Viability Assessment by Delayed Enhancement Cardiovascular Magnetic Resonance
Will Low-Dose Dobutamine Dull the Shine?

Raymond J. Kim, MD; Warren J. Manning, MD

Since mechanical revascularization methods such as coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention became available, the issue of identifying dysfunctional yet viable myocardium has been of crucial clinical importance. Among patients with ischemic cardiomyopathy and viable myocardium, mechanical revascularization is associated with improved systolic function, symptoms, and survival,1–3 yet the best method to identify viable myocardium remains disputed. Current options include positron-emission tomography (PET) to assess myocardial metabolic activity, single-photon emission computed tomography (SPECT) with technetium-99m sestamibi or thallium-201 to assess myocardial perfusion and membrane integrity, and dobutamine echocardiography or cine cardiovascular magnetic resonance (CMR) to assess myocardial contractile reserve. Each approach, however, has limitations. For example, the index measured may not reflect the quantity of viable myocytes but rather a physiological parameter, such as perfusion or contractile reserve, that has only an indirect relation to viability. Other limitations include partial volume effects due to poor spatial resolution (SPECT, PET), attenuation and scatter artifacts (SPECT), and the occasional inability to visualize all parts of the left ventricle (dobutamine echocardiography).

More recently, studies have demonstrated the effectiveness of a new CMR technique, delayed contrast-enhanced CMR (DE-CMR) for detecting myocardial infarction and determining viability with much higher spatial resolution than SPECT.4,5 Data from animal models of ischemic injury demonstrate that DE-CMR can distinguish between reversible and irreversible myocardial injury independent of wall motion, infarct age, or reperfusion status.4,6,7 Human studies demonstrate that DE-CMR is effective in identifying the viability area independent of wall motion, infarct age, or reperfusion status.4,6,7 Human studies demonstrate that DE-CMR is effective in identifying the viability area.
CMR (sensitivity of 75% and specificity of 93%, estimated visually from Figure 2 of their article) are better than the results of previous reports.

This improvement may be related to their use of steady-state free precession techniques for cine imaging. Steady-state free precession provides signal-to-noise ratio superior to that obtained by conventional gradient-echo techniques, along with excellent contrast between myocardium and blood. Nonetheless, it is known that contractile reserve has reduced predictive accuracy if more severe dysfunction is present at rest. For example, in akinetic segments, the sensitivity of dobutamine echocardiography for predicting functional improvement may be as low as 26%. Several explanations have been proposed for this reduced sensitivity in the setting of severe resting dysfunction. Notably, experimental studies of chronic low-flow ischemia have shown that some viable regions are so delicately balanced between reductions in flow and function, with exhausted coronary flow reserve, that any inotropic stimulation merely results in ischemia and precludes the ability for enhanced contractility. DE-CMR, on the other hand, appears to have greater accuracy in segments with the most severe dysfunction. 

Future studies will be needed that compare dobutamine CMR to DE-CMR for different levels of resting dysfunction.

Kim et al first reported that DE-CMR could be used to predict functional improvement after revascularization. The likelihood of functional improvement for a given region was inversely related in a progressive stepwise fashion to the transmural extent of scar by DE-CMR. For example, the percentage of segments improving ranged from 78% for those without scar to 2% for those with >75% scar. The relationship was even steeper for segments with at least severe hypokinesis at baseline (86% improving for no scar to 0% improving for >75% scar). Recently, Schwartzman et al demonstrated similar findings for a patient cohort with more severe cardiomyopathy (LV ejection fraction 28±10%), with 82% of regions with no scar improving, compared with only 18% with ≥50% scar. In contrast, Wellnhofer et al found a less steep relationship, with only 69% of regions without scar improving. In this regard, the findings of Wellnhofer et al about the predictive accuracy of DE-MRI are worse than the results of previous reports.

There is a wealth of data in animal models of ischemic injury directly comparing DE-MRI to the histopathology. These data demonstrate a nearly exact relationship between the size and shape of nonviable myocardium by DE-MRI to that by histopathology (Figure). Given this relationship, how do we then explain that Wellnhofer et al found that 31% of regions that are presumably 100% viable after revascularization? This question brings to focus the difference between the correct definition of viability (the presence of living myocytes) and the often-used clinical definition (the improvement in contractile function after revascularization). Because testing for viability by microscopy or histological staining is not practical in a clinical setting, the latter definition became the expedient choice for clinical purposes.

If contractile function improves after revascularization, it is safe to assume that there is a significant amount of viability; however, the converse is not true. In fact, analysis of transmural needle-biopsy specimens taken during CABG demonstrates that some regions that do not improve after revascularization do have a significant amount of viability. For example, in their samples, Dakik et al report that the extent of viability was 69±21% of total myocardium. The presence of viability without functional improvement may be due to several factors. First, the use of a single evaluation of ventricular function soon after revascularization may lead to an underestimation of the true rate of functional recovery because the time course of recovery may be up to 14 months. Second, even if technically successful, coronary revascularization may be incomplete, particularly in patients with extensive atherosclerosis and diffuse disease. On this point, it should be noted that nearly half (45%) of the patients studied by Wellnhofer et al had CABG before study enrollment, and the vast majority (86%) had percutaneous coronary intervention for the study intervention. Third, tethering of regions with extensive scarring to viable regions may inhibit the response of viable regions to revascularization.

On this point, Wellnhofer et al speculate that contractile reserve is superior to DE-CMR because tethering may also inhibit contractile reserve in viable regions, thus leading to the correct prediction of no functional improvement. This approach, however, ignores the possibility that withholding revascularization from viable regions that are mechanically inhibited from fully thickening may not be an appropriate clinical choice.

Even if functional improvement after revascularization is assumed to be the appropriate clinical end point, the data from both the Wellnhofer et al report and original Kim et al report demonstrate that there is a smooth progressive relationship between the likelihood of functional improvement and the transmural extent of scar by DE-MRI. This indicates that the use of a single cutoff value for scar on which to base predictions of functional improvement would not have a physiological basis and would be suboptimal. In fact, the ability to approach viability as a continuum rather than in a binary manner is one of the greatest strengths of DE-MRI. For example, the negative predictive value of
dobutamine CMR found by Wellnhofer et al is approximately 83% (estimated from data in Figures 1 and 2 in their article14). In contrast, using a cutoff of 25% scar, the negative predictive value of DE-CMR is 79% (estimated). However, the negative predictive value rises to 88% if a cutoff of 50% scar is used. In the original Kim report,11 the negative predictive value was 92% for a cutoff of 50% scar. This means that for segments with ≥50% scar (34% of all dysfunctional segments in the study by Wellnhofer et al14), one can predict that these segments will not improve after revascularization with equal or higher confidence than with dobutamine CMR.

This conclusion is somewhat different than that reported by Wellnhofer et al. It should be noted, however, that the method of ROC curve analysis used by Wellnhofer et al is problematic because the presented ROC curves are each formed from a single data point (ie, single decision threshold). Even when two different threshold values are tested for DE-CMR, the authors plot these data as two separate ROC curves rather than on one curve as appropriate. The purpose of ROC curve analysis is to provide a description of the diagnostic performance of a test that is more informative than providing the sensitivity and specificity of the test based on a single decision threshold. Thus the curve should be formed from multiple sensitivity versus 1-specificity pairs that describe the effect of changing the decision threshold. Because each of the ROC curves by Wellnhofer et al is based on a single data point, it is inappropriate to compare tests by comparing areas under the ROC curve. Instead, the data should have been reported using the conventional descriptors such as sensitivity, specificity, positive and negative predictive value, and accuracy.

Which test should we choose? When clinicians consider their noninvasive imaging options for viability assessment, many issues need to be considered, including availability, accuracy, cost, resource utilization, safety, and ease of implementation. Both DE-CMR and dobutamine CMR require intravenous access, but DE-CMR does not require infusion of a pharmacological stress agent in the magnet. Thus DE-CMR is safer, requires less intense monitoring, is easier to implement, and is faster to complete. DE-CMR also appears to be somewhat easier and faster to interpret. Since widespread clinical attention was drawn to DE-CMR more than 4 years ago,11 numerous centers have reproduced the major findings and demonstrated value in conditions beyond that of ischemic myopathy.

Has the report of Wellnhofer et al14 taken some of the “shine” from DE-CMR? Quite the contrary. The data so far, including those from Wellnhofer et al, demonstrate that for dysfunctional regions with ≥50% scar by DE-CMR, the negative predictive value is quite high and likely will be higher than that found by dobutamine CMR. For regions with <25% scar, it is possible that dobutamine CMR may provide a higher positive predictive value than DE-CMR. However, in this group, there is such a large amount of viability, and the potential for benefit is so great, that it likely is sensible to be concerned about the possibility of a false-negative dobutamine CMR result. Thus, in this group, with all other clinical issues being equal, it may be preferable to err on the side of overestimating rather than underestimating the clinical bene-

fit of revascularization. For regions with 25% to 50% scar, one should recognize that this group represents only a small portion of dysfunctional segments: 18% in the Wellnhofer et al study14 and 14% in the original Kim et al report.11 Nonetheless, it is likely, according to the data of Wellnhofer et al, that if one dichotomizes this group into those that are contractile reserve positive and those that are negative, these two groups will have significant differences in the rate of functional improvement after revascularization. In this case, however, the clinical issue is changed. The question of whether one can predict a subgroup with high likelihood of functional improvement is only part of the issue. Perhaps a more important question is whether a substantial amount of viability (eg, 50% to 75%) may be sufficient to provide clinical benefit even without functional improvement after revascularization. Samady et al20 demonstrated that the survival rate after CABG was similar among patients with LV dysfunction whether or not function improved after revascularization. They speculate that their result may be due to an intermediate level of viability that increases the likelihood of a good clinical outcome but is, meanwhile, insufficient to provide improved resting function. It is likely that improved clinical outcome is related to several factors, including prevention or even reversal of adverse remodeling, improved contractile response under stress, prevention of recurrent myocardial ischemia/infarction, and prevention of arrhythmias.

References


**KEY WORDS:** Focused Perspectives ▪ revascularization ▪ magnetic resonance imaging ▪ myocardial contraction ▪ hibernation
Viability Assessment by Delayed Enhancement Cardiovascular Magnetic Resonance: Will Low-Dose Dobutamine Dull the Shine?
Raymond J. Kim and Warren J. Manning

_Circulation_. 2004;109:2476-2479
doi: 10.1161/01.CIR.0000130730.63776.69

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/21/2476

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/