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^{18}F-FDG PET and Myocardial Viability Assessment: Trials and Tribulations

In this issue of *The Journal of Nuclear Medicine,* Abraham et al. report a second post hoc analysis (*1*) of the PET and Recovery Following Revascularization (PARR 2) trial of ^{18}F-FDG PET–directed versus standard clinical management of patients with coronary artery disease and poor left ventricular (LV) function (*2*). The analysis, which they call the Ottawa-FIVE substudy, is based upon differences in ^{18}F-FDG PET availability, clinical practice, and experience at the participating centers in the study. The authors make some observations that may further explain the results obtained in PARR 2, describe some lessons learned, and raise possible directions for future studies in this area.

See page 567

LV systolic function is the most powerful long-term prognostic indicator in patients with coronary artery disease (*3*). Ischemic heart disease is the leading cause of LV dysfunction and heart failure (*4*). Myocardial viability testing can identify patients with ischemic heart disease and LV dysfunction who can potentially benefit from improved cardiac contractile function and prognosis after successful revascularization.

Since the initial report in 1986 of the clinical utility of ^{18}F-FDG PET for myocardial viability assessment in patients with ischemic heart disease and LV dysfunction (*5*), evidence has accumulated of the prognostic benefits of successful coronary revascularization in such patients who have viable myocardium demonstrated on cardiac imaging tests, including ^{18}F-FDG PET.

Improvements in symptoms, functional class, regional wall motion, and resting LV ejection fraction have been widely reported in these studies. Meta-analysis of such studies (*6*) has shown prognostic benefit with revascularization of such viable myocardium and conversely a poor prognosis if patients with demonstrated viability receive medical therapy alone. Further, in patients with LV dysfunction without demonstrated viability, revascularization does not appear to alter LV function or long-term outcome significantly, and such patients may have a more complicated postoperative recovery when revascularization is undertaken (*7*).

Since publication of these individual observational studies and metaanalyses, therapeutic options for patients with congestive heart failure have expanded. There have been significant advances in methods of revascularization and surgery for mitral regurgitation associated with LV dilation and in pharmacologic and device therapies. Understanding of the importance of LV remodeling and LV volumes in determining response to revascularization has also evolved.

Concomitantly with these advances, clinicians have called for investigators to go beyond the observational studies using viability testing and to perform randomized trials incorporating viability imaging as part of the work-up for revascularization and other management options in patients with LV dysfunction. The design, recruitment, and adherence to predetermined protocols in the clinical treatment of such patients are challenging, as the current report demonstrates.

^{18}F-FDG PET viability studies are performed with a blood flow tracer and ^{18}F-FDG as a marker of myocardial metabolic activity. ^{18}F-FDG PET can show 4 patterns of blood flow and metabolism in myocardial segments: normal; mildly reduced (matched pattern consistent with subendocardial scarring); severely reduced (matched pattern consistent with transmural scarring); or, uniquely, mismatched (reduced flow with preserved metabolism), which indicates viable myocardium capable of contractile recovery. Only ^{18}F-FDG PET shows this mismatch pattern, which can be associated with functional recovery even when other viability tests such as those of contractile reserve may be negative (*8*). This information is also different from that obtained by modalities that primarily identify myocardial scar tissue (*9*). This mismatch criterion is used in the Ottawa-FIVE analysis.

Ottawa-FIVE is a retrospective analysis of the PARR 2 trial. OTTAWA-5 was conducted on 111 patients at multiple Canadian centers to evaluate the utility of flow–metabolism mismatch on ^{18}F-FDG PET versus a standard (no PET) approach to direct patient management in the setting of advanced LV dysfunction and coronary artery disease. The standard approach could include a viability test other than ^{18}F-FDG PET, but this approach was not reported further. OTTAWA-5 was not powered for a hard endpoint, with only 6 deaths along with 4 myocardial infarctions and 22 readmissions for a total of 32 events. The overall event rate was 19% in the PET arm and 41% in the no-PET arm—a significant difference.

A study powered for mortality would require substantially higher numbers

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For correspondence or reprints contact: Kevin C. Allman, Royal Prince Alfred Hospital, Missenden Rd., Camperdown, NSW, Australia 2050.
E-mail: kevinca@med.usyd.edu.au

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of enrollments. Achieving these higher numbers is especially challenging in the current environment of numerous trials of medical and device therapies in patients with LV dysfunction—trials that frequently run parallel with viability or revascularization studies incorporating a number of different imaging modalities and that may compete with these studies for patient recruitment. Studies powered only for events such as readmission are unlikely to satisfy those clinicians who call for randomized controlled trials of viability imaging–directed management.

The primary result of the PARR 2 trial was negative, with some 25% of patients' management deviating from the ^{18}F-FDG PET–recommended option. In a post hoc subanalysis of the sickest patients, a trend toward benefit for ^{18}F-FDG PET–directed management was shown. The extent of serious comorbidities was high.

The ^{18}F-FDG PET arm included 56 patients. Of these, 19 showed an extensive mismatch, 21 a moderate mismatch, and 15 a small mismatch. Hence, most of the mismatches were moderate or extensive. Patients whose treatment deviated from the ^{18}F-FDG PET–based recommendation tended to have less extensive viability rather than more extensive viability, as demonstrated on ^{18}F-FDG PET imaging. This finding illustrates the importance of the extent of demonstrated mismatch in terms of predicting prognostic benefit, as was previously demonstrated (*10*) and confirmed by the PARR 2 group in its first post hoc analysis (*11*). As the PARR 2 and Ottawa-FIVE authors also point out, clinicians in less experienced centers may have been less inclined to recommend revascularization when imaging showed some but not extensive myocardial viability.

A number of other factors were identified that may have affected the results, and some of these are examined further in Ottawa-FIVE. For example, patients were recruited, investigated, and treated at a number of sites with varying levels of experience, expertise, and facilities. Outcomes from the central most experienced recruiting center (in Ottawa) are compared with those from the other participating centers, some of which did not have timely access to ^{18}F-FDG, performed relatively few ^{18}F-FDG PET viability studies, or were primarily PET oncology centers. Accordingly, participating centers differed in their levels of prior resources and clinical activity in viability imaging and subsequent decision making and management. Compared with patients in the other centers, patients in the Ottawa center, despite having slightly worse LV function and being older, fared better with ^{18}F-FDG PET–directed management than with no PET management. In addition, compared with some of the remote centers, the Ottawa center may have had more substantial preexisting experience and a more vertically integrated approach to investigation, communication between professionals, team decision making, and therapy.

The ^{18}F-FDG PET studies were not evaluated at a core laboratory. Such an approach, including central interpretation of test results and forwarding of a treatment recommendation to other centers, may have improved confidence in clinical decision making at the other centers.

Finally, the importance of gathering further prospective data on the clinical utility of ^{18}F-FDG PET remains. Achieving this goal will require creative and innovative approaches to study design, recruitment, protocol adherence, and data analysis. ^{18}F-FDG PET is the only imaging technique that can demonstrate the phenomenon of flow–metabolism mismatch rather than simply characterize tissue as scarred or presumably viable. We need to better understand the importance of this mismatch pattern and how its extent, in interaction with other clinical variables, informs therapeutic decisions and subsequently affects patient prognosis.

Patients with advanced LV dysfunction require the investigational and therapeutic benefits of large, well-resourced specialty units. Further well-designed prospective studies performed in such centers, with integrated multidisciplinary teams having expertise on both ^{18}F-FDG PET and heart failure management, are most likely to show the clinical utility of ^{18}F-FDG PET viability imaging that the Ottawa-FIVE investigators sought and clinicians continue to seek.

Kevin C. Allman
Royal Prince Alfred Hospital
University of Sydney
Sydney, Australia

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