SPECT Myocardial Perfusion Imaging: Poststress, End Systolic Images and the Ongoing Effort to Improve Diagnostic Accuracy

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It is fair to state that interpretation of SPECT myocardial perfusion images, as with most scintigraphic studies, reflects a mixture of art and science. Increasingly, efforts have been, and are being, made to improve the diagnostic accuracy of SPECT myocardial perfusion imaging (MPI) by enhancing image quality while at the same time reducing radiation burden, via the scientific, technologic approach. Examples include the introduction of solid-state cadmium zinc telluride detectors, cardiac-optimized collimation, and improved image reconstruction software designed to mitigate factors such a patient motion, photon scatter, and tissue attenuation as well as spatial resolution and partial-volume effect (*1,2*). Although these image-quality issues are much more pronounced in SPECT than in PET, PET is not immune. However, given the fundamental physics involved, PET imaging is better able to correct such errors, a fact previously noted by this group (*3*) and many others (*4–6*). It also has been appreciated for some time that apparent tracer distribution in single-photon myocardial perfusion

See page 1882

images, whether planar (*7*) or SPECT (*8*), may be altered by factors such a left ventricular volume and regional contraction independent of the true distribution of tracer in the myocardium (*7,8*). Thus, increases in both left ventricular volume and regional contractile abnormality, especially apical akinesis or dyskinesis, have been shown to result in apparent perfusion defects despite the absence of true perfusion abnormality (*7,8*). In this issue of *The Journal of Nuclear Medicine,* Kitkungvan et al. (*9*) have in essence turned the partial-volume effect to the scan interpreters' advantage by demonstrating a simple method for improving diagnostic accuracy of SPECT myocardial perfusion images with mild, borderline uptake defects. Such defects usually present the most problems in determining whether the image is abnormal. In contrast, accuracy in interpretation of more prominent defects was not improved by reference to the gated, end systolic image.

WHAT TO LOOK FOR

In reviewing the article by Kitkungvan et al., there are several issues to be aware of. The authors recognize certain limitations related to the retrospective nature of the work, including unidentified confounders and referral bias. They indicated they could not compensate for the latter but argued it did not materially affect the results of their study because the false-positive rate for whole-cycle (i.e., ungated) images was comparable to that reported by others (*10*). They also were well aware of the limitations of using visually interpreted coronary angiograms (≥70% stenosis standard for abnormal) as the gold standard for the study but indicated they did so, again, to conform with real-world clinical practice. Thus, angiograms with visually moderate stenosis less than 70% would be classed as normal, a substantial problem of which the authors, who invented fractional flow reserve (*11*), are well aware but again apparently accepted for the purposes of the current paper to conform with standard clinical practice.

The authors indicated that both gated and ungated images were acquired in routine clinical fashion per American Society of Nuclear Cardiology guidelines. Thus, acquisition duration apparently was not increased beyond recommended duration to improve end systolic image quality. Further, no mention is made of how many cases had to be rejected for inadequate end systolic image quality due to arrhythmias such as atrial fibrillation or frequent ventricular ectopic activity. End systolic image quality also may be suboptimal in obese patients and others with prominent soft-tissue attenuation. So clearly, the method will not work for all patients but certainly is worth looking at because the data are gathered in any case.

As noted above and shown in Figure 4 of the article, the gated end systolic scan reduced the false-positive rate, thereby increasing the true-negatives, all as judged against the coronary angiogram, and so in turn enhanced diagnostic accuracy. The effect was confined to borderline defects and made no difference in interpretation of images with prominent perfusion abnormalities. The true-positive and false-negative rates were unchanged by use of the end systolic image, an observation largely preordained given the experimental design (scan vs. invasive coronary angiogram [ICA; gold standard]) and issue of referral bias for ICA.

Figure 1 of the article is of interest because it demonstrates how cardiac motion itself will contribute to the partial-volume effect and potentially create the impression of an inferior wall or apical defect—a point worth remembering because such motion is not captured by standard patient motion algorithms.

Likewise, Figure 2 is noteworthy because it displays what might be taken as an anterior wall defect in a mid-short-axis section (Fig. 2A)

of the conventional image from a patient with normal coronary artery. However, the septal segment is clearly normal. Accordingly, given an intact native coronary circulation without coronary artery bypass graft surgery, the left anterior descending artery runs to the left ventricular apex in many cases, supplies the interventricular septum (anterior two thirds), and so is extremely unlikely to have a lesion ($\geq 70\%$ stenosis) in its proximal or even mid one third, which would limit flow to an isolated segment of anterior wall while sparing the septum and apex. Thus, one should be extremely circumspect in reading such apparent defects as true perfusion abnormalities. Artifact is far more likely and in the case shown with an opposite 180° defect on the inferior wall (Fig. 2B), patient motion must be carefully considered.

OPPORTUNITIES FOR IMPROVEMENT AND FUTURE DIRECTIONS

Opportunities for improvements and future directions in MPI clearly rest in an area that the senior author of the present paper has been a leader in for more than 35 y (12) and that even appears in the title of the current article, namely PET. Readers of the *Journal* are well aware of the widespread availability of the scanners and the relative ease of obtaining and using ^{18}F-FDG for clinical oncology as well as other indications. Although [82]Rb generators have made PET MPI feasible in many of the health care settings that lack on-site cyclotron capability, a variety of issues both with the [82]Sr generator and with the tracer itself have hampered widespread use. Administrative considerations related to cost, reimbursement, and organizational structure also have been, and in many cases continue to be, important barriers. In almost all centers with on-site cyclotron capability, ^{13}N-ammonia or ^{15}O-water is used instead.

Hopefully, help is on the way. An ^{18}F-labeled tracer, flurpiridaz (13–15), is currently in phase 3 clinical trials. What is truly attractive about the tracer is its potential for use in making quantitative measurements of absolute myocardial blood flow (13,15), which is the future of MPI, as reviewed in a recent state-of-the-art paper by the senior author of the current publication along with a substantial number of leaders in the field (16). Results of a phase 3 clinical trial were reported (invited presentation) at the International Conference on Nuclear Cardiology and Cardiac CT meeting in Madrid in May 2015 (17). This trial compared the diagnostic accuracy of PET ^{18}F-flurpiridaz with SPECT ^{99m}Tc-methoxyisobutylisonitrile MPI for the detection of anatomically significant coronary artery disease (assessed by ICA). Quantitative measurements of absolute myocardial blood flow were not used nor was coronary stenosis severity assessed physiologically. Nonetheless, area-under-the-curve analysis of the diagnostic accuracy data demonstrated statistically significant, superior results with ^{18}F-flurpiridaz versus SPECT ^{99m}Tc-methoxyisobutylisonitrile. It was also reported that the accuracy of ^{18}F-flurpiridaz was superior to that of ^{99m}Tc-methoxyisobutylisonitrile in selected patient populations, which may be more difficult to image with SPECT, such as those who are obese (body mass index ≥ 30), women, and those with multivessel coronary artery disease. Thus, although the initial phase 3 study is encouraging, one would hope that in the future a physiologic investigation would be embarked on in which quantitative measurements of absolute myocardial blood flow with ^{18}F-flurpiridaz were used to assess coronary stenosis severity. Clinical

outcomes based on those assessments would be determined to test the hypothesis that the PET quantitative myocardial blood flow approach is superior to that of anatomic ICA (or coronary computed tomographic angiography)-based decision making regarding coronary revascularization outcomes (15).

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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