The clinical applications of myocardial contrast echocardiography

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Abstract Recent updates in the field of echocardiography have resulted in improvements in both image quality and techniques allowing echocardiography to maintain its position as the primary non-invasive imaging modality. In particular, the development of new ultrasound contrast agents and imaging techniques have now made possible the assessment of myocardial perfusion. Myocardial contrast echocardiography utilises acoustically active gas filled microspheres (microbubbles), which have rheology similar to that of red blood cells. The detection of myocardial perfusion during echocardiographic examinations permits simultaneous assessment of global and regional myocardial structure, function, and perfusion, enabling the optimal non-invasive assessment of coronary artery disease. Myocardial contrast echocardiography is equally adept in assessing chronic coronary artery disease, acute coronary syndromes and hibernating myocardium. © 2007 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Ultrasound contrast agents have been in clinical use for nearly 40 years but in the last decade refinements in both the types of agent as well as echocardiographic technologies has resulted in a new range of clinical applications. In the early days of contrast agents, imaging left sided structures with contrast enhancement was not possible because the bubbles were too large to cross the pulmonary vasculature. Modern day contrast agents have the ability to opacify the left heart and can be useful in, for example, endocardial border definition for patients with difficult echo windows. Myocardial contrast echocardiography (MCE) is an emerging technique for detection of perfusion...
abnormalities in patients with coronary artery disease. The article examines the precise nature of contrast agents in current clinical use as well as defining the specific clinical applications of MCE.

**Myocardial perfusion**

The techniques for quantitative assessment of myocardial perfusion are dependant on an understanding of the components of myocardial blood volume and myocardial blood flow. Whilst the coronary blood volume comprises the coronary arteries, arterioles, capillaries, venules, veins and coronary sinus, the myocardial blood volume is made up of vessels which are <300 microns in diameter, most of which (>90%) lies within the capillaries. Once injection of a myocardial contrast agent has occurred, within a few seconds, the agent will be present within the myocardial capillaries and once a steady state is achieved the signal intensity represents the myocardial blood volume (A). The rate of increase in intensity following bubble destruction with a high energy pulse represents red blood cell velocity (β) and the product of the A × β represents myocardial blood flow (MBF). To quantify MBF the use of specialist software is required to determine regions of interest, at rest and stress, in the 4 apical segments: midanterior septum, and midanterior segment representing the anterior coronary circulation and in the midinferior, midposterior, and midlateral segments representing the posterior circulation. The software can automatically construct background-subtracted plots of peak myocardial contrast intensity, A, versus pulsing intervals, from which the slope of the replenishment curve depicting mean microbubble velocity, β reserve and MBF can be derived. Coronary flow reserve (i.e., stress MBF/rest MBF) and β and A reserve can then be calculated.

**Clinical applications of MCE**

**Coronary artery disease**

Coronary artery disease is very common in the western world but with the advent of thrombolytic therapy and more recently primary angioplasty mortality rates from myocardial infarction have been declining. However in the emergency department, a prompt diagnosis is essential in the management of patients presenting with acute chest pain. The serum troponin level may be elevated in certain patients for reasons other than myocardial necrosis and so in some patients, particularly those with negative cardiac enzymes or in those where there is diagnostic uncertainty as to whether the ECG changes warrant thrombolytic therapy, other tests are required. In this situation, 2D resting echocardiography can be very useful for detection of wall motion abnormalities but may not be reliable in all patients such as those with left ventricular hypertrophy. Myocardial contrast echocardiography is a rapid bedside technique which can detect perfusion abnormalities in patients with acute coronary syndromes (ACS). In addition, MCE has prognostic importance in patients with suspected CAD.

**Stable disease**

One of the early studies in man compared the use of MCE with sestamibi SPECT in 30 patients with known or suspected coronary artery disease undergoing dipyridamole stress. The overall concordance for the detection of CAD was 86% and identification of the perfusion abnormality location was similar between the two techniques. There are a number of studies which have compared perfusion abnormalities by MCE to coronary angiography as a gold standard. In one series of 85 patients, of whom 70 underwent coronary angiography, the sensitivity of MCE for CAD detection was 91%. More recently in 123 patients who underwent coronary angiography it was found that MCE and SPECT had similar sensitivity (84% vs. 82%) and specificity (56% vs. 52%) for the diagnosis of CAD. Such studies suggest that MCE is a reliable and accurate technique for the identification of CAD in patients with suspected ischaemia heart disease. Table 1 shows all studies comparing the ability of MCE with coronary angiography, as a gold standard, to diagnose CAD.

**Acute coronary syndromes**

The portability of MCE to the bedside makes it a very powerful tool in assessment of patients with acute myocardial infarction (AMI) and it is possible to rapidly stratify patients to high and low risk in the acute emergency setting. In a study of 114 patients admitted to an emergency department with chest pain but no ST segment elevation on the ECG, the accuracy of standard diagnostic testing (electrocardiograph, cardiac enzymes and regional wall motion abnormalities on resting 2D echocardiography) were compared to MCE using qualitative triggered imaging. All patients underwent either coronary angiography or SPECT. The sensitivity of MCE for the diagnosis of ACS was higher (77%) than the other methods (ST change 28%, troponin I 34%, wall motion abnormalities 49%). The specificities were similar...
In another similar study, 100 patients presenting with chest pain to the emergency department underwent quantitative MCE, 37 of whom had ACS diagnosed by standard criteria. The sensitivity of quantitative MCE for the diagnosis of ACS was 94% and the specificity 84%. In two studies the usefulness of MCE in the triage of patients presenting with chest pain and no ST elevation on the ECG have been demonstrated. In one study the incremental prognostic benefit of MCE over conventional parameters and regional function by echo were shown in over 1000 patients. In another study the advantages of MCE over regional function and conventional TIMI risk scoring assessment was demonstrated. Hence MCE is a clinically useful imaging tool in the management of patients with undiagnosed chest pain in the emergency department. In patients with myocardial infarction undergoing coronary angiography, MCE appears to be better than SPECT at predicting the extent of CAD. The best technique for the assessment of myocardial viability following infarction is an area of ongoing debate and the contribution of MCE is discussed in the following section.

### Myocardial viability

Following AMI or even during a prolonged ischaemic insult, left ventricular dysfunction is common. It is thought that the impairment in ventricular function is reversible particularly if the myocardium is hibernating or stunned. Stunned myocardium refers to the transient left ventricular dysfunction which often occurs following a period of acute ischaemia (such as successful reperfusion following AMI). Hibernating myocardium is usually found in the setting of chronic CAD when ventricular dysfunction improves following revascularisation. Unfortunately in many patients with chronic CAD and impairment of ventricular function, despite adequate restoration of blood flow, ventricular function does not improve as the myocardium is completely infarcted. Therefore a reliable method is required to distinguish between infarcted and viable myocardium allowing the identification of patients with chronic ischaemia ventricular impairment with hibernating myocardium that would benefit from revascularisation.

#### Table 1

<table>
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<th>Author</th>
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RT, real time; TR, triggered replenishment.

(86–93%). In another similar study, 100 patients presenting with chest pain to the emergency department underwent quantitative MCE, 37 of whom had ACS diagnosed by standard criteria. The sensitivity of quantitative MCE for the diagnosis of ACS was 94% and the specificity 84%. In two studies the usefulness of MCE in the triage of patients presenting with chest pain and no ST elevation on the ECG have been demonstrated. In one study the incremental prognostic benefit of MCE over conventional parameters and regional function by echo were shown in over 1000 patients. In another study the advantages of MCE over regional function and conventional TIMI risk scoring assessment was demonstrated. Hence MCE is a clinically useful imaging tool in the management of patients with undiagnosed chest pain in the emergency department. In patients with myocardial infarction undergoing coronary angiography, MCE appears to be better than SPECT at predicting the extent of CAD. The best technique for the assessment of myocardial viability following infarction is an area of ongoing debate and the contribution of MCE is discussed in the following section.

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### Post-myocardial infarction

In patients with AMI it has been shown that MCE can provide incremental value in the assessment of myocardial viability to dobutamine stress echocardiography and in addition MCE, with or without
the combination of dobutamine echo, can predict the recovery of left ventricular function. In a study of 30 patients who underwent primary percutaneous intervention (PCI), MCE was performed before reperfusion and at 3–5 days and 4 weeks after reperfusion. It was found that in 68 segments with no perfusion prior to PCI, 51 (75%) had restoration of perfusion at 3–5 days. For segments without perfusion at 3–5 days, 95% had severe hypokinesis or akinesis at 4 weeks. For segments with normal perfusion at 3–5 days, 90% had normal wall motion or mild hypokinesis at 4 weeks, whereas those with partial perfusion at 3–5 days were divided between normal wall motion, hypokinesis, and akinesis. It has also been shown that MCE can predict transmurality of infarction. In the first study to show this cardiac magnetic resonance (CMR) and MCE was performed in 42 patients who were 7–10 days post-thrombolytic therapy for AMI. Both qualitative (contrast intensity) and quantitative (MBF and peak contrast intensity) MCE demonstrated an inverse correlation to transmurality extent of infarction, defined by CMR. In another study of patients with AMI, MCE was performed 3–5 days after administration of thrombolytic therapy and compared to CMR performed at 2 weeks. Left ventricular volumes were lower and ejection fraction was higher by CMR in those patients who had viable myocardium by MCE compared to those who demonstrated non-viability. In comparison to SPECT, MCE is more accurate in defining the transmurality extent of infarction. In another study with 35 patients with AMI, MCE was performed immediately before, 1 h and 24 h after primary PCI. Left ventricular end diastolic volume was measured at 4 weeks to provide an estimation of left ventricular remodeling (>15% increase in size). It was found that patients with remodeling had larger perfusion defects by MCE before 1 h and 24 h after PCI compared to those who had no remodeling. Similar findings have been confirmed by others. In the assessment of viability following AMI, MCE at 1 week has been shown to be a predictor of contractile reserve at 3 months and is considered to be as accurate as CMR for this. The sensitivity and specificity of MCE for the prediction of functional recovery was 87 and 90%, respectively.

Chronic ischaemic left ventricular dysfunction
Chronic ischaemic left ventricular dysfunction is usually a result of multi-vessel CAD and for this reason many of the studies examining viability in this clinical setting involve patients due for coronary bypass surgery (CBG). One of the earliest studies of 35 patients, with a mean ejection fraction of 36%, awaiting revascularisation by PCI or CBG compared MCE and dobutamine echo. Revascularisation was successful in 23 patients and follow up echo was performed 1–2 months later and over 80% of hypokinetic segments showed functional improvement. Both MCE and dobutamine echo were effective at predicting viable segments but there was no difference between the two techniques. However this study was over 10 years ago and more recent data do suggest that MCE is a better technique. In one study of 20 patients who had MCE and 2D echo 1–5 days prior to CBG and 3–4 months later. Patients also had dobutamine echo and SPECT prior to surgery. It was found that sensitivity (90%) and specificity (63%) of quantitative MCE was higher than SPECT or dobutamine echo at prediction of functional recovery. Other groups have also shown similar findings supporting the role of MCE for identification of viable myocardium in chronic ischaemia.

Heart failure
Another potential clinical use for MCE is in patients with acute heart failure although there is little data for this. Certainly it is important to distinguish ischaemic aetiology of heart failure from non-ischaemic causes. There is one study to support the role of MCE for this and it was found that the sensitivity and specificity of MCE for the detection of CAD in this clinical setting was 82 and 97%, respectively.

Future directions
The future of MCE is very promising particularly with the advent of 3D echocardiographic probes and with further refinements and developments in software it may be soon possible for the assessment of myocardial perfusion using this technique. Another exciting area is the possibility of the local delivery of drug therapy to the myocardium using contrast agents as the medium — so far this has only been used experimentally.

Conclusions
In the last decade MCE has grown from a promising technique to a powerful clinical tool for the evaluation of patients with acute cardiac disease. It can provide detailed information regarding functional status and severity of ischaemic heart disease very rapidly. MCE is safe. There are some
training issues which mainly relate to the limited exposure of trainees to expert supervision. If these can be addressed, MCE should become more widely practiced in the next few years.

References

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