Clinical Value of F-18-Fluorodeoxyglucose Positron Emission Tomographic Imaging of Myocardial Viability Is Dependent on Adherence to Treatment Strategy Based on Imaging Results

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It has been 30 years since publication of the landmark article in the New England Journal of Medicine, by Tillisch et al, which reported improvement in regional wall motion after revascularization of dysfunctional myocardium that demonstrated viability by positron emission tomographic (PET) imaging. Viability was defined as a mismatch between myocardial blood flow and F-18-fluorodeoxyglucose (FDG) uptake, where resting flow was diminished in areas of enhanced FDG uptake. In contrast, regions of myocardium that showed a match between reduced blood flow and reduced FDG uptake were considered to have poor or no viability. There was no significant reversibility in wall motion abnormalities after revascularization in such nonviable segments. Since that report, a large number of observational studies and one randomized trial, using various noninvasive techniques, have been performed to assess the clinical value of viability imaging for decision making on which patients with ischemic cardiomyopathy would benefit most from revascularization versus medical therapy. Despite these many studies, controversy persists to this day as to whether viability imaging is useful for making such clinical decisions.

Observational studies have clearly shown that in addition to improved regional and global left ventricular (LV) function, revascularization in patients with ischemic cardiomyopathy and substantial viability in hibernating myocardium are associated with other improved outcomes, such as survival, reduction in heart failure symptoms, increased exercise tolerance, and reverse LV remodeling. In most of these studies, the greater the amount of hibernating myocardium, the better the outcome with revascularization. It seems from a published meta-analysis that the optimal threshold for amount of viability needed to improve survival with revascularization was calculated at 25.8% for PET-FDG and 38.7% for single-photon computed tomographic imaging. In a recent meta-analysis of nonrandomized studies comprising 4328 patients with coronary artery disease (CAD) and LV dysfunction, revascularization was associated with a significant mortality benefit compared with medical therapy in patients with viable myocardium. No mortality benefit with revascularization was seen in patients without viable myocardium. This meta-analysis confirmed a previous one by Allman et al, in which mortality was substantially higher in patients with viable myocardium treated medically compared with revascularization. It should also be pointed out that in these observational, nonrandomized studies, patients with predominantly nonviable myocardium had a higher mortality than patients with viable myocardium after surgical revascularization. This implies that medical therapy may be preferable to revascularization in patients with ischemic cardiomyopathy who have poor viability. Certain factors such as severe comorbidities (eg, severe renal dysfunction), frailty, poor target vessels for revascularization, marked remodeling with significantly reduced end-diastolic thickness, and severe secondary ischemic mitral regurgitation make revascularization less effective, even in the presence of viability. Bonow et al found that mortality was highest among ischemic cardiomyopathy patients with nonviability and a large end-systolic volume index (≥84 mL/m²).

Conversely, presence of inducible ischemia, in addition to hibernation, might result in a better outcome with revascularization than just the demonstration of presence of hibernation. The limitations of these nonrandomized observational studies have been well characterized. One limitation is that medical therapy for ischemic cardiomyopathy has markedly improved since many of these observational studies were published. Conversely, outcomes have improved with revascularization in clinically high-risk patients with ischemic cardiomyopathy.

PET-FDG imaging is the most sensitive (92%) of the noninvasive techniques for viability assessment. This noninvasive imaging technique was used for viability assessment in the study by Ling et al, who reported outcomes on 648 consecutive patients with a mean LV ejection fraction of 31% who underwent either revascularization or medical therapy. Because patients were not randomized, adjustment was made for possible confounders using Cox proportional hazards modeling, with propensity scoring to adjust for nonrandomized treatment allocation. All-cause mortality was reduced in the revascularization group, especially when the extent of viability exceeded 10% of the LV. With medical therapy alone, risk of death increased in proportion to the amount of viable myocardial segments. This study is perhaps the most robust one of the observational studies reported to date.
PET-FDG imaging was also used in the first prospective, randomized study to evaluate outcomes of a PET-assisted management strategy in patients with CAD and depressed LV function. This was the PARR-2 study (PET and Recovery Following Revascularization), which used a primary intention-to-treat analysis after 12 months of follow-up. Patients with CAD and a LV ejection fraction of ≤35% were randomized to undergo either PET-FDG viability imaging or to be managed without undergoing PET imaging. The physicians managing the patients who were randomized to a PET-FDG–assisted strategy were given a recommendation by the core laboratory based on the likelihood of LV functional recovery should revascularization be performed. The report to managing physicians described in detail the extent of viable and nonviable myocardium. Patients treated without a PET scan underwent standard care according to the discretion of their physicians, who made decisions on revascularization based on data not including PET imaging information. The results of the study revealed a trend toward improved outcomes in the PET-FDG cohort, which did not reach statistical significance. However, when the analysis was performed including only patients where there was adherence to the management recommendations based on PET-FDG findings, a significant improvement in the primary outcome was observed in the PET-FDG imaging–assisted group, compared with the standard-care group. The primary outcome was defined as the time to the composite event of cardiac death, myocardial infarction, or rehospitalization for cardiac causes.

In this issue of Circulation: Cardiovascular Imaging, Mc Ardle et al11 report the long-term follow-up of the PARR-2 patients randomized to either a PET-assisted management or standard care. Approximately 200 patients in each group were followed up for 5 years. Again, as seen at the 1-year follow-up, no difference in the primary outcome (time to composite event: cardiac death, infarction, or rehospitalization for cardiac causes) was seen at 5 years (hazard ratio, 0.82). Similar to the 1-year follow-up findings, when only patients who adhered to recommendations for treatment based on PET-FDG results were included, the hazard ratio for the time to the primary outcome was 0.73 (P=0.042). It should mentioned that >25% of patients in the PET-FDG arm did not adhere to the recommendations made after review of the imaging results; 84% of this subgroup had either medium or high levels of viability. An example of not adhering to recommendations based on PET-FDG imaging results would be referring a patient to medical therapy alone with high levels of myocardial viability in regions of severe regional dysfunction. Interestingly, in contrast to the results of the nonrandomized study of Ling et al9 described previously, no difference in mortality was observed between the PET-FDG and standard-care groups. The major contributor to the composite end point favoring the PET-FDG group was a decrease in rehospitalization for cardiac causes. The patients in the study by Ling et al9 were older and seemed to be sicker, with a higher prevalence of diabetes mellitus and previous coronary artery bypass graft (CABG) surgery. Another issue that might have impacted the results of the PARR-2 trial was that physicians taking care of patients in the standard-care group could proceed with alternate testing at their discretion. This presumably may have included non-PET viability testing. Results of such testing might have influenced decision making in which revascularization was performed based on extensive viability seen on the non-PET viability test (eg, single-photon computed tomographic imaging and dobutamine echo).

It should be mentioned that a post hoc substudy (Ottawa-FIVE) of the PARR-2 trial described the results in 111 patients in a center with vast PET experience and a history of integrating PET-FDG into clinical practice.12 As undertaken for the overall PARR-2 trial, patients in the Ottawa-FIVE substudy were randomized to the PET-FDG strategy or to a standard-care group. The results of this substudy showed that 41% of patients in the standard-care group experienced the composite end point. A significant benefit using Cox proportional hazards regression was seen for the PET-FDG group (hazard ratio, 0.34). This finding implies that when PET-FDG was optimally used in decision making, the outcome for those patients undergoing viability testing were better compared with management without the benefit of PET viability information.

No discussion about the value of viability imaging can transpire without mention of the results of the STICH trial (The Surgical Treatment for Ischemic Heart Failure), which showed that patients randomized to CABG plus medical therapy had a lower rate of death from cardiovascular causes, and the composite end point of death from any cause or hospitalization for cardiovascular causes, compared with patients randomized to medical therapy alone.13,14 No difference was seen with respect to the primary end point of death from any cause. A nonrandomized viability substudy was undertaken in 601 of the 1212 patients enrolled in the STICH trial.15 Neither PET-FDG nor cardiac magnetic resonance (CMR) imaging was performed in patients undergoing viability testing. Only single-photon computed tomographic imaging or dobutamine echo was used for assessment of viability in the STICH trial. This substudy did not show a significant interaction between presence of viability (in a binary fashion) and treatment assignment with respect to mortality. The limitations of the STICH viability substudy have been previously identified16. As mentioned, the substudy was not randomized, and the most sensitive viability test, PET-FDG, was not used in any patients. The results of the viability tests that were used were not blinded. Only 19% of the patients had nonviable myocardium. Fewer patients had previous CABG than in the previous observational studies. Only slightly more than one third of the patients had 3-vessel CAD.

Thus, clinicians contemplating using noninvasive viability imaging to make decisions on revascularization plus optimal medical therapy versus optimal medical therapy alone are faced with a dilemma. The PARR-2 trial10,11 is the only randomized viability trial published to date. The results of long-term 5-year follow-up of patients in this trial, reported in this issue of the journal,11 are similar to those of the initial study reporting the 12-month follow-up. A PET-FDG strategy did not significantly reduce cardiac events compared with standard care, except when there was adherence to treatment recommendations derived from PET-FDG results. The reduction in the composite event was driven by the reduction in hospitalizations for cardiac causes. While awaiting more definitive trials, it may be prudent to perform viability imaging, preferably with PET-FDG, in the highest risk patients with ischemic
cardiomyopathy. Patients with a very low LV ejection fraction, 3-vessel CAD with good target vessels for revascularization, and a large LV end-systolic volume with some ischemic mitral regurgitation may benefit from viability imaging. Those with extensive areas of hibernation (reduced wall motion with viable myocardium perfused by stenotic vessels) may have better outcomes with CABG, than with optimal medical therapy alone, as seen in the study by Ling et al.7 Ischemic cardiomyopathy patients with extensive myocardial zones of nonviability may be better candidates for optimal medical therapy including internal cardiac defibrillator implantation with or without cardiac resynchronization therapy. We showed many years ago that ischemic cardiomyopathy patients with poor viability had a markedly higher rate of cardiac death or transplantation after CABG than patients with good viability.17 In this prospective observational study, patients with preoperative poor viability and patients with good viability, as assessed by quantitative rest–redistribution thallium-201 scintigraphy, were similar with respect to age, comorbidities, resting LV ejection fraction, and extent of CAD.

In conclusion, this controversy as to whether viability imaging is clinically useful for decision making, in identifying those ischemic cardiomyopathy patients who are expected to benefit more from revascularization than medical therapy alone, is not yet definitively resolved by the findings of any of the previously published clinical trials. Evidence for the value of viability imaging will have to await the results of new trials, such as the AIMI-HF trial (Alternative Imaging Modalities in Ischemic Heart Failure).18 This trial is randomizing patients with likely CAD and LV dysfunction to single-photon computed tomographic imaging, PET, or CMR imaging for assessment of viability and ischemia. The long-term results of the PARR-2 trial17 give impetus to the conduction of such new trials to determine more precisely the role of viability imaging in this era of improved medical and device therapy for ischemic heart failure.

Disclosures
None.

References

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