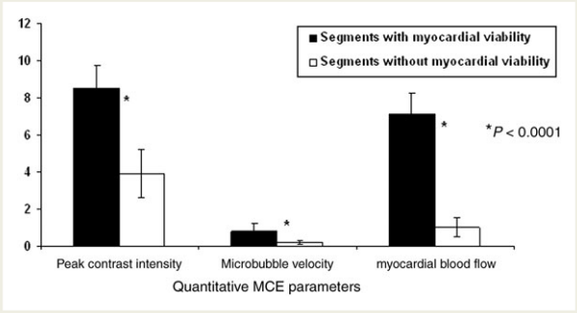

Figure 3 Accuracy of peak contrast intensity (decibels [dB]), microbubble velocity (dB/s), and myocardial blood flow (dB^2/s) to predict contractile reserve (collateral flow)

Similar to collateral flow, low flow through an open IRA can also be assessed using the above approach. Myocardium supplied with low anterograde flow will fill more slowly than normal myocardium. Myocardial replenishment within 15 cardiac cycles following destruction–replenishment imaging signifies intact microvasculature, and preserved residual myocardial viability. This has been confirmed in a study of 96 AMI patients imaged at a mean of 5 days following AMI. It was demonstrated that failure of myocardial replenishment within 10 cardiac cycles during high power imaging resulted in lack of recovery of function in 84% of the time.[55] *Figure 4A* and *B* shows examples of two patients with apicoseptal AMIs and flow-limiting left anterior descending artery. The patient depicted in *Figure 4A* shows homogeneous contrast opacification suggestive of myocardial viability and later showed improved function after revascularization; the patient in *Figure 4B*

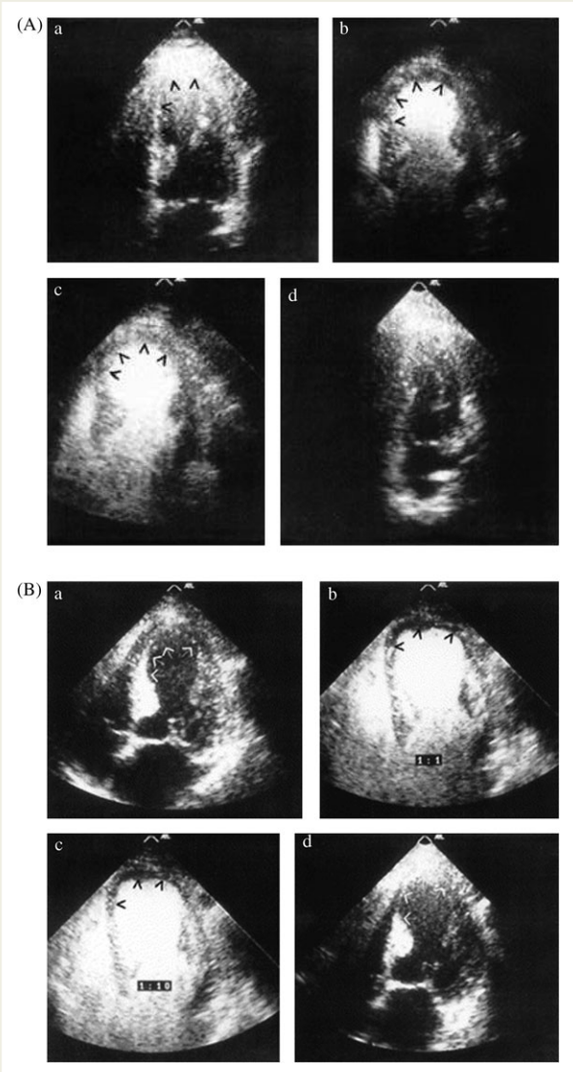

Figure 4 (*A*) Four-chamber view showing an akinetic septum and apex (*Aa*) with absent contrast opacification in this region at short triggering intervals (*Ab*) but homogeneous opacification with delayed triggering (*Ac*), and normal resting function 6 months later (*Ad*). (*B*) Four-chamber view showing an akinetic septum and apex (*Ba*) with no contrast opacification in this area with early (*Bb*) or delayed (*Bc*) triggered imaging and failure of recovery of systolic function at follow-up (*Bd*)

has only minimal contrast opacification suggestive of lack of myocardial viability and subsequently failed to improve after revascularization.[55]

The extent and severity of perfusion defects detected by MCE has a strong inverse relationship with recovery of function at 3 months following STEMI.[56] It is also demonstrated that improvement of LV function occurred only when >20% of the dysfunctional segments demonstrated adequate perfusion grades of perfusion assessed 3–5 days after PCI correlated well with contractile reserve assessed 1 month later. Almost all segments with good perfusion demonstrated contractile reserve; conversely,

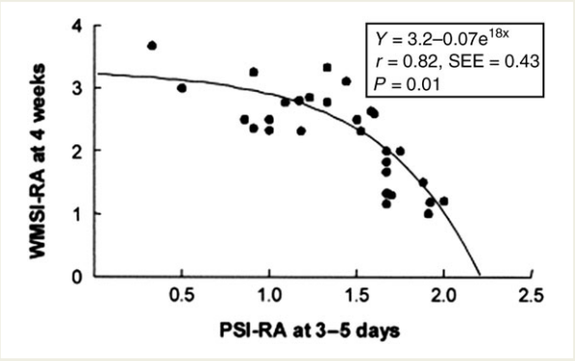

Figure 5 Relationship between perfusion score index in the risk area (PSI-RA) assessed by myocardial contrast echocardiography 3–5 days after PCI and wall motion score index in the risk area (WMSI-RA) at 4 weeks

almost all segments with no perfusion failed to show contractile reserve. A threshold myocardial perfusion beyond which there was strong correlation between perfusion and contractile reserve was also observed (*Figure 5*).[51] MCE has also been shown to accurately reflect transmurality of myocardial necrosis. During AMI, myocardial necrosis progresses from the endocardium to the epicardium as a wavefront. Hence, the greater the extent of myocardial necrosis, the greater the transmural extent of infarction (TEI). Thus, the severity of MCE defect seen will correspond to the TEI. Furthermore, the extent of reduction of MBF will also reflect TEI. This was confirmed in a study of 42 patients[42] presenting with STEMI, where MCE- and gadolinium-enhanced cardiovascular MRI (*Figure 6*) were performed 7 days after AMI to estimate TEI. Both peak contrast intensity and MBF assessed by MCE showed a strong inverse correlation with TEI (*Figure 7*).

Does determination of myocardial viability with myocardial contrast echocardiography provide incremental value over left ventricular ejection fraction?

Resting LVEF after AMI has been shown to be a powerful predictor of outcome. The extent of LV dysfunction reflects the extent of myocardial necrosis and hence the severity of LV dysfunction is directly related to mortality. In a recent study, which involved 112 patients, it was shown that a strong relationship existed between the extent of myocardial necrosis and the extent of wall motion abnormality 7 days after AMI.[57] However, since the extent of myocardial necrosis ultimately determines outcome, the assessment of myocardial necrosis using MCE is likely to prove to be a more powerful measure of outcome than severity of LV dysfunction. This was shown in the study mentioned above where the extent and intensity of perfusion defect was a superior predictor of subsequent recovery of LV function than baseline LV function.[57] Furthermore, the authors showed that the extent of baseline wall-thickening abnormality was

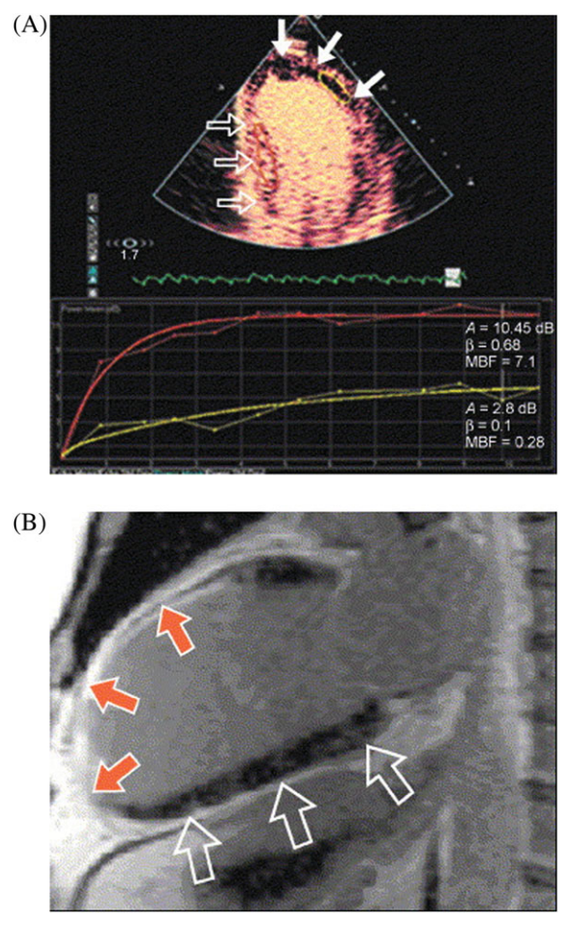

Figure 6 Example of a patient who sustained an anterior STEMI. (*A*) (top) Apical two-chamber view on MCE with absence of contrast opacification (solid arrows) at the apex and anterior wall, which were akinetic. The normal remote segments (outlined arrows) show normal contrast intensity. (*A*) (Bottom) replenishment curves in the akinetic segment (yellow) demonstrates very low peak contrast intensity (*A*), microbubble velocity (β), and MBF, in comparison with remote normal segment (red). (*B*) The corresponding image on CMR demonstrates >75% TEI (delayed hyperenhancement) in the akinetic segments and no infarction in the remote normal segments

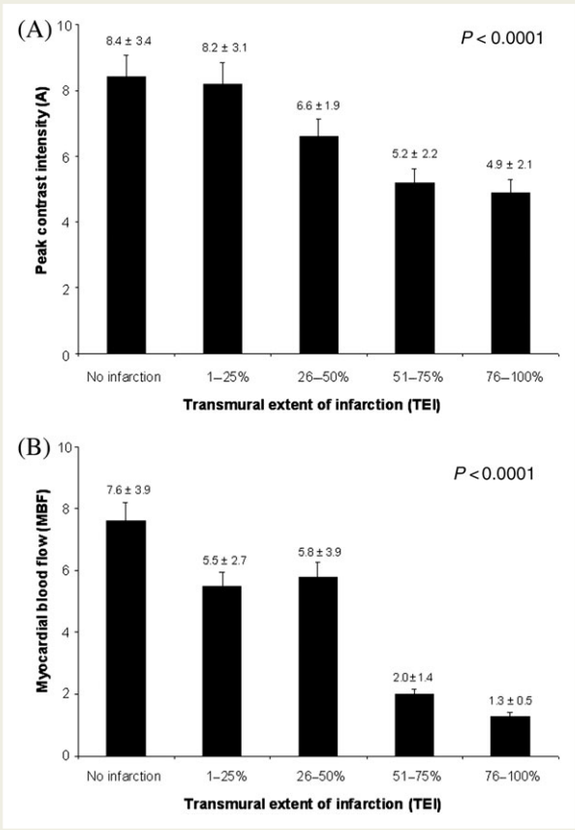

Figure 7 Quantitative MCE in relation to TEI in dysynergic segments post-AMI and thrombolysis. (*A*) Peak contrast intensity. (*B*) MBF

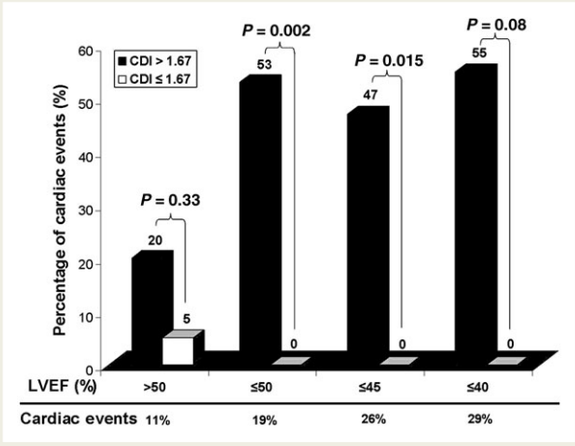

Figure 8 Occurrence of cardiac death or non-fatal AMI in various LVEF groups according to contrast defect index (CDI)

larger than the extent of perfusion defect. The larger functional abnormality was due to stunned myocardium. Indeed, when a subset of these patients were followed up for hard cardiac events after AMI, the extent of perfusion defect, not the extent of LV function, was a more powerful predictor of mortality or recurrent AMI.[58] Although patients with normal LVEF had a better outcome irrespective of the size of MCE defect (80% had small MCE defect), patients with LVEF < 50% had a worse outcome when MCE defect was larger compared with when it was small (*Fig. 8*). This underscores the fact that MCE, not wall motion abnormality, accurately differentiates stunned from necrotic myocardium. The ideal method of MCE to detect myocardial viability has been validated in both experimental[18,19] and clinical studies.[24,48,54,58] The lack of perfusion 15 s after replenishment whether during low or high MI imaging virtually rules out myocardial viability.

Thus, to summarize, MCE performed prior to hospital discharge has been shown to accurately differentiate 'stunning' from

Table 4 Accuracy of resting intravenous MCE and DSE for the prediction of myocardial viability following AMI

Authors	Type of imaging	No. of patients (n = 548)	MCE perfusion		Wall motion with DSE	
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Sbano *et al.*[63]	High MI	50	95	52	95	87
Senior *et al.*[66]	High MI	96	62	83	72	87
Aggeli *et al.*[65]	High MI	34	88	61	87	72
Hillis *et al.*[64]	Low MI	33	86	44	71	82
Main *et al.*[61]	Low MI	46	69	85	50	88
Swinburn *et al.*[68]	Low MI	19	68	88	58	85
Hillis *et al.*[59]	High MI	35	80	67		
Lepper *et al.*[67]	High MI	35	94	87		
Janardhanan *et al.*[42]	Low MI	42	82	83		
Hickman *et al.*[62]	Low MI	56	83	78		
Greaves *et al.*[24]	Low MI	15	88	74		
Janardhanan *et al.*[56]	Low MI	50	92	75		
Main *et al.*[60]	Low MI	34	77	83		
		Mean	82	74	72	84

MCE, myocardial contrast echocardiography.

necrosis,[55,59,60] delineate transmural extent of infarction,[42] predict recovery of regional and global LV systolic function in the recuperative phase,[5,6,42,53,56,60,67] and also provide incremental viability data when performed in conjunction with the clinical reference standard, low-dose dobutamine echocardiography,[61] and finally predicts outcome independent of clinical markers of prognosis including LV dysfunction.[8,58] *Table 4* summarizes the diagnostic accuracy of intravenous MCE to predict myocardial viability from various studies.[24,42,56,59–68]

Detection of myocardial ischaemia

Residual IRA and remote coronary stenosis are common after AMI despite apparently successful thrombolysis.[19] Patients with significant residual IRA stenosis and multivessel disease (MVD) after thrombolytic treatment represent a high-risk subgroup. Thus, accurate identification of these patients has important implications, both for risk stratification and for early revascularization.[9,69]

Resting epicardial CBF remains normal even in the presence of a severe luminal stenosis and does not decrease until more than 85–90% of the luminal diameter is encroached by a stenosis. Although resting flow remains unchanged in non-critical stenosis, flow during maximal hyperaemia is reduced when the luminal diameter stenosis severity exceeds 50%. The MBV fraction decreases during hyperaemia in the presence of stenosis, and this decrease is proportional to stenosis severity.[70] A decrease in MBV occurs as a result of capillary derecruitment in order to maintain a constant hydrostatic pressure in the face of a drop in perfusion pressure across a stenosis caused by hyperaemia.[70] This drop in MBV in the stenosed myocardial bed during hyperaemia and delay in microbubble replenishment is the basis of a perfusion defect detected by MCE. The accuracy of vasodilator MCE for the detection of flow-limiting coronary artery stenosis, in patients with suspected coronary artery disease (CAD), has been proved in a number of studies.[70,72] Indeed, the assessment of perfusion provides incremental diagnostic accuracy over wall motion assessment for both detection and prognostication of CAD.[73,74]

A 73 patient study demonstrated the ability of intravenous MCE to detect residual IRA stenosis and presence of remote flow-limiting CAD in patients with recent STEMI and thrombolysis.[75] Of the 57 patients demonstrating myocardial viability and residual IRA stenosis, MCE detected IRA stenosis and MVD in 50 (88%) of the 57 patients and 23 (72%) of the 32 patients. It also correctly detected the absence of IRA stenosis and MVD in three of the four (75%) and 38 (93%) of the 41 patients. *Figure 9* shows examples of MCE at rest and stress; the images demonstrate the ability of both qualitative and quantitative MCE to detect the presence of residual IRA stenosis and MVD.[75] It is conceivable that the assessment of perfusion with MCE for the detection of IRA stenosis and MVD is likely to be superior to wall motion assessment alone based on previous studies.[73,74]

Safety and feasibility of myocardial contrast echocardiography

Because of safety considerations, the possible interaction between ultrasound and tissue has received much attention. However, no adverse events or haemodynamic changes have been reported in any of the above-mentioned human studies performed in patients with STEMI.

Nevertheless, Food and Drug Administration (FDA) has recently declared that echo contrast agents should not be administered in patients with unstable coronary disease in view of deaths observed in such patients in post-marketing surveillance. However, the role of contrast agent contributing to the deaths in these patients is not

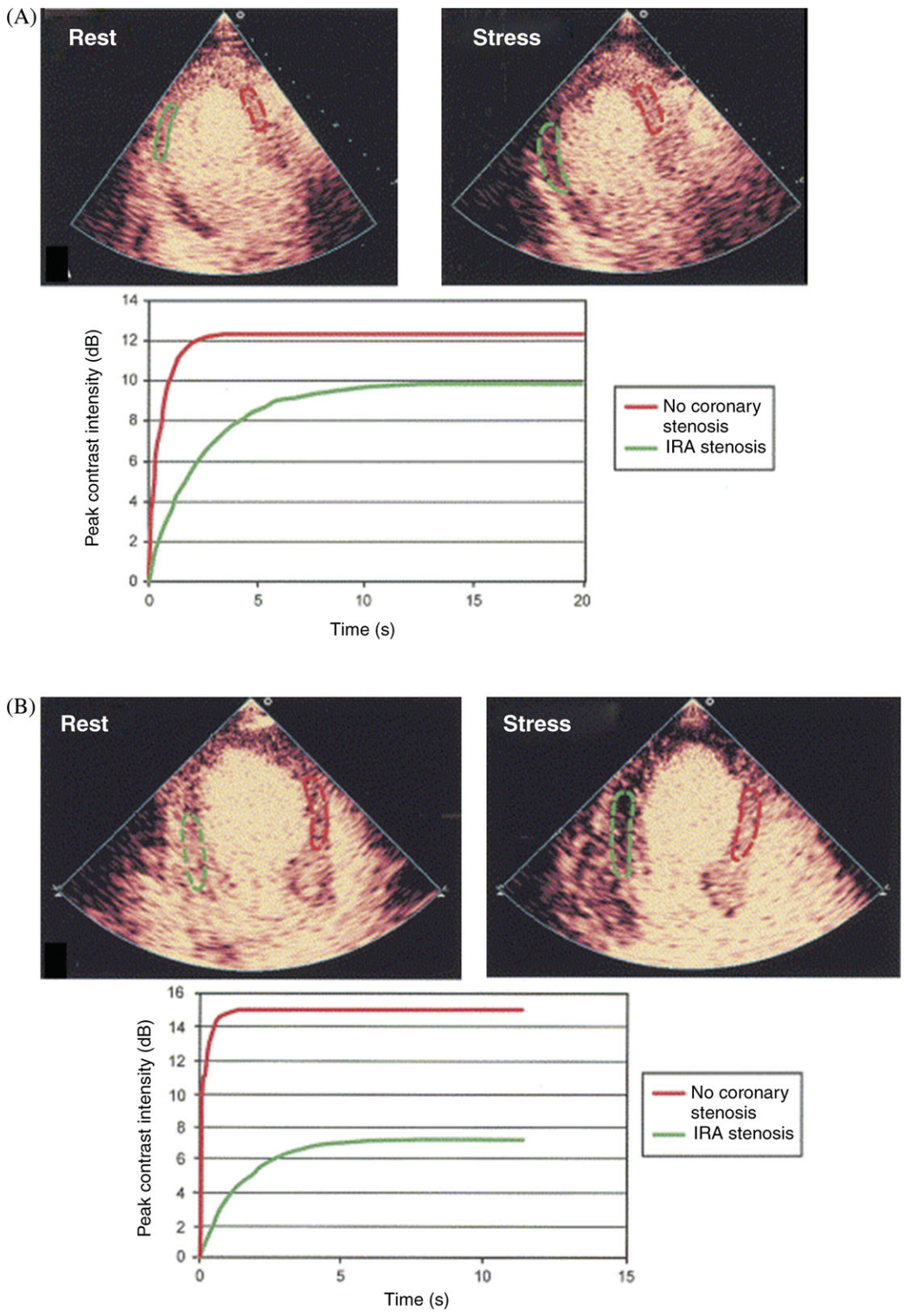

Figure 9 (*A*) Apical three-chamber view shows reversible perfusion defect (posterior wall) at the infarct site. (*B*) Apical three-chamber view shows reversible perfusion defect in the remote, normally contracting mid-posterior segment in a patient with an anterior acute myocardial infarction. (Graphs) Replenishment curves demonstrate reduced peak contrast intensity (MBV—α) and rate of replenishment (myocardial blood velocity—β) during stress, suggesting residual infarct-related artery (IRA) stenosis (*A*) and multivessel disease (*B*). Red indicates no coronary stenosis; green indicates significant coronary stenosis

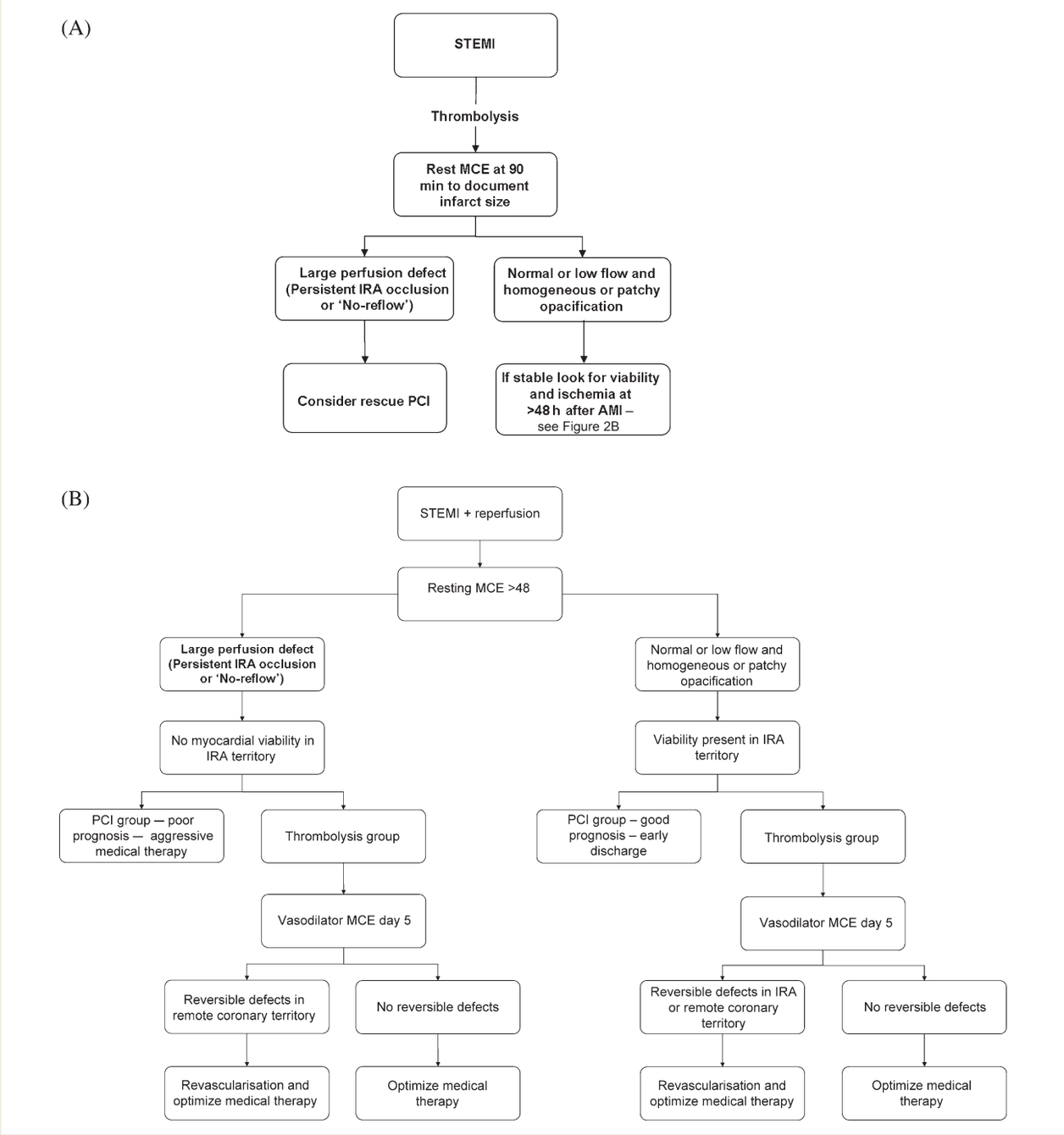

Figure 10 (*A*) Schematic diagram for the proposed role of MCE in assessment of patients in the acute phase of STEMI. (*B*) Schematic diagram for the proposed role of MCE in assessment of patients with recent STEMI following reperfusion

clear and is likely to be due to the underlying pathology. Furthermore, the usefulness of MCE in STEMI is such that the benefit far outweighs the risk certainly in comparison with other competing techniques. However, even under the restrictions mentioned, MCE can be used for risk stratification in stable patients after AMI. Recent MCE AMI studies have demonstrated that adequate imaging is not possible in only 5–7% of patients because of poor echocardiographic windows.[36,59] In patients with STEMI, adequate assessment of perfusion with MCE has been shown to be possible in >90% of segments.[42,56,60,61]

Limitations

As with the initial implementation of any new technique, whether diagnostic or therapeutic, there are often issues of availability, expertise and delivery of a 24 h service. Transthoracic 2D

echocardiography and primary PCI, understandably, faced the same reservations by physicians when they were first introduced. However, 2D echocardiography is now an integral part of most hospitals with 24 h availability. Primary PCI/rescue PCI has also become increasingly available, now spreading from teaching institutes to district general hospitals. The availability of MCE is likely to undergo a similar transition, with its initial use being in institutes with extensive experience. However, MCE is unlikely to be utilized prior to reperfusion therapy because of time constraints.

Summary

Myocardial contrast echocardiography is a reliable, bedside technique for the assessment of patients presenting with STEMI. In stable patients after STEMI, MCE can assess resting LV function accurately and establish the extent of residual myocardial viability which has prognostic implications. Furthermore, especially those who are unlikely to exercise vasodilator stress can accurately unmask residual stenosis in both the IRA and the remote coronary territory artery following thrombolysis which has both prognostic and therapeutic implications. MCE, furthermore, may be utilized for the assessment of efficacy of newer therapeutic intervention following PCI designed to improve microvascular perfusion. *Figure 10A* and *B* summarizes the role of MCE following initial reperfusion therapy for subsequent risk stratification and management.

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CLINICAL VIGNETTE

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Serial imaging and histology illustrating the degradation of a bioabsorbable magnesium stent in a porcine coronary artery

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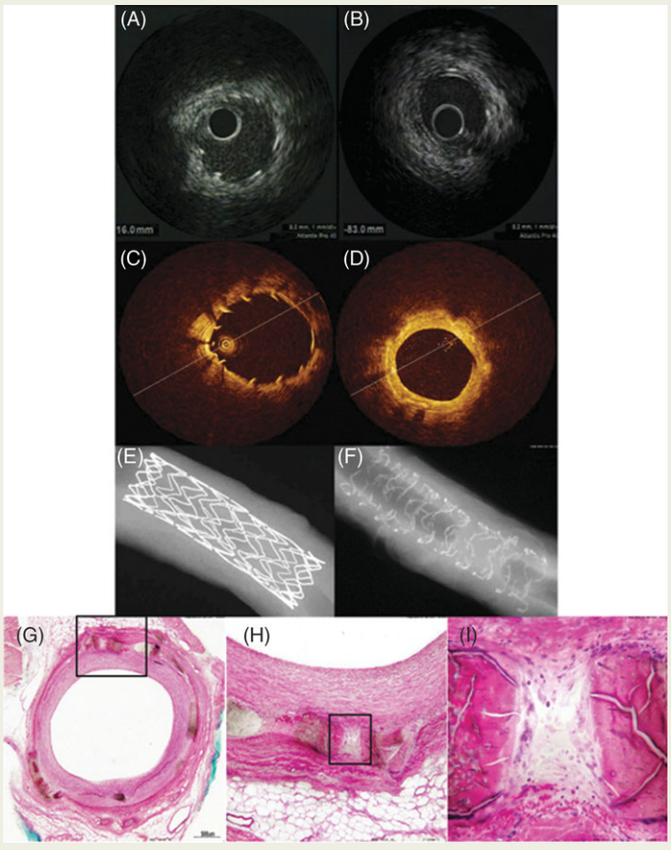
Magnesium alloy stents have demonstrated swift degradation within 90 days of implantation in porcine and human coronary arteries. These stents are radiolucent and thus cannot be visualized by angiography. To assess the rate of degradation, bioabsorbable magnesium alloy stents were deployed in porcine coronaries, and serial imaging by intravascular ultrasound (IVUS) (Panels A and B) and optical coherence tomography (OCT) (Panels C and D) was performed at implant and at 3-month follow-up. The stent struts were clearly visible by both technologies at implant, but were degraded at follow-up. Low-voltage X-ray of these stents at implant and follow-up demonstrated degradation and loss of structural integrity at the later time point (Panels E and F). Histopathology at 3 months revealed that the struts had degraded (Panels G–I). These imaging modalities demonstrate the rapid degradation of the absorbable magnesium stent as intended in <90 days. This may result in early recoil of the vessel because of the lack of radial force exerted by the bioabsorbed stent at this early stage of healing. We propose that serial IVUS and OCT imaging can be employed to assess the rate of stent degradation and its impact on vessel recoil and restenosis.



Panel A. Intravascular ultrasound of the stented segment at implant.

Panel B. Intravascular ultrasound of the stented segment at 3-month follow-up.

Panel C. Optical coherence tomography of the stented segment at implant.

Panel D. Optical coherence tomography of the stented segment at 3-month follow-up.

Panel E. Low-voltage X-ray photograph of the stented vessel at implant.

Panel F. Low-voltage X-ray photograph of the stented vessel at 3-month follow-up.

Panel G. Histopathology of the stented vessel at 3-month follow-up: low power magnification, cross-section through stented segment.

Panel H. Histopathology of the stented vessel at 3-month follow-up: medium power magnification, stent strut has degraded.

Panel I. Histopathology of the stented vessel at 3-month follow-up: high power magnification, stent strut has degraded.