EDITORIAL
Planar, SPECT, PET: The Quest to Predict the Unpredictable?

In this issue of *The Journal of Nuclear Medicine*, Go et al. (*1*) report on the results of a comparison between two radionuclide imaging modalities for assessment of myocardial perfusion: positron emission tomography (PET) and single-photon emission computed tomography (SPECT). The prolonged coronary vasodilatory effect of intravenous dipyridamole made it possible to assess almost simultaneously regional myocardial perfusion with both rubidium-82 (^{82}Rb), a short-lived positron emitter, *and* with thallium-201 (^{201}Tl), a relatively long-lived single-photon emitter. Employing identical computer display, the variables involved in the interpretation were reduced to those of the radioisotopes and of the acquisition and reconstruction techniques. Rubidium-82 PET imaging was shown to have a substantially higher sensitivity and predictive accuracy (93% and 90%, respectively) for detection of coronary artery disease than ^{201}Tl SPECT imaging (76% and 77%, respectively). On the other hand, the specificity of both techniques was similar (78% and 80%). Recently, Stewart et al. (*2*) in a somewhat less rigorous comparative protocol demonstrated the reverse: a comparable sensitivity and predictive accuracy for ^{82}Rb PET and ^{201}Tl SPECT, however, significantly improved *specificity* for ^{82}Rb PET imaging in comparison to ^{201}Tl SPECT (80% versus 57%). This improved specificity was presumably achieved by significant reduction of SPECT artifacts with PET imaging. Both studies suggest, however, a modest superiority of PET imaging over SPECT imaging for *detection* of coronary artery disease.

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TO DETECT MORE AND MORE CORONARY LESIONS?

It seems appropriate to reflect on these findings and their potential clinical significance. There is a general perception that more complex imaging techniques provide more accurate diagnostic information. SPECT imaging has been reported to be an improvement over planar thallium imaging (*3–7*); PET now appears to be better than SPECT (*1*, *2*). Do the results by Go et al. (*1*) necessarily imply that *the* optimal modality for imaging myocardial perfusion is PET? Certainly, a significant number of mild-to-moderately severe coronary artery stenoses are missed by presently available conventional imaging techniques. Should it be the ultimate goal of myocardial perfusion imaging to detect *all* coronary artery lesions? Even those that generally are not considered to be of hemodynamic significance, i.e., <50% luminal narrowing? The experience over the last several years has shown that once lesions are visualized on a coronary angiogram (and abnormal perfusion imaging tends to lead to coronary angiography), it is difficult to practice restraint and to defer revascularization procedures. The subsequent proliferation of interventions, driven by improved imaging technology, would have considerable impact on the cost of health care. On the other hand, the soundness of such revascularization procedures should be questioned. Coronary bypass grafting of subcritical coronary lesions may lead to early graft closure. Angioplasty is in principle a procedure that traumatizes the coronary intima. This is a justified risk in vessels with severe disease. However, it is conceivable that in mild-to-moderate coronary lesions the procedure may cause more harm than good and may initiate an undesirable cascade of events and interventions.

IDENTIFICATION OF THE HIGH-RISK PATIENT

During the last decade of myocardial perfusion imaging, it has been recognized that not merely the *detection* of the disease, but the recognition of patients at *high risk* is of importance. Numerous investigators have demonstrated the prognostic value of abnormal and normal planar ^{201}Tl images. Poor prognostic indicators are the extent and severity of myocardial perfusion defects, the magnitude of defect reversibility, the presence of increased ^{201}Tl lung uptake, and transient left ventricular dilatation (*8–12*). On the other hand, totally normal planar ^{201}Tl images are associated with excellent prognosis, irrespective of anatomy (*13–15*). Thallium-201 SPECT imaging in now widely used for clinical imaging. Although no comparable data on prognostic significance of the extent of SPECT perfusion abnormalities have been reported (except for prediction of restenosis after PTCA), it is reasonable to assume that similar information can be derived employing this technique. An appropriate question to ask is whether abnormalities that are missed by present state-of-the-art conventional imaging techniques are of critical *clinical significance*. It is not clear whether the improved sensitivity by PET as reported by Go et al. (*1*) is of clinical significance for patient manage-

ment. Perhaps it is preferable for patient management to employ a technique that is not *too* sensitive and does not detect *all* coronary artery disease. Such an imperfect imaging technique would function as a coarse clinical filter to separate high-risk patients from low-risk patients. It appears that the goal of clinical exercise imaging should be to identify those patients, in whom revascularization would make a significant difference in clinical outcome and survival.

STABLE CHRONIC STENOSIS VERSUS PLAQUE INSTABILITY

Perfusion imaging after exercise or after pharmacologic stress only provides a *one time "snapshot"* of the ability of the coronary vasculature to meet increased demands: The hemodynamic significance of luminal obstruction and coronary reserve is tested. Over the last several years it has become evident, that coronary artery disease is a dynamic process that may change gradually or acutely. For instance, an apparent insignificant luminal narrowing of, for example, 30% may change acutely by either plaque fissure, hemorrhage, or massive deposition of platelets into an occlusive lesion and result in unstable angina or acute myocardial infarction (*16–23*). Serial coronary angiography has shown that the site of acute changes in coronary morphology cannot be well predicted from the severity of coronary stenosis on preceding coronary angiograms (*24*). Considering these apparently unpredictable changes, it is not surprising that the demonstrated predictive value of exercise thallium imaging (which only tests hemodynamic significance of a lesion at that time) is by no means perfectly accurate. The future challenge for radionuclide testing is in designing diagnostic procedures that detect indicators for "plaque instability." Recently, we demonstrated evidence of silent left ventricular dysfunction during routine daily activities in patients who had undergone thrombolytic therapy for acute myocardial infarction (*25*). Employing ambulatory left ventricular function monitoring, spontaneous and often asymptomatic dramatic decreases in left ventricular contraction were detected. These spontaneous episodes of apparent *silent myocardial ischemia* were highly predictive of subsequent coronary events. Of note was that in this selected group of patients, pre-discharge submaximal ^{201}Tl and radionuclide exercise ventriculography were not predictive of coronary events.

Since there was no evidence of an increased metabolic demand, and blood pressure or heart rate remained unchanged during the decrease in left ventricular ejection fraction, a potential pathophysiologic explanation of these findings appears to be a spontaneous decrease in coronary blood *supply*. It is conceivable that this transient vasoreactivity could be an indication of "plaque instability" and could be the missing piece of the puzzle in predicting outcome in coronary artery disease.

The quest for improved sensitivity in detecting *fixed coronary stenosis* by better imaging technology is important. However, it addresses only *one aspect* of coronary artery disease. We would propose that it may be equally important to explore methods for detecting indicators of *plaque instability*, and, thus, predict the apparent unpredictable. In addition to monitoring the effect of plaque instability on left ventricular function, future imaging techniques will be aimed at direct visualization of atherosclerotic plaques (*26*) or sites of platelets activation (*27*).

THE UNIQUENESS OF PET

PET technology is an exciting advancement in cardiac imaging and will complement the more conventional imaging techniques. The comparative studies by Go et al. (*1*) and others (*2*) demonstrate that with optimal imaging techniques it is possible to avoid artifacts that haunt ^{201}Tl SPECT imaging. PET has an important role in showing the way and direction for conventional imaging techniques. The recent modification of ^{201}Tl imaging protocols is an example of cross-fertilization by PET (*28, 29*). When the limitations of conventional exercise/2-3-hr delayed ^{201}Tl imaging for complete visualization of viable myocardium were recognized (*30, 31*), PET provided a benchmark for differentiation between viable and infarcted tissue (*32*). This stimulated the development of alternative imaging protocols, employing resting thallium injection or late redistribution imaging, to extract the same information with regard to myocardial viability using conventional imaging techniques (*33*).

PET imaging will have an important place in cardiovascular nuclear medicine. However, the improved detection of coronary artery stenosis in comparison to conventional imaging techniques should not constitute the major thrust of the technique. The significance and uniqueness of PET cardiovascular imaging is its ability to probe noninvasively *myocardial metabolism* and provide new insights and answers to important clinical questions concerning ischemic and cardiomyopathic heart disease. The lessons to be learned from future PET research will have to be translated into new or alternative imaging modalities, utilizing *conventional* (and less expensive) imaging techniques, with an aim toward deriving the same or similar information useful for clinical management of patients.

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