Assessing Myocardial Ischemia and Viability: Is It Still a Relevant Question?

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Left ventricular (LV) function is a well-established and powerful predictor of poor outcome, especially when associated with the clinical syndrome of heart failure(1). Among patients with severe LV dysfunction, those with coronary artery disease (CAD) have the worse long-term outcome (2,3). A critical and relatively common clinical problem is the distinction between ischemic and non-ischemic cardiomyopathy, especially because of the limitations of coronary angiography (4). The etiology of heart failure has important implications for risk stratification (2, 3), and also impacts management decisions especially the possible need for revascularization, and the selection of pharmacologic therapies(5). However, the determination of heart failure etiology in an individual patient may be difficult even if obstructive CAD is present on angiography(4). Indeed, patients with HF and no angiographic CAD may have typical angina or regional wall motion abnormalities on noninvasive imaging, while patients with angiographically obstructive CAD may have no symptoms of angina or history of myocardial infarction (MI). Thus, the appropriate classification for any given patient is not always clear, and it often requires the complementary information of coronary angiography and non-invasive imaging.

The study by Aramayo and colleagues (6) in this issue of the journal provides important information about the potential complementary role of Positron Emission Tomography (PET) imaging for characterization of the extent of ischemia/viability in a relatively small cohort of patients (n=27) with severe LV dysfunction (mean LVEF: 29%) and angiographically demonstrated CAD. The study sought to describe the relationship between the degree of angiographic stenosis, myocardial blood flow, and the pattern of myocardial viability as defined by PET perfusion and metabolic imaging, which included the use of radiolabeled glucose (FDG). They described four different myocardial patterns of viability in these patients: 1) normal perfusion and glucose uptake, 2) concordant reduction in perfusion and glucose uptake reflecting non-viable myocardium (so-called PET match), 3) reduced perfusion with preserved glucose uptake reflecting hibernating myocardium (so-called PET mismatch), and 4) preserved perfusion with reduced glucose uptake reflecting primarily stunned myocardium (so-called reversed PET mismatch). As expected, they found no correlation between the degree of angiographic stenosis and rest myocardial blood flow. Indeed, it is well established that coronary autoregulation and collateral flow help maintain normal levels of tissue perfusion at rest even in the presence of critical luminal narrowing (7-9), which play a protective role against myocardial ischemia at rest. Although not addressed in this study, however, maximal flow and coronary flow reserve is often severely reduced in the setting of significant angiographic stenosis (>80%) and leads to myocardial ischemia and post-ischemic stunning(10). An important finding of the study was that the degree of angiographic stenosis was not associated with a consistent pattern of myocardial viability. For example, a PET match pattern was sometimes associated with mild angiographic CAD, while severe obstructive CAD was sometimes associated with PET mismatch. The study also has some limitations, including the relatively small number of patients, the lack of stress imaging to define the magnitude of myocardial ischemia, and the fact that its cross-sectional design without followup assessments after treatment limits its mechanistic insights. Nonetheless, these findings have important pathophysiologic and clinical implications. They highlight the complementary role of anatomic and functional information to help define the underlying etiology of myocardial dysfunction, which as discussed above helps inform clinical decision-making in this difficult group of patients.

One of the strengths of this study is the elegant and unique use of quantitative PET imaging to assess myocardial perfusion and metabolism. However, this imaging technique is not always accessible. Several other non-invasive imaging approaches are currently available to identify physiological markers of myocyte ischemia/viability in regions with systolic myocardial dysfunction. Indeed, imaging approaches targeting myocardial perfusion, contractile reserve, and/or direct assessment of myocardial scar have all demon-

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strated to be also effective in delineating the extent of ischemia, viability, and scarred myocardium(11). The process of selecting the "ideal" approach or approaches to ischemia/viability assessment in the individual patient is usually more complex than it first appears. First, one should be aware that the predictive accuracies of the various tests are profoundly influenced by the level of local expertise in the use of any of the available methods. Second, because there are no studies in large series of patients comparing these technologies, it remains unclear whether some patient subsets are better evaluated by a particular test or perhaps a combination of tests. Third, there appears to be a rather significant reduction in the accuracy of ischemia/viability testingfor predicting functional recovery in patients with severely depressed LV function (LVEF < 30%) regardless of the imaging modality(12). This is likely related to the fact that clinical predictions of functional recovery based on viability information alone are inadequate because they ignore the multifactorial influences affecting changes in LV function after revascularization (13,14).Indeed, it is now evident that other factors including the presence and magnitude of stress-induced ischemia, the stage of cellular degeneration within viable myocytes(15), the degree of LV remodeling(16,17), the timing and success of revascularization procedures(18), and the adequacy of the target coronary vessels can affect the functional outcome after revascularization. Consequently, because the probability of improvement in LV function after revascularization is multi-factorial, it is likely that relying on anyone of these indexes of tissue viability or its absence in isolation will lead to suboptimal clinical results. Thus, a combination of tests providing complementary insights regarding cellular viability may be beneficial for more accurate predictions of functional recovery.

The study by Aramayo and colleagues (6) together with that of many others before it provide clear demonstration about the power of noninvasive imaging approaches to provide detailed tissue characterization among patients with heart failure. There is consistent data from single-center, observational studies demonstrating that the presence of ischemic, viable myocardium among patients with severe LV dysfunction identifies patients at higher clinical risk, and that prompt revascularization in selected patients is associated with improved LV function(11), symptoms(19), and survival(20)as compared to medical therapy alone. More recently, the PARR-2 study demonstrated that image-guided decisions regarding revascularization can also help improve clinical outcomes following revascularization if treatment decisions adhere to imaging recommendations (21). Nonetheless, the main criticism of those studies is that they were retrospective and medical therapy did not reflect current accepted management of heart failure nor was it standardized in any way.

The results of the STICH trial (22), especially its ancillary viability(23) and ischemia(24)studies have challenged all prior data as they failed to demonstrate a significant interaction between ischemia or viability information, revascularization, and improved survival compared to optimal medical therapy. This casts significant uncertainty as to whether noninvasive characterization of ischemia, viability, and scar can actually provide useful information to guide management decisions.This issue is currently undergoing intense debate in the medical community (25,26). As we begin to incorporate the results of the STICH trial into our practice, it is important to consider the strengths and weaknesses of the STICH sub-studies.

The STICH viability and ischemia sub-studies are the largest reports to date relating myocardial viability and ischemia to clinical outcomes of patients with CAD and LV dysfunction associated with heart failure. They are also the firsts to assess these relationships prospectively among patients who were all eligible for CABG as well as optimal medical management alone. More importantly, medical therapy in the STICH trial was standardized and followed current published guidelines. However, these studies also have important limitations. First, viability data was only available in half and ischemia information in only a third of the STICH population, which is likely to introduce some selection bias. In fact, patients in the STICH viability study had higher prevalence of prior MI, lower frequency of limiting angina symptoms, lower LVEF, and more advanced LV remodeling as compared to those who did not receive viability imaging before randomization. Second, the definition of viability in STICH sub-study was quite broad resulting in 81% of the total study population being considered as having "viability" by study criteria. This number is quite different from that seen in other studies such as the Christmas trial (59%) (27), which used similar imaging modalities as the STICH trial. Third, neither PET nor MRI was used to evaluate ischemia or viability. An important additional consideration to understand the generalizability of the STICH sub-studies is that patients in the main trial in general, and those in the viability and ischemia studies in particular had end-stage LV remodeling. Indeed, the mean LV end-diastolic volume index (to body surface area) was greater than 120 m^L/m^2, and LV end-systolic volume index approached 100 m^L/m^2 (23). This degree of advanced LV remodeling has generally been associated with generally poor outcomes regardless of the presence of ischemia or viability and treatment applied(16,17). In summary, the STICH trial and its imaging sub-studies suggest that among patients with heart failure and end-stage LV remodelling, identification of moderate ischemia or viability is not associated with a significant survival advantage from revascularization. While the benefits of optimal medical therapy in patients with ischemic cardiomyopathy are undeniable, we cannot and should not generalize the STICH findings to patients with heart failure, severe systolic dysfunction, but mild-to-moderate LV remodelling, as these patients were not studied in the STICH trial.As

data from randomized clinical trials in such patients are limited, we should continue to carefully integrate clinical, anatomic, and functional information regarding ischemia and viability from non-invasive imaging as shown by Aramayo and others, and individualize this often difficult management decisions based on the best available evidence and sound clinical judgement.

Conflicts of interest:
None declared.

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