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Editorial

Biomarker Screening for Viable Myocardium in Ischemic Cardiomyopathy: Interesting… If Viability Is Important

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See article by Zelt et al., pages 1478–1488 of this issue.

Revascularization decisions in patients with ischemic cardiomyopathy (ICM) remain a commonly encountered but complex process in clinical cardiology. Many factors need to be considered including the extent of anginal symptoms, the presence or absence of myocardial viability, patient comorbidities, and previous revascularization. Clinicians frequently rely on advanced imaging modalities to assess the extent of inducible ischemia and myocardial viability. The goal of imaging is to detect the presence of viable or hibernating myocardium, defined as "a state of myocardial hypocontractility during chronic hypoperfusion which recovers functionally upon revascularization,"[1] and scar, which is irreversible and will not recover. Hibernating myocardium is associated with changes in left ventricular (LV) structure and function that might recover significantly after revascularization.[2] The adaptive molecular and genetic mechanisms that underlie the process of hibernation are intricate and particularly operate at the level of the mitochondrial membrane potential.[3]

Dobutamine stress echocardiography and single photon emission computed tomography nuclear scintigraphy are the most frequently used imaging modalities for determining myocardial viability worldwide because of widespread availability. However, contrast-enhanced magnetic resonance and positron emission tomography (PET) are considered the gold standards for viability assessment, defined by recovery of segmental contractile function, with positive predictive ability in the range of 73%-84%, and negative predictive ability in the range 90%-93%.[4] The major limitation of both modalities is limited access, particularly for PET.

PET imaging provides perfusion (with either ^{82}Rb or ^{13}N-ammonia) as well as myocardial metabolism (with ^{18}F-fluoro-2-deoxyglucose [FDG] PET). This enables the identification of the extent of ischemia as well as a geographic assessment of abnormal myocardial tissue that can be characterized as either scar or hibernating myocardium. Automated programs are now available that can provide reproducible measurements to quantify these parameters. On the basis of a threshold value of 10% hibernating myocardium, a survival benefit for revascularization was shown in a group of 648 patients with significant ICM (mean resting ejection fraction [EF] of 31%) compared with medical therapy in a nonrandomized study at the Cleveland Clinic.[5] The extent of ischemia was not predictive of a survival benefit with revascularization.

In the current issue of the *Canadian Journal of Cardiology*, Zelt and colleagues report a novel and interesting relationship between 2 cardiac biomarkers (N-terminal pro b-type natriuretic peptide [NT-proBNP] and high-sensitivity cardiac troponin T [Hs-cTnT]) and the extent of hibernating myocardium determined using ^{18}F-FDG PET imaging in 39 patients with clinical heart failure or severe LV systolic dysfunction (mean EF 28%).[6] Although the serum biomarkers were elevated above normal in the overall study group (median of 1997 pg/mL and 34 pg/mL for BNP and cTNT, respectively), there was a significant correlation of biomarkers levels with the extent of hibernating myocardium. The relationship between increased serum biomarkers and hibernating myocardium was particularly evident in the presence of $\geq$ 10% hibernating myocardium. A level of NT-proBNP $>$ 3066 pg/mL or hs-cTnT $>$ 66 was predictive of identifying patients with $\geq$ 10% hibernating myocardium. This relationship was independent of EF, age, and estimated glomerular filtration rate. In contrast, the extent of scar was unrelated to the serum biomarker levels.

These observations, although interesting, should be regarded as preliminary. The study was small with only 8 patients who actually met the criterion of moderate to severe hibernating myocardium (ie, $\geq$ 10%) and needs to be replicated in much larger sample sizes.

The underlying mechanism(s) relating hibernating myocardium to increased serum biomarkers are speculative at present and require further investigation. Prasad et al. have reported increased gene expression of BNP in hypocontractile compared with normally contracting myocardium in myocardial biopsies taken from patients before bypass

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surgery.[7] The adaptive mechanisms occurring in hibernating myocardium can progress over time, resulting in myocardial structural changes, cell death, and eventual replacement with fibrosis.[3] The expression of BNP and troponin within hibernating myocardium might be identifying earlier stages when the possibility for reversibility still exists. The potential that this window of opportunity for revascularization can be predicted by simple and readily available serum biomarkers is an exciting concept.

There could be some very interesting clinical consequences if the biomarker- hibernating myocardium relationship is deemed robust. First, serum biomarkers are inexpensive and if the levels are predictive of significant hibernation, this could be a useful screening (or 'gate-keeping') test to optimize use of a scarce resource, PET imaging. Second, future studies will need to address whether the serum biomarkers in conjunction with hibernation determination improve the selection of patients who will benefit from revascularization. Third, will the biomarkers change over time as a marker of hibernation or in response to revascularization? Finally, are both biomarkers necessary, or will other biomarkers be more predictive? The current observations from Zelt and colleagues[6] have opened a very intriguing new direction of research.

The ultimate question that remains unanswered is does revascularization of hibernating/viable myocardium actually matter? In other words, does identification of hibernating myocardium change meaningful clinical outcomes?

It should be emphasized that the randomized clinical trial evidence in support of the benefits of PET viability imaging to improve clinical outcomes in patients with ICM is still far from conclusive. The randomized Surgical Treatment for Ischemic Heart Failure (STICH) trial recently published 10-year data, which showed survival benefit of patients with dilated cardiomyopathy who were treated with surgical revascularization and medical therapy compared with medical therapy alone.[8] A viability substudy, however, did not show any benefit of viability testing.[9] This substudy was done with dobutamine echocardiography and single photon emission computed tomography perfusion imaging, both with lower sensitivity for detection of hibernating/viable myocardium than FDG PET. The patients were not randomized, and selection was on the basis of the discretion of the treating physician, who did not have to follow the imaging results. The patients were deemed suitable candidates for bypass surgery as a requirement for participating in the trial. In contrast, only one-third of patients underwent bypass surgery in the non-randomized viability study from Ling et al.[5]

The randomized controlled **P**ET **a**nd **R**ecovery Following **R**evascularization (PARR)-2 trial, which included authors from the current study, used PET imaging for viability assessment of patients with LV dysfunction. Revascularization decisions were on the basis of randomization of patients to a PET-FDG strategy vs standard care. There were no significant differences in patient outcomes at 1 year or at 5 years.[10,11] However, when the data were analyzed according to adherence to image-guided recommendations, there was a significant but modest benefit in patient outcomes with the PET-FDG strategy at 1 year and 5 years.[10,11] The importance of following the image-guided recommendations was further reinforced by the post hoc results at 1 site with an established clinical practice routine of integrating the PET-FDG imaging. The composite end point occurred in 19% of the PET-FDG group compared with 41% in the standard care group.[12]

Given the limitations of the current evidence, we are eagerly awaiting the results of the **I**maging **M**odalities to **A**ssist With **G**uiding and **E**valuation of Patients With **H**eart **F**ailure (IMAGE-HF): 1A trial, which compares downstream outcomes secondary to single photon emission computed tomography-, contrast-enhanced magnetic resonance-, and PET-determination of viability. If improvements in outcomes are observed, robust predictors of viable/hibernating myocardium will be important to identify.

Disclosures

The authors have no conflicts of interest to disclose.

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