REVIEW

Assessment of coronary microcirculation with myocardial contrast echocardiography: current and future clinical applications

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Myocardial contrast echocardiography (MCE) is a relatively new technique that utilises the intravascular injection of microbubbles of air.¹ As these bubbles traverse the coronary microcirculation, they produce myocardial opacification that can be seen and measured. During their transit through the myocardium these bubbles remain entirely within the intravascular space and, if they are small, they act as tracers of red blood cell flow.^{2,3} Thus MCE can be used to assess the coronary microcirculation in the beating heart.

Current applications of MCE

Until recently the clinical applications of MCE were limited to the cardiac catheterisation laboratory and the operating room, because microbubbles capable of producing myocardial opacification from a venous injection were not available. In both the catheterisation laboratory and in the operating room the intra-arterial injections of microbubbles of

air have been found to be safe.^{4,5} In the experimental setting⁶ and in the cardiac catheterisation laboratory^{7,8} MCE showed the presence and functional significance of collateral perfusion during myocardial infarction. MCE is superior to coronary angiography, which can define only vessels $>100\ \mu\text{m}$ in diameter: most myocardial collaterals are considerably smaller.⁹

MCE, which can define vessels with a diameter $<10\ \mu\text{m}$, showed that collateral perfusion, which protects the myocardium during acute infarction,^{7,8} was more abundant in patients with coronary artery disease than had formerly been believed.⁷ Regional function is improved when blood flow is provided to infarcted myocardium with abundant collateral perfusion.⁸ Figure 1 shows short axis views of the heart from a patient with a recent antero-septal infarction and an occluded left anterior descending artery who had akinesia of the antero-septal wall and the apex. Injection of microbubbles into the right coronary artery resulted in opacification not only of the right coronary bed but also the medial half of the left anterior descending artery bed (arrows in fig 1A). When the microbubbles were injected into the left main artery, there was opacification in the lateral part of the bed of the occluded left anterior descending artery (arrows in fig 1B) as well as in the left circumflex bed. Thus this short axis view showed that the entire left anterior descending artery bed was supplied by either right-to-left (A) or left-to-left (B) collaterals. After successful angioplasty of the left anterior descending artery the function of the formerly akinetic antero-septal myocardium improved markedly.

Microvascular flow is abnormal in infarcted myocardium even after reflow and this abnormality occurs exclusively within the confines of the infarct.¹⁰⁻¹² Thus by defining the topography of abnormal perfusion within an infarct zone after reflow, it is possible to determine the extent of myocellular damage.^{13,14} Areas with less microvascular perfusion have less viable myocardium and vice versa. The microvascular perfusion pattern cannot be predicted by angiographic patency. More than a quarter of patients with open infarct-related arteries after reperfusion have extensive microvascular damage that is associated with a lack of improvement in myocardial function.^{13,14}

Figure 1 Right-to-left collaterals noted when microbubbles are injected into the right coronary artery (A) and left-to-left collaterals noted when microbubbles are injected into the left main artery (B) in a patient with a recent antero-septal infarction and an occluded left anterior descending artery. See text for details. From Sabia et al, *Circulation* 1992;85:2080-9, reprinted with the permission of the American Heart Association.

Figure 2 (A) Three different perfusion patterns in the same bed in a patient with a recent anteroapical infarction and an open left anterior descending artery. B and C are magnifications of areas with 0 and 0.5 scores. See text for details. From Ragosta, et al, *Circulation* 1994;89:2562-9, reprinted with the permission of the American Heart Association.

Figure 2 shows an apical four chamber view in a patient with a recent anteroapical and apical infarction and an open left anterior descending artery that demonstrated good angiographic flow. The entire interventricular septum and apex showed severe dysfunction on the initial evaluation. MCE showed three different contrast patterns within the dysfunctional zone. There was homogeneous opacification in the upper septum, patchy opacification in the middle septum, and no opacification in the apex. A month later the function in this infarct bed correlated with the degree of myocardial opacification on

MCE at the time of initial catheterisation, with near normal function in the upper septum, moderately reduced function in the middle septum, and no function in the apex.

In the operating room, MCE has been shown to define regions of the myocardium not receiving adequate perfusion during antegrade cardioplegia delivery through the cross-clamped aortic root.⁵ This information allows the surgeon to bypass these regions first and perfuse them with cardioplegia via the grafts in order to prevent perioperative infarction. In addition MCE can help to determine whether revascularisation has been adequate and if it has not, any technical factors associated with unsuccessful revascularisation, such as inadequate distal anastomosis, can be immediately recognised and reversed in the operating room.

Figure 3 Lack of myocardial perfusion in the posterior wall during cardioplegia delivery (A). This improved dramatically after bypass to the right coronary artery (B). Better perfusion after bypass is indicated by time-intensity curves obtained from the myocardium (C). From Villanueva et al, *J Thorac Cardiovasc Surg* 1992;104:1524-31, reprinted with permission of Mosby-Year Book.

Figure 4 Example of successful reperfusion with no infarction and hence complete myocardial salvage. MCE showed an anterior perfusion defect during occlusion of the left anterior descending artery in a dog (A). There was a corresponding defect on technetium autoradiography (B). After reperfusion MCE showed no defect (C) and postmortem triphenyl tetrazolium chloride staining of the heart did not show an infarct (D). From Villanueva, et al, *Circulation* 1993;88:596–604, reprinted with the permission of the American Heart Association.

Potential clinical applications of MCE using venous injection of contrast

Acute myocardial infarction

- (a) Diagnosis of acute infarction by demonstrating lack of flow to a myocardial region (figs 4 and 5)
- (b) Estimation of the size of the area at risk (the region of the myocardium at risk for necrosis) (figs 4 and 5)
- (c) To determine whether reperfusion has been successful (figs 4 and 5)
- (e) To determine the extent of myocardial salvage after reperfusion (figs 4 and 5)

Chronic artery disease

- (a) Detection of disease (fig 6)
- (b) Quantify potential extent of ischaemia (fig 6)
- (c) Quantify potential magnitude of ischaemia (fig 6)
- (d) Risk stratification for determining management strategies
- (e) Preoperative risk assessment

Quantification of myocardial perfusion, especially myocardial blood volume and microvascular reserve

Non-invasive assessment of endothelial function

- (a) Identify patients likely to have atherosclerosis
- (b) Quantify effects of risk modification
- (c) Determine which drugs offer beneficial effects

Figure 3 shows images from a patient with a severely stenotic dominant right coronary artery who at baseline showed no myocardial opacification in the posterior half of the heart when microbubbles were injected into the cross-clamped aorta during cardioplegia delivery. After that vessel was bypassed and microbubbles were reinjected into the aorta, perfusion of the posterior half of the heart was improved. MCE can also be used to define the spatial distribution of myocardial perfusion during retrograde infusion of cardioplegia.¹⁵

Potential future applications of MCE

More recently, it has been possible to opacify the myocardium with a venous injection of contrast.^{16–18} These new microbubbles cross the lungs, enter the left ventricular cavity, and then opacify the left ventricular myocardium. This approach could vastly increase the clinical applications of MCE, and may replace nuclear perfusion imaging in many patients. The table lists possible clinical applications of MCE. Because the results from venous contrast agents are only preliminary, the examples given are based on left atrial injections in animals.^{19,20}

Consider two patients with an acute evolving myocardial infarction who present to the emergency room with chest pain and a non-diagnostic electrocardiogram. MCE shows a perfusion defect in the anteroapical region in both patients (A in figs 4 and 5). The contrast enhanced images are colour coded to accentuate differences in grey scale intensities, with greater intensities appearing as yellow and white and lesser intensities appearing as reds and oranges. Lack of perfusion to the anteroapical region was confirmed with technetium autoradiography, a post-mortem technique that can accurately define the area at risk of necrosis (B in figs 4 and 5). The lack of perfusion on MCE demonstrates not only the presence but also the size of the area at risk which, in the two examples (figs 4 and 5) is large and therefore of greater clinical relevance.¹⁹

Had these examples occurred in patients given thrombolytic therapy because of the information in figs 4A and 5A repeat MCE would have confirmed that reflow had been achieved, because there was perfusion in the anteroapical region (C in figs 4 and 5). In fig 4C microvascular perfusion was homogeneous throughout the myocardial thickness—that is, myocardial salvage was complete. This was confirmed by the absence of infarction in the heart slice corresponding to the MCE image (fig 4D) which was stained with triphenyl tetrazolium. The subendocardial contrast defect in fig 5C suggested a lack of myocardial salvage in the endocardial half of the myocardium. This was confirmed when triphenyl tetrazolium chloride staining showed subendocardial infarction in a heart slice corresponding to the MCE image (fig 5D). Thus in these two theoretical patients, MCE not only showed coronary occlusion

Figure 5 Example of successful reperfusion with partial myocardial salvage in a dog. An anterior perfusion defect was noted on MCE during left anterior descending coronary artery occlusion (A) with a corresponding defect on technetium autoradiography (B). After reperfusion an endocardial defect was noted on MCE (C) and a subendocardial infarction was noted on postmortem triphenyl tetrazolium chloride staining of the heart (D). From Villanueva, et al, *Circulation* 1993;88:596-604, reprinted with permission of the American Heart Association.

and the success of reperfusion, but also the extent of myocardial salvage after reflow.¹⁹

Like nuclear perfusion imaging techniques, MCE can also be used in patients with known or suspected chronic coronary artery disease to detect disease and to define how much myocardium is susceptible to ischaemia. In most patients with coronary artery disease perfusion at rest appears normal because resting blood flow is normal. During pharmacologically induced hyperaemia, however, there is a perfusion mismatch because regions supplied by stenotic vessels do not demonstrate as much of an increase in flow as those with normal vessels.

Figure 6 shows images from four stages in a dog after left atrial injection of contrast.²⁰ During baseline (A) and pharmacologically induced hyperaemia (B) and in the absence of any coronary stenosis flow to the two beds was identical. When, during hyperaemia, a stenosis was placed on either the left anterior descending (C) or the left circumflex (D) artery, relative hypoperfusion (denoted by arrows) was noted in regions supplied by these vessels. These areas of hypoperfusion

corresponded well with actual flow abnormalities measured using radiolabelled microspheres and the ratios of intensities from the two beds also correlated closely with the ratios of perfusion to the two beds.²⁰ Thus both the spatial extent and amount of myocardium susceptible to ischaemia can be defined by MCE, which can form the basis for risk stratification and management of patients with coronary artery disease.

As well as the topography of abnormal perfusion (figs 1 to 6) more complex aspects of myocardial perfusion such as myocardial blood flow and volume (volume of blood within the myocardial microvasculature) can also be measured by MCE.²¹⁻²⁴ Although blood flow and volume are usually closely coupled, they may not be, as when a coronary vasodilator, such as dipyridamole or adenosine, is used to measure coronary flow reserve. Coronary flow reserve is then expressed as the ratio of hyperaemic basal blood flow.

Coronary flow reserve depends on the ability of the coronary microvasculature to dilate. Because there is no method of directly assessing the coronary microvasculature, measurement of coronary blood flow has been used to assess coronary microvascular reserve. The problem with measuring coronary blood flow as an indicator of coronary reserve is that potent coronary vasodilators abolish autoregulation, and under these circumstances coronary blood flow is determined by the coronary driving pressure. Thus any change in aortic pressure will lead to either an over or under estimation of the coronary reserve. Direct estimation of pharmacologically induced changes in myocardial blood volume by MCE, however, gives a more appropriate assessment of microvascular reserve.^{23, 24}

Another important application of MCE that is developing is the assessment of coronary endothelial function, which can become abnormal in smokers or those with hypercholesterolaemia long before atherosclerosis develops. If endothelial dysfunction can be detected before atherosclerosis develops, risk factor modification may prevent its development. Sonicated albumin microbubbles, which are carried rapidly through normal myocardium,²² move more slowly in the presence of endothelial dysfunction.²⁵⁻²⁷ This exciting discovery could be useful in the non-invasive assessment of coronary endothelial function.

Conclusions

Until now there has been no method to study coronary microvasculature in vivo. MCE provides a direct assessment of the coronary microvasculature and has the potential of being non-invasive. The aspects of the coronary microcirculation that can be examined with MCE include anterograde and collateral perfusion patterns; microvascular damage as a marker of infarct size and absence of damage as an indication of myocardial viability;

Figure 6 Colour coded end diastolic images in a dog at baseline (A) and during pharmacologically induced hyperaemia (B to D) without stenosis (B) and with stenosis of a left anterior descending artery (C) and stenosis of the left circumflex artery (D). From Ismail, et al, *Circulation* (1995;91:821–30), reprinted with the permission of the American Heart Association.

quantification of myocardial blood flow, volume, and microvascular reserve; and assessment of endothelial function. The use of MCE in patients is just beginning, as are advances in microbubble engineering and methods of quantification and display of MCE data. The development of contrast agents capable of producing myocardial opacification from venous injection may lead to MCE replacing nuclear imaging techniques for the assessment of coronary artery disease in many patients.

Supported in part by grants from the National Institutes of Health, Bethesda, Maryland (R01-HL48890) and the American Heart Association (both National Center, Dallas, Texas and Virginia affiliate, Glen Allen, Virginia). S Kaul is an Established Investigator of the American Heart Association, Dallas, Texas.

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