Myocardial contrast echocardiography in acute myocardial infarction: time to test for routine clinical use?

Coronary angiography has been used as the gold standard to determine whether reperfusion has been successful. TIMI (thrombolysis in myocardial infarction) grades have been developed for this purpose and have been shown to provide prognostic information. It has, however, been known for a quarter of a century that reflow in the infarct related artery does not necessarily imply tissue perfusion. It is also known, that regions within the myocardium that show poor tissue perfusion after reflow (no reflow or low reflow) have histological evidence of tissue necrosis. That myocardial contrast echocardiography (MCE) can define regions of no reflow was demonstrated nearly 15 years ago in a dog model.

As is unfortunately often the case, the medical community either ignored or was unaware of these experimental data. Not surprisingly, therefore, the first report of MCE documenting no reflow in patients who underwent reperfusion for acute myocardial infarction (AMI) published about five years ago was hailed as new knowledge. A number of clinical studies since then has confirmed these findings. Approximately a quarter to a third of patients with TIMI grade 3 flow on coronary angiography have poor tissue perfusion, which is associated with poor recovery in regional function and a worse prognosis. The paper by Czitrom et al in this issue adds to this body of knowledge.

MCE uses microbubbles that remain in the intravascular space. Because 90% of the myocardial microvasculature consists of capillaries, the spatial distribution of these bubbles in the myocardium provides an assessment of regional capillary integrity. Areas with necrosis are associated with capillary damage and impaired microvascular function. A non-invasive assessment of capillary structure and microvascular function, therefore, provides a simple means of assessing tissue perfusion and integrity. The ultimate test for the success of reperfusion is whether tissue perfusion has been achieved. MCE appears to be an ideal tool for assessing whether reperfusion has occurred, as well as determining the extent of necrosis.

The aforementioned clinical studies, and the one by Czitrom et al in this issue used intracoronary injections of microbubbles in the cardiac catheterisation laboratory. No commercially available microbubbles that can be administered intravenously have yet been approved for MCE. Several agents are currently being evaluated in phase II and

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**Table 1** Venous ultrasound contrast agents evaluated for MCE in the author’s laboratory

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>US distributor</th>
<th>Size (µm)</th>
<th>Concentration (∗10⁻⁹)</th>
<th>Shell composition</th>
<th>Gases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optison*</td>
<td>Molecular Biosystems (San Diego, California, USA)</td>
<td>Mallinckrodt Medical (St Louis, Missouri, USA)</td>
<td>3.9</td>
<td>0.8</td>
<td>Denatured albumin</td>
<td>Air and perfluoropropene</td>
</tr>
<tr>
<td>Definity</td>
<td>ImuRx Pharmaceutical (Tucson, Arizona, USA)</td>
<td>Dupont Pharmaceuticals (North Billerica, Massachusetts, USA)</td>
<td>2.5</td>
<td>1.2</td>
<td>Lipids and surfactants</td>
<td>Air and perfluoropropene</td>
</tr>
<tr>
<td>Imagent</td>
<td>Alliance Pharmaceutical (San Diego, California, USA)</td>
<td>Schering</td>
<td>5.0</td>
<td>0.5</td>
<td>No shell (surfactant stabilised)</td>
<td>Nitrogen and perfluoroxyane</td>
</tr>
<tr>
<td>Sonovue</td>
<td>Bracco sPA (Milan, Italy)</td>
<td>Bracco Imaging (Princeton, New Jersey, USA)</td>
<td>2.5</td>
<td>0.2</td>
<td>Lipids and surfactants</td>
<td>Air sulphur hexafluoride</td>
</tr>
<tr>
<td>Levovist†</td>
<td>Schering (Berlin, Germany)</td>
<td>Berlex (Princeton, New Jersey, USA)</td>
<td>2–4</td>
<td></td>
<td>No shell (palmitic acid stabilised)</td>
<td>Air</td>
</tr>
<tr>
<td>N100100</td>
<td>Nycomed-Amersham (Oslo, Norway)</td>
<td>Nycomed-Amersham</td>
<td>3–5</td>
<td></td>
<td>Protein and surfactant</td>
<td>Air and perfluorocarbon</td>
</tr>
<tr>
<td>Quantison</td>
<td>Andaris (Nottingham, UK)</td>
<td>Advanced Magnetics (Princeton, New Jersey, USA)</td>
<td>3.2</td>
<td>1.5</td>
<td>Denatured albumin (thick shell)</td>
<td>Air</td>
</tr>
</tbody>
</table>

Size and concentration are in vitro measurements.

*Approved in the USA and parts of Europe for left ventricular cavity opacification.
† Approved in Europe for Doppler signal enhancement.
In the USA, each year approximately five million people present to the emergency department with chest pain. Because the initial ECG is unreliable for excluding an AMI and because cardiac enzymes become positive much later, most of these patients are admitted to hospital for observation. Fewer than 20% of the admitted patients have an acute ischaemic syndrome and the rest are discharged the next day. This “rule out” AMI protocol costs US$10 billion annually. MCE, where regional function and perfusion can be assessed online, could assist in selecting only high-risk patients for hospital admissions and thus could dramatically reduce costs.

Given this information, how could one use MCE in patients with suspected AMI when intravenous microbubbles become available? Figure 3 lists various scenarios where MCE could be used. It could first document the occurrence of AMI by defining severe hypoperfusion. It could also help determine the size of the risk area. If the risk area is small because of occlusion of a small artery or abundant collateral flow, initial treatment can be conservative. If the risk area is large in size, thrombolysis or mechanical reperfusion should be instituted immediately.

Myocardial perfusion could then be reassessed immediately after thrombolysis. No change in the size of the risk area would indicate unsuccessful reperfusion and these patients could perhaps undergo rescue angioplasty. Complete or near complete myocardial opacification after attempted reperfusion would indicate either almost complete myocardial salvage or an underestimation of infarct size because of reactive hyperaemia. The most urgent question after attempted reperfusion is whether it has been successful and MCE can provide this information immediately.

Estimation of infarct size could be problematic immediately after reperfusion because of reactive hyperaemia. This phenomenon occurs only in the absence of a residual critical stenosis of the infarct related artery and abates within hours of reperfusion. Therefore, repeat MCE any time after 12 hours of reperfusion would provide an accurate assessment of infarct size. If the information concerning infarct size were required immediately, a coronary vasodilator could be administered. This procedure unmasks the abnormal microvascular function within the infarct zone and provides an accurate assessment of infarct size despite ongoing reactive hyperaemia (fig 1).

The predominant opinion regarding the cause of the no reflow phenomenon is that it occurs secondary to tissue necrosis. A contrary opinion is that it may be the cause of necrosis. In the former case, any attempt to alter microvascular function after reflow are unlikely to change infarct size. In the latter, pharmacological or other interventions aimed at improving microvascular function could salvage additional myocardium and reduce infarct size. Recent clinical studies using MCE have reported that the “low reflow” phenomenon seen after reperfusion and located at the periphery of the infarction can be reversed by verapamil and nicorandil treatment, and that this reversal is associated with improved regional function and outcome. If these findings are confirmed in larger studies, then pharmacological treatment aimed towards reversal of microvascular dysfunction could be initiated in patients with low reflow to reduce infarct size. MCE could then be repeated to determine the success of this intervention.

A transmural zone of no reflow probably indicates a transmural AMI. Patients with this finding are likely to have infarct expansion, left ventricular dilatation, and heart failure. They are, therefore, likely to benefit the most from early institution of angiotensin converting enzyme (ACE) inhibitor treatment. If the no reflow is not transmural, ACE inhibitors may not be necessary because normal
tissue is likely to buttress the infarct and prevent infarct expansion. A rationale such as this based on pathophysiological principles should prove to be superior to crude predictors such as left ventricular function and infarct location for selecting patients who would benefit the most from ACE inhibitors.10

The scenarios described here appear plausible given our knowledge of the pathophysiology of AMI and data from animal studies. Obviously, clinical studies are needed to confirm the value of MCE in each of these scenarios. Because each patient with AMI is unique, MCE has the potential for providing valuable information concerning the ischaemic and reperfused myocardium on a patient by patient basis. This information can then be used to individualise and optimise management. Intravenous contrast agents approved for MCE are eagerly awaited to test whether MCE should be used routinely in patients with AMI and other acute ischaemic syndromes.

Dr Kaul is supported in part by a grant (R01-HL48890) from the National Institutes of Health, Bethesda, Maryland, USA.

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**STAMPS IN CARDIOLOGY**

**Embryology of the heart**

A unique design is seen in the Danish 1988 stamp issued to commemorate the 40th anniversary of the World Health Organisation. It was released on 7 April—World Health Day—and features the development of the arterial trunks and brachiocephalic arteries. The six paired arches are shown forming the definitive vasculature.

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