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EDITORIAL

What Should We Expect from Cardiac PET?

As cardiac positron emission tomography (PET) matures into the clinical arena and the modality attains widespread use, it is essential that the process of image interpretation not be limited to those with years of PET experience. At first glance by the inexperienced observer, PET cardiac images appear a lot simpler to interpret than single-photon emission computed tomography (SPECT) studies. After all, for years we have been reminded of the advantages of cardiac PET over SPECT, i.e., higher spatial resolution, attenuation correction, hardly any imaging artifact compared to those reported for SPECT (*1*), in short, images that are truly quantitative. Thus, our expectations might be that PET perfusion images from normal patients are homogeneous and that any inhomogeneity, no matter how small, may be safely interpreted as a perfusion defect. Moreover, upon learning this simple rule, we are safe to correlate these PET perfusion studies against the "gold standard," coronary arteriography, and that we should expect the nearly perfect accuracy reported by some investigators (*2,3*).

For those making the transition from cardiac SPECT to PET, it is important to understand that much of the experience gained in SPECT is transferable to PET, but nevertheless, there is another set of rules that needs to be learned for this new modality. It is desirable that tools be developed that assist the PET neophyte in interpreting these studies and that these tools resemble those used in SPECT. Previously, Hicks et al. (*4*) reported on the use of polar maps to quantify paired cardiac PET studies to analyze size of perfusion defect, intensity, statistical significance of and changes in perfusion or metabolism, including comparison to a normal database. This methodology also included comparison of stress-stress images to evaluate progression/regression of stenosis, early and late resting rubidium images for determining myocardial viability based on ^{82}Rb washout kinetics and perfusion-metabolic comparisons for quantifying ischemia, viability and necrosis after acute myocardial infarction.

In this issue of the *Journal*, Laubenbacher et al. report on another automated polar map analysis program, this time for the evaluation of cardiac ^{13}N-ammonia perfusion PET studies (*5*). As with other similar techniques reported for SPECT (*6–8*), one of the main expectations of this approach is to increase the objectivity of the interpretation and to reduce interobserver and intraobserver variability, two attributes particularly helpful to the PET neophyte. Their approach features several technical advancements, including a three-dimensional sampling and surface display of myocardial activity similar to more recent SPECT approaches (*9,10*) but without the need to generate oblique angle images. The approach reported by Laubenbacher et al. (*5*) uses a normal

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For correspondence or reprints contact: Ernest V. Garcia, PhD, PET Center, Emory University School of Medicine, 1364 Clifton Rd., NE, Atlanta, GA 30322.

database generated from patients with a low likelihood of disease and criteria for abnormality developed using ROC analysis to best separate normals from abnormals, which are similar to techniques used in SPECT quantification (*11*). In contrast to the report by Hicks et al. (*4*) who did not perform neither an analysis of the normal myocardial perfusion distribution of ^{82}Rb or ^{13}N-ammonia nor a correlation with coronary arteriography, the report by Laubenbacher et al. provides more details in these areas.

One fair question of these sophisticated quantification and imaging techniques applied to coronary artery disease (CAD) is: Do their results meet our expectations? In contrast to gender-specific differences in bull's-eye displays reported in SPECT imaging (*12*), Laubenbacher et al. report no statistically significant difference in tracer distribution dependent on gender in patients with a low likelihood of CAD. This result is expected due to the fact that attenuation correction should eliminate most of the counting differences due to body habitus. However, a definitive statement that there are no gender-specific differences in normal ^{13}N-ammonia myocardial distribution should await a statistical comparison of much larger normal patient populations. Laubenbacher et al. also suggest that a mean normal tracer distribution throughout the left ventricle is homogenous.

Nevertheless, their reported values for mean normal tracer distribution ranges from 66% to 85% (a 78% variation) as well as a significant statistical difference between the distal lateral wall and a somewhat hotter distal septum and inferior distal walls. They also report differences in relative tracer activity between the proximal and distal walls. There are a number of technical factors, most of which they point out, that may account for these differences. Among these are: ungated acquisition blurring the myocardial wall, the relationship between the size of the myocardial wall and the spatial resolution of the system, limited scatter correction and not enough patients in the normal database. Laubenbacher et al. point out that these regional differences in normal tracer distribution are not observed in other reports on ^{15}O and ^{82}Rb PET studies with similar technical limitations and thus are not due to PET imaging. Nevertheless, we are not aware of published reports on ^{15}O and ^{82}Rb where normal myocardial distributions were quantitatively determined and statistically analyzed.

Of course, it is also possible that the hypothesis stated by Laubenbacher et al., that there is a real regional variation in the normal myocardial distribution of ^{13}N-ammonia, is correct, as has been suggested for the heterogeneity of normal myocardial ^{18}F-deoxyglucose distribution (*13,14*). Importantly, the large lateral/septal wall count inhomogeneity and the large decrease of counts in the inferior wall (in males) observed in SPECT ^{201}Tl (*12*) and (somewhat less) in ^{99m}Tc-sestamibi studies (*11*) due to the lack of attenuation compensation is not present in normal myocardial ^{13}N-ammonia distribution, which does make these PET perfusion studies easier to interpret visually. Thus, these normal PET tracer distributions are more homogeneous than those reported for SPECT (*12*), but there is still some degree of heterogeneity that quantitative comparison to a normal database can help interpret.

Does their accuracy for detecting CAD meet our expectations? It should be pointed out that the authors warn that definite diagnostic accuracy requires a prospective multicenter trial in a larger patient population employing their normal database and the abnormality criteria that they established. Nevertheless, it is a misnomer to call their findings "the accuracy of their technique" when the method was never tested prospectively by them, not even in a small, in-house validation. When the thresholds for detecting disease are allowed to vary in order to find the best cut-off points that separate normals from abnormals, those findings are better called agreements with the gold standard rather than the accuracy of the technique. This is because one would expect the best possible results when the same population that is used to develop the criteria for abnormality is used to test that criteria. Yet, their best agreements with angiography, using a very small population of 29 patients [13–16 patients had CAD (depending on the criteria)], was 85% for detecting the presence or absence of CAD and 91%, 79% and 88% for localizing disease to the LAD, LCx, and RCA vascular territories respectively.

These results were obtained by mixing the normal limit comparison of different polar maps (stress, ratio {rest/stress} and difference {rest-stress}) as independent mechanisms for detecting and localizing CAD. Perhaps better, or at least more comprehensive results could have been obtained had all this information been fused together. Moreover, the patients in the normal database were not age-matched to the study population, and adenosine was used to stress the reference group, whereas 35% (12/34) of the study group were stressed with dipyridamole. Although these results are favorable when compared to myocardial perfusion SPECT, they fall short of perfection. But should we expect PET to be close to perfect? First, ^{13}N-ammonia PET and coronary arteriography measure two different things, i.e., myocardial perfusion versus vessel anatomy. Even if both techniques measured the same exact parameter of vessel anatomy, it is well documented that the interobserver agreement of coronary arteriography is far from perfect (*15,16*).

Even though Laubenbacher et al. used quantitative assessment of one angiographic view to evaluate the quantification of myocardial perfusion, there is still angiographer subjectivity in selecting the projection angle as well as which frame to quantify. Moreover, even if the quantitative method used is well validated, the original developers point out that two orthogonal views are often required for accurate quantification of stenoses (*17*) rather than the one view used by Laubenbacher et al. One would have to question how a perfusion modality could be expected to agree with a ves-

sel anatomy modality better than the gold standard can agree with itself. The accuracy of the method also depends on the prevalence of disease in the population being tested. Comparing the accuracy of a new technique to that reported for an old technique is like trying to hit a moving target. In today's environment of containing health care costs, patients who are easy to diagnose because of very high or very low pretest likelihoods of disease hardly ever reach a PET facility. The patients we are more likely to find, and correctly so, are those with close to a 50% pretest likelihood of disease, a 40%–60% stenosis as determined from a previous coronary arteriogram or those with previous multiple PTCAs and CABGs. One could always try to find and use the easy patients to show superior results for any technique, but the results reported would in no way predict what other users would expect using the technique in their more complicated populations. It is not rational to expect a technique that uses this complicated test population to be perfect. Moreover, it needs to be technically superior in order to be even slightly better than techniques validated 5–10 yr ago. Clearly, if the purpose of a study is to prove that a new technique is better than a previously established technique, the approach should be to perform a prospective validation using a large patient population in which patients undergo both studies in a random fashion and are then compared to the same gold standard.

As with myocardial SPECT, Laubenbacher et al. point out that there is a role not only for polar map representation but also for comparison to a normal database. They have provided us with the realization that at least for PET ^{13}N-ammonia myocardial perfusion imaging one should not expect perfectly homogenous myocardial distributions in normals or perfect agreement with angiography, but rather improvements over SPECT imaging. Laubenbacher et al. have helped provide us with familiar tools to assist those learning to interpret cardiac PET studies which should promote the widespread clinical utilization of this important imaging modality.

Ernest V. Garcia
Robert L. Eisner
Randolph E. Patterson
Emory University School of Medicine
Atlanta, Georgia

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