

Measuring myocardium at risk in acute myocardial infarction—A continuing challenge

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In patients with acute myocardial infarction (AMI) with ST elevation, early reperfusion therapy with either direct percutaneous coronary intervention¹ or thrombolytic agents² significantly reduces mortality. The decline in mortality is partially related to a reduction in infarct size. Myocardial perfusion imaging can be utilized in these patients to measure both myocardium at risk (MAR) when a patient first arrives in the emergency department and final infarct size several days later. The difference between MAR and final infarct size represents “myocardial salvage.” Dividing the amount of myocardial salvage by the amount of MAR provides a “salvage index.”

Early studies in the 1980s that measured infarct size and myocardial salvage used thallium (Tl)-201.^{3,4} The subsequent introduction of technetium (Tc)-based perfusion radioisotopes facilitated this process, especially for measuring MAR. In contrast to Tl-201, Tc-99m undergoes minimal redistribution over time,^{5,6} permitting a delayed image acquisition several hours after injection, and after administration of reperfusion therapy, that still reflects myocardial perfusion at the time of injection in the emergency department. Another advantage of Tc-99m over Tl-201 is its higher peak energy window, which permits more accurate identification of the boundaries of a perfusion defect^{7,8} and increases the accuracy of gated images.

Infarct size and myocardial salvage have been extensively validated as surrogate endpoints for mortality in the setting of AMI.^{9,10} Although these measurements are not routinely made clinically, they have been applied as endpoints in over 30 AMI trials comparing different therapeutic strategies or examining the efficacy of novel

agents or devices.¹¹ Infarct size alone has been used as the endpoint in the majority of these trials, and particularly the more recent ones, since it is logistically easier. Patients only need to undergo one imaging study more than 120 hours (5 days) after reperfusion therapy when they are clinically stable. In contrast, the measurement of myocardial salvage requires an early imaging study to determine MAR. Although the intravenous injection of a dose of Tc-99m sestamibi in the emergency department is not difficult, a supply of Tc-99m sestamibi must be readily available (the isotope must be prepared every 6 hours by a technologist to comply with the package insert), and imaging needs to generally be performed within 6 hours of injection. Many hospitals have been unable to meet these requirements.

What are the advantages of measuring myocardial salvage rather than measuring infarct size alone? The use of myocardial salvage rather than infarct size as an endpoint in clinical trials should permit a smaller patient sample size. However, the difference in sample size is more modest than expected, as each parameter has a similar relationship between its variability (expressed as the standard deviation) and the expected difference with treatment.¹² As a result, several positive clinical trials have reported similar results for both myocardial salvage and infarct size.^{13,14} The gain in statistical power with the measurement of MAR is best achieved with an analysis of covariance.¹²

Another advantage of measuring salvage is the insight that it provides into treatment efficacy in an individual patient. Studies in animals¹⁵ and humans¹⁶ have demonstrated that the amount of MAR can vary widely, even for a coronary artery occlusion in the same territory. Two patients may both have final infarct size of 20%, but in one patient MAR may have been 60%, whereas in the other patient MAR may have been 20%. Measuring salvage provides knowledge of treatment efficacy in these two patients that would not be available from measurement of infarct size alone.

In this issue of the *Journal*, Sciagra et al¹⁷ describe a novel approach for the measurement of MAR. These investigators take advantage of the concept of myocardial stunning to estimate MAR from the extent of myocardium with impaired regional wall thickening on a gated SPECT Tc-99m sestamibi image performed at an average of 5 days post-AMI. In 36 patients with first

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AMI treated within 6 hours by primary percutaneous coronary intervention, there was a close correlation (Spearman's $\rho = .92$, $P < .0001$) between the new "thickening" salvage index and the conventionally performed "perfusion" salvage index obtained from standard acute and delayed images. A rigorous Bland–Altman analysis showed that the 95% limit of agreement between the two salvage indices was $\pm .25$. Both indices were significantly associated (univariable analysis) with 1-month follow-up gated SPECT left ventricular ejection fraction.

These provocative results suggest that myocardial salvage can potentially be measured by acquiring a simple, "one-stop-shop" delayed gated SPECT image in place of the more difficult approach that depends on the acquisition of both acute and delayed perfusion images.

The study of Sciagra et al¹⁷ does have limitations. As acknowledged by the authors, their sample size was small. The regional perfusion and wall thickening images were interpreted subjectively by a single observer rather than applying a quantitative threshold technique, which has been used in most studies to measure infarct size and myocardial salvage.¹¹ Such subjective measurements are usually associated with greater variability, and therefore require a larger sample size in clinical trials. Patient misclassification may potentially off-set any reduction in sample size achieved by measuring salvage rather than infarct size alone. In this study the misclassification rate applying the thickening salvage index in place of the perfusion salvage index was 17% (6/36). Finally, the optimal timing of acquiring the single gated SPECT image is unknown. In this study imaging was performed at an average of 5 days with a range of 2–8 days. Previous work from our laboratory cited by Sciagra et al¹⁷ indicated that measurement of infarct size at 48 hours would over-estimate infarct size in some patients.¹⁸ Unfortunately, myocardial stunning has already started to resolve at that time in some patients.¹⁹ The optimal timing for a single gated SPECT image is therefore likely to differ between patients.

Despite these limitations, the novel approach developed by Sciagra et al is commendable, and merits further investigation. Future studies will hopefully address the issues of quantitation, misclassification, and timing, and provide comparisons to magnetic resonance imaging (MRI). MRI is another imaging modality that is being increasingly utilized to measure infarct size.^{20,21} Although MRI can detect smaller infarctions and is more reproducible, this does not necessarily translate into an advantage as an endpoint in clinical trials.¹⁰ Two comparative studies have reported similar infarct sizes and standard deviations using MRI and SPECT,^{22,23} which would imply similar required sample sizes for both

approaches. An emerging literature has also investigated the ability of MRI to measure MAR in a delayed time-frame by identifying myocardial edema.^{24–26} These efforts with MRI, as well as the current paper by Sciagra et al, reflect ongoing interest in developing a method to accurately measure MAR (and myocardial salvage) in a delayed, logistically simple manner that does not interfere with the administration of reperfusion therapy. However, these approaches require more extensive validation before they can be applied with confidence as endpoints in clinical trials.

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