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EDITORIAL COMMENT

Myocardial Viability Imaging

Dead or Alive?*

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The concept of hibernating myocardium originated from observations in the 1970s that the myocardial dysfunction seen in patients with chronic coronary artery disease (CAD) was not always permanent (1). The fact that revascularization with coronary artery bypass grafting (CABG) could result in the recovery of contractile function in previously akinetic segments led to the development of numerous imaging techniques to differentiate viable from nonviable myocardium. Although enhanced regional and global left ventricular (LV) function can be demonstrated and often translates into symptomatic benefit in patients with severe ischemic LV dysfunction, the impact on survival of identifying and then revascularizing viable but dysfunctional myocardium remains unclear. Previous outcome studies using various imaging modalities to assess viability were small and retrospective in nature, and predated the era of modern medical therapy (2,3). Only recently have 2 prospective, randomized trials comparing medical therapy to surgical or percutaneous revascularization based on preintervention viability testing been completed and reported,

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but they raise more questions than answers (4,5). Both the viability substudy of the multicenter STICH (Surgical Treatment for Ischemic Heart Failure) trial and the HEART (Heart Failure Revascularisation Trial) were negative for their primary endpoints of all-cause mortality. Although HEART was underpowered because of underenrollment, the STICH substudy demonstrated lower rates of the secondary composite endpoint of cardiovascular death or cardiovascular hospitalization. Nonetheless, these results question the clinically accepted dogma of routinely requiring viability assessment prior to all revascularization procedures in these high-risk patients.

How can we reconcile the results of Gerber et al. (6), reported in this issue of the *Journal*, with those of STICH and HEART? The authors measured viability using delayed-enhancement cardiac magnetic resonance imaging (DE-CMR), which depends upon the premise that regions of nonviable fibrosis and scar have increased volumes of distribution and reduced contrast washout rates of gadolinium compared with normal myocardium, and thus appear hyperenhanced. DE-CMR viability is assessed on a regional, segmental basis with >50% transmural involvement of the wall defining a nonviable segment. Significant viability is present if ≥4 dysfunctional segments have ≤50% transmural hyperenhancement. In this nonrandomized, observational study of 144 patients with mean LV ejection fraction of 24 ± 7%, 86 patients underwent "full revascularization" via either CABG or percutaneous coronary intervention (PCI), 12 underwent "incomplete PCI," and 46 were treated medically. The primary endpoint was all-cause mortality. The worst outcome was observed in patients with DE-CMR viability who were treated medically or with incomplete PCI, whereas the best survival rate was seen in those with completely revascularized viable myocardium. Patients with nonviable myocardium had intermediate survival rates, irrespective of their revascularization status. In patients with viability, medical therapy was associated with a 4.6-fold increased risk of death compared with those who were completely revascularized, whereas there was no significant difference in survival with medical therapy versus revascularization in patients without viability. The authors also performed further propensity score matching to try to minimize baseline group differences, which were significant and included more severe heart failure symptoms and lesser extents of myocardial viability in the medically treated/incompletely revascularized patients. The data support those of prior smaller, nonrandomized studies using nuclear and dobutamine echocardiography to assess viability, as summarized in a meta-analysis (2) but are incongruent with STICH and HEART. What factors account for the differences?

Although the present study is unique in that it is the only published outcome study using DE-CMR in which revascularization versus medical therapy was compared, and the authors should be commended for their perseverance and careful work, there are limitations with the study design. Selection bias is extremely difficult to overcome in a nonrandomized study, propensity matching analysis notwithstanding, particularly when the diagnostic study being assessed is bound to influence the clinician's choice of therapy. It is unclear what constituted medical therapy and how compliant patients were. This particularly applies to those treated with CABG in whom medical therapy *should* be optimized maximally post-operatively but may not always occur. Optimal "medical therapy" should also arguably include the implantation of cardiac resynchronization devices and implantable cardioverter-defibrillators (ICDs), which occurred at a surprisingly low rate in this cohort with severe ischemic LV dysfunction overall, with a possible bias against those with viable myocardium and those who were revascularized (rates of ICD

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implantation were: n = 5, 25% of the medically treated with nonviable myocardium, vs. n = 1, 4% of the medically treated with viable myocardium, vs. 0% in the revascularized group). Twelve (30%) of the cardiac deaths were sudden, and presumably arrhythmic. Patients who have undergone CABG or PCI, but do not sufficiently recover their LV function, remain at high risk for sudden cardiac death and thus, meet criteria for an ICD with or without cardiac resynchronization therapy placement, which affects mortality. There was also no confirmation of "full revascularization" versus "incomplete revascularization" in terms of actual perfusion at both the epicardial and myocardial level. Moreover, there was no follow-up CMR imaging reported in this study, which could have provided significant insight into pathophysiological mechanisms why revascularization is or is not beneficial in these patients. Were there perioperative ischemic events/infarctions or ischemia/infarction caused by subsequent graft occlusions that contributed to the worse outcome of the revascularized, nonviable patients? Is prognosis directly related to the extent of functional recovery? A prior publication by Gerber et al. (7) included a subset of 22 patients from the current cohort who underwent repeat DE-CMR 10 ± 7 months following complete revascularization, and global LV function improved from 25 ± 8% to 33 ± 10% (B. Gerber, personal communication), but the extent of functional recovery and its relationship to outcome is not known for the other treatment groups.

The pathophysiology of hibernation involves reduced myocardial blood flow, particularly to the subendocardium, and may be evident at rest but always manifests as reduced coronary flow reserve (8). Structural changes also occur, most prominently in dysfunctional regions but also in remote, normally contracting segments (8). These consist of reductions in microvessel density and cross-sectional area, depletion of myocyte contractile elements, and collagen replacement within the extracellular matrix, which may be of varying severity and reversibility and likely affect the success of revascularization (8). Because of its versatility, CMR has the potential to address many aspects of the pathophysiological response of the chronically ischemic, dysfunctional ventricle to revascularization. Transmural extent of DE assesses only 1 aspect of this complex process, that of scar/collagen replacement, and suffers from reduced diagnostic performance for predicting functional recovery when there is intermediate extents of transmurality (9,10). The ability of CMR to assess resting perfusion and coronary flow reserve, myocardial energetics, and quantitative regional wall motion using tissue tagging during rest and stress provocation (inotropic reserve) should be capitalized upon because there may be better predictive value in assessing multiple aspects of viability in a tiered approach rather than 1 component. In addition, a multipronged approach may lead to insights regarding the mechanisms behind the dissociation between functional recovery and improved outcomes that is often seen, that is, improved outcome *despite* lack of functional recovery that may in part be attributable to preservation of the infarct border zone integrity that leads to reductions in ventricular arrhythmogenesis (11).

As evident by STICH, HEART, and the current study, enrollment in these types of protocols is extremely difficult, and underenrollment will continue to be a significant concern for any future trials. Differences in baseline clinical characteristics will also be strong confounding factors in nonrandomized trials. To overcome some of these issues, in addition to clinical outcomes and mortality, it would be vital for future study designs to incorporate comprehensive imaging both at baseline and in follow-up to better understand and characterize the pathophysiological state of the myocardium before and after interventions with the goal of developing tailored therapeutic plans based on each individual's specific myocardial phenotype, which may require the assessment of a combination of factors that define viability (perfusion status and perfusion reserve, metabolism, scar extent and peri-infarct anatomy, and/or contractile reserve) in a tiered approach that remains to be defined.

Thus, rumors of its demise are greatly exaggerated: myocardial viability testing is alive and well, but we need to improve how we use it.

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