Current Status and Future Directions in Nuclear Cardiology

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HISTORICAL PERSPECTIVES

Although radionuclides were used to image the heart before 1970, their uses were restricted to measuring transit times and blood volumes and to evaluating patients for pericardial effusion before cardiac ultrasound came into widespread use. The field began about 25 years ago following the publication of two seminal papers describing stress perfusion imaging and gated blood pool scintigraphy (*1,2*). Strauss and Zaret, working together at the Travis Air Force Base in California in 1972, injected ^{42}K intravenously into patients during treadmill exercise and imaged with an Anger camera. The first images appear of poor quality compared to present day images, but they demonstrated that myocardial perfusion could be imaged in man at rest and at peak exercise using an intravenously injected radiotracer. A noninvasive test to assess the distribution of myocardial blood flow had the potential to become a widely applicable test. This potential has certainly been realized. In 1993, approximately 700,000 nuclear cardiology procedures were performed in the U.S., based on Medicare billing alone (*3*).

Following this initial work with ^{42}K, it was immediately recognized that ^{201}Tl, a cyclotron-produced potassium analog, yielded better images. In the early days of thallium imaging, two injections of thallium were made, one at rest and the second at peak treadmill stress. The two parts of the test were separated by at least one day. The phenomenon of thallium redistribution was first observed by Pohost while working at the Massachusetts General Hospital. In the early days of the technology, the scintillation cameras were usually located at considerable distances from the treadmills, resulting in considerable time lapses between injection and imaging. Pohost observed that the sensitivity of the technique to detect ischemic perfusion defects was reduced when more time elapsed between injection and imaging. He pursued this observation which led to the body of work describing the major component of thallium redistribution which is differential washout. Thallium washes out more slowly from ischemic than from nonischemic myocardium (*4*). Although re-uptake of thallium into the defect from residual blood pool activity was suspected to contribute to redistribution, this concept was more recently supported by the work of Dilsizian and colleagues from the NIH who demonstrated that thallium defects that appear to be unchanged on delayed imaging, show further fill-in when thallium blood activity is boosted by thallium reinjection (*5*).

The first published paper on gated blood pool imaging represented the first description of a noninvasive method to look at global and regional ventricular function. Prior to this time, similar information could only be obtained during cardiac catheterization. In the first paper describing the techniques of gated blood pool scanning, only end-diastolic and end-systolic frames were represented (*2*). Very rapidly the technology developed for multi-gated acquisitions, yielding up to 30 or 40 frames per cardiac cycle, allowing sufficient temporal resolution to evaluate the entire cardiac cycle. At about the same time Jones pioneered the technology of first pass radionuclide angiography using a multicrystal scintillation camera (*6*).

The use of vasodilators as pharmacologic stress agents began with the work of Gould who described the use of intravenous dipyridamole to measure coronary flow reserve noninvasively (*7*). The first clinical work performed in large patient groups was reported by Leppo (*8*). The FDA approval of intravenous dipyridamole in 1991 was a major step in establishing this type of testing. Prior to clinical availability of intravenous dipyridamole, it was necessary to grind up dipyridamole tablets with a mortar, suspend the red powder in juice and ask the patient to swallow the unpalatable mixture. Variable gastric absorbtion produced unreliable blood levels of dipyridamole.

Pioneers in the field of tomography of the heart include Ritchie who published the first technical papers and Berman and his group at Cedars-Sinai who can be credited with fully

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developing SPECT imaging of the heart (*9,10*). In addition to developing quantitative techniques for assessing tracer uptake, their group was the first to describe many of the aspects of SPECT imaging which we now perform routinely.

In a brief 25 years, nuclear cardiology has grown from an embryonic to a fully mature field. It continues to be the only widely available technology which can measure coronary flow distribution noninvasively and therefore has very wide application in the diagnosis and management of patients with coronary heart disease.

CURRENT ISSUES

Myocardial Perfusion Imaging as a Diagnostic Tool

Stress myocardial perfusion imaging, with ^{201}Tl or with one of the newer ^{99m}Tc-based agents, has been shown to be a powerful noninvasive modality for diagnosing coronary artery disease. Although exercise stress testing with the electrocardiogram alone can be helpful in detecting disease, with a reported mean sensitivity of 68% and a mean specificity of 77% (by meta-analysis of 147 published reports involving 24,074 patients) this technique has significant limitations (*11*). Even in situations in which the electrocardiogram accurately assesses the presence of stress induced ischemia, the test is poor at determining both the location and severity of disease (*12*).

Stress radionuclide myocardial perfusion imaging provides superior diagnostic accuracy over the electrocardiogram alone. In a report of pooled data from 33 published studies of qualitative assessment of planar ^{201}Tl imaging, Kotler and Diamond reported a sensitivity of 84% and a specificity of 87% (*13,14*). Diagnostic accuracy is enhanced by quantitative analysis of planar images, with a reported average sensitivity of 91% and a specificity of 89% (*15*). Imaging with single-photon emission computed tomography (SPECT) has been shown to improve the diagnostic accuracy of stress radionuclide myocardial perfusion scintigraphy, affording better lesion contrast than planar techniques and decreasing, although not eliminating, spatial overlap of myocardial regions. In a study of 136 patients undergoing both planar and tomographic imaging, Fintel et al. demonstrated that SPECT was more accurate than planar imaging for the overall detection of coronary artery disease, and for the specific detection of disease in the left anterior descending and left circumflex coronary arteries (*16*). Tomographic imaging was found to be particularly advantageous in men and in patients with milder forms of coronary artery disease. Of extreme importance in clinical decision-making, SPECT was shown in this study and others to be superior to planar imaging in identifying multivessel coronary artery disease (*17–19*). Overall, the sensitivity for the detection of coronary disease with SPECT is about 96%, while the specificity is about 83% (*13,20–23*).

Quantitative techniques have also been applied to SPECT imaging. Quantitation serves to decrease intra- and interobserver variability, helps in training inexperienced readers and provides an objective second opinion to experienced readers. Circumferential count profiles are generated for variable numbers of short axis slices comprising the left ventricle and for the apex from the apical portion of the vertical long axis slice. Counts are expressed as percentages with 100% assigned to the pixel in the heart with the highest counts. Defect severity, extent and reversibility can be determined from the circumferential profiles alone without comparing the scan to a normal data file. However for determining whether or not a mild defect is normal or abnormal, comparing the scan to a sex-predicted normal data file is very helpful. Programs incorporating normal data files display mean values for the normal males or females plus or minus 2 standard deviations of the means. If the scan being interpreted shows segments with count reductions below 2 standard deviations of the sex-matched normal database then the segment is considered abnormal. The circumferential profile data can also be displayed as polar maps.

SPECT decreases inter- and intraobserver variability, which has been reported to range from 3%–16% and 4%–11%, respectively (*24,25*). However, SPECT has many technical limitations and requires great attention to detail, such as assuring a satisfactory flood field uniformity and center of rotation, and avoiding reconstruction errors and patient motion. All of these factors can result in image artifacts. In addition, image interpretation is often impaired by soft tissue attenuation from breast, lateral chest wall fat and diaphragm, adjacent visceral activity, myocardial hot spots, apical variations, and noncoronary disease such as left bundle branch block, myocardial hypertrophy and cardiomyopathy (*26*).

The calculation of the diagnostic accuracy of perfusion imaging is also influenced by the source of referral of patients included in the study. The decision to perform cardiac catheterization is frequently based on perfusion image results. Because a patient with a normal image is less likely to undergo cardiac catheterization than a patient with an abnormal image, this leads to an increase in the false positive rate and a decrease in specificity (reportedly as low as 34% in some studies) (*13*). Efforts to overcome this bias are made by using noncatheterized age-matched patients, with a low pretest probability of having coronary artery disease, and deriving a normalcy rate.

The diagnostic value of a radionuclide perfusion study is also influenced by the patient's age, type of chest pain, gender and risk factors. While perfusion imaging usually does not add significant diagnostic value (although it may add prognostic information) in a patient with a high likelihood of coronary disease, it has been shown to add incremental diagnostic value in patient's with an intermediate likelihood of disease (*27,28*).

Pharmacologic Stress Testing

Many patients referred for stress myocardial perfusion imaging cannot exercise adequately because they are elderly and have significant physical limitations, including orthopedic or neuromuscular disorders, previous stroke, severe peripheral vascular disease or simply poor exercise tolerance. Other patients are taking medications that suppress heart rate, such as beta-blockers. Pharmacologic nuclear stress testing, using either the vasodilators dipyridamole or adenosine or synthetic catecholamines such as dobutamine and arbutamine, are being

performed with increasing frequency, presently representing 28% of nuclear stress tests (1994 ASNC survey of 192 nuclear cardiologists) (*29*). Pharmacologic stress testing has been shown to be safe, and it provides diagnostic accuracy comparable to that of exercise (*30–32*).

Myocardial Perfusion Imaging as a Prognostic Tool

Although stress perfusion imaging has strong diagnostic utility, it is equally useful as a prognostic tool. Perfusion imaging has been shown to be as good as or better than cardiac catheterization for identifying high-risk patients in three populations: with known or suspected coronary artery disease; following myocardial infarction; and prior to noncardiac surgery (*33*).

In a study of 100 consecutive patients without prior myocardial infarction who underwent exercise planar thallium imaging and cardiac catheterization for evaluation of chest pain, Brown and coworkers found that the number of reversible thallium defects was the most significant predictor of death or nonfatal myocardial infarction over a 3- to 5-yr period, and that the number of diseased vessels on cardiac catheterization did not add additional prognostic information (*34*). Staniloff et al., performing a 1-yr follow-up on 819 patients referred for planar ^{201}Tl stress testing, found an increasing rate of cardiac death, nonfatal myocardial infarction, and late coronary artery bypass grafting as defect number and severity increased (*35*). Subsequent exercise planar and SPECT perfusion studies, as well as studies using pharmacologic stress, have all supported this initial work, establishing the value of perfusion imaging as an important prognostic tool (*36–40*). Whereas the presence of scan findings associated with extensive myocardium at risk is associated with decreased event-free survival, the absence of any significant defects (i.e., normal scan) even in the presence of angiographically documented coronary artery disease is associated with an excellent prognosis. Many studies have looked at the prognostic value of a normal thallium scan. The combined results in 3,573 patients were summarized by Brown (*33*).

Stress myocardial perfusion imaging has also been found to be a useful prognostic test for evaluating patients following myocardial infarction. In a widely cited study, Gibson and associates performed low-level thallium stress tests within two weeks of infarction, and found that increased risk of cardiac events was associated with the extent of defect reversibility and increased thallium lung uptake (*41*). Dipyridamole perfusion imaging affords an opportunity to risk stratify postinfarction patients sooner than can be done with exercise stress testing (*42*).

Pharmacologic stress testing has been shown to be particularly useful for evaluating the cardiac risk of patients undergoing noncardiac surgery, especially those having peripheral vascular surgery. The latter patient group has a high incidence of coronary disease and, consequently, significant peri- and postoperative cardiac event rates. In addition, many of these patients are physically limited, often masking ischemic symptoms. It is neither necessary nor cost effective to perform preoperative screening on all patients, but only for patients in an intermediate to high risk group based on clinical variables (e.g., Q waves on the electrocardiogram, a history of prior myocardial infarction, angina, a history of congestive heart failure and diabetes) who are going for major surgical procedures (*43*).

Use of Ancillary Image Findings

Although the extent and reversibility of perfusion defects has strong diagnostic and prognostic value, other scan findings are also important. It was first observed in 1981 that increased ^{201}Tl lung uptake seen on the initial planar stress images correlates with more severe coronary artery disease, a high left atrial pressure and a reduced resting ejection fraction (*44*). Subsequent studies have demonstrated that increased thallium lung uptake on planar imaging is a significant predictor of adverse outcome, superior to clinical, stress, electrocardiographic or other thallium scan variables (*45*). However, the enhanced ability of SPECT to assess the extent of disease may preclude additional diagnostic value from thallium lung uptake (*46,47*).

Some patients undergoing stress perfusion imaging demonstrate left ventricular cavity dilatation, either transient (stress images only) or fixed (in both stress and rest/delayed images). Stress induced transient left ventricular cavity dilatation is the result of ischemic thinning and bulging of the ventricular walls, most commonly involving the apex. Dilatation on both stress and delayed images is the result of left ventricular failure. Weiss et al. reported that transient ventricular dilatation on planar thallium imaging had a 95% specificity for identifying multivessel coronary artery disease, more predictive than the presence of multiple perfusion defects (*48*).

Technetium-99m-Based Imaging Agents

Although ^{201}Tl has been the most widely used radiopharmaceutical for cardiac imaging, its physical properties make it a suboptimal imaging agent. Technetium-99m, with its higher energy and shorter physical half life, allows larger amounts of radioactivity to be administered to patients and results in higher count rates and improved image quality. The two technetium-based compounds currently approved in the U.S. for myocardial perfusion imaging are ^{99m}Tc-teboroxime and ^{99m}Tc-sestamibi (*49*).

The reported diagnostic accuracy of both planar and SPECT imaging with ^{99m}Tc-teboroxime are comparable to ^{201}Tl (*50*), but the rapid cardiac washout of this tracer makes SPECT imaging logistically difficult, and differential washout of tracer leads to underdiagnosis of stenotic lesions unless a multidetector camera is used and total imaging time is less than four minutes (*51*).

Technetium-99m-sestamibi is finding increasing use in the U.S. According to a recent ASNC survey, 34% of myocardial perfusion imaging studies are performed using sestamibi (*29*). The diagnostic accuracy of this agent is equal to ^{201}Tl, and it may be better for identifying individual coronary stenoses (*52–54*). Studies have confirmed that the strong prognostic value of thallium imaging also applies to sestamibi imaging (*55,56*).

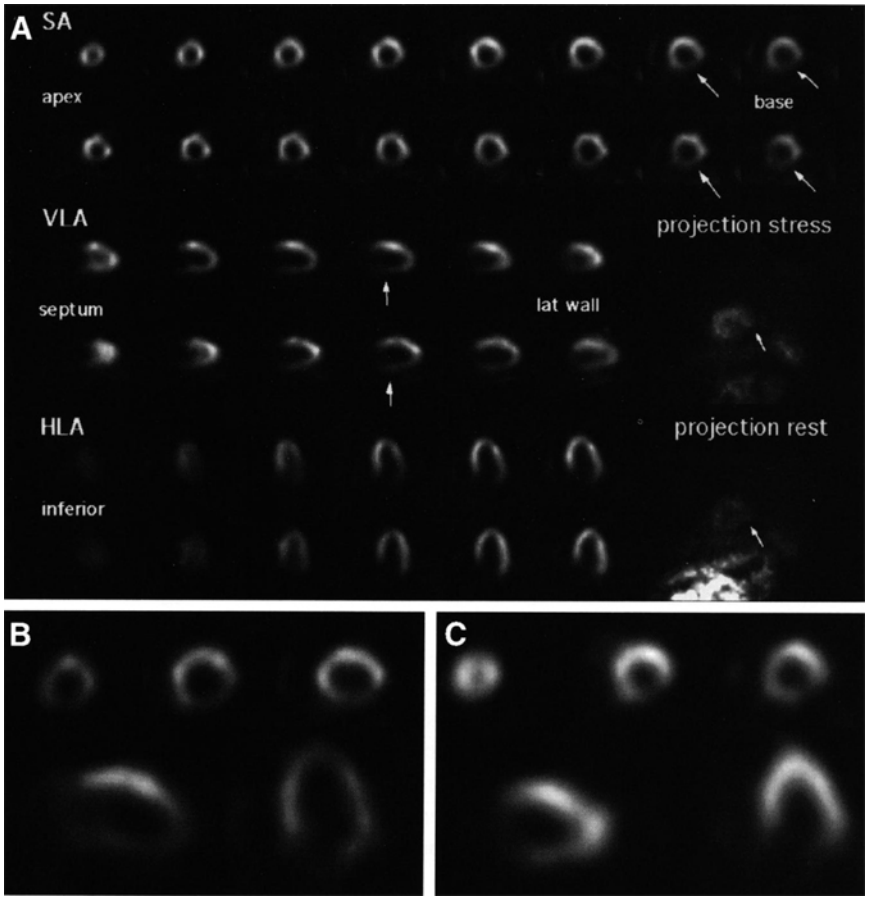

FIGURE 1. (A) Tomographic display of stress (top rows of each set of images) and rest (bottom rows of each set of images) sestamibi from an obese 52-yr old man being evaluated for chest pain. There is a mild fixed inferior wall perfusion defect (arrows in the basal slices). The unprocessed, raw images (projection stress and projection rest) suggest that the defect may be an artifact due to soft tissue attenuation from the dome of the left diaphragm overlying the inferior surface of the left ventricle (arrows). Gated tomograms on the same patient at end-diastole (B) and end-systole (C). The three images in the top rows are, from left to right, apical, mid and basal short-axis slices. The images in the bottom rows are mid-vertical long-axis and mid-horizontal long-axis slices. All walls thicken normally, making a prior infarction as a cause of the mild fixed defect less likely than the effect of diaphragmatic attenuation.

Unlike ^{201}Tl, redistribution of ^{99m}Tc-sestamibi is minimal once it is taken up by myocardial cells. This property provides a unique method for assessing acute ischemic syndromes. Symptomatic patients can be injected with radioisotope tracer at the bedside, and imaged at a later time when clinically stable. In one study using this technique, SPECT imaging had a sensitivity of 96% and a specificity of 79% for the detection of coronary artery disease, compared with 35% and 74%, respectively, for the electrocardiogram (*57*). Sestamibi can also be injected in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram. A recent study showed that all patients who were later determined to have a myocardial infarction or coronary artery disease had a perfusion defect, while none of the patients with a normal image were subsequently diagnosed as having coronary artery disease, and none had a major cardiac event during an 18-mo follow-up period (*58*). The high-count statistics afforded by ^{99m}Tc-sestamibi also allow simultaneous assessment of wall motion and left ventricular ejection fraction by either a first-pass acquisition or by gating the acquisition of the SPECT perfusion images (*59–61*). Gated SPECT images yield important complementary information to the perfusion images by identifying abnormal contraction in parts of the heart showing normal or near normal perfusion. These images can also be useful for distinguishing mild fixed defects that are actually attenuation artifacts (anterior due to breast, inferior due to diaphragm) from infarction (*62*). Figure 1 is an example of a mild fixed defect that was shown to be likely artifactual because of normal wall thickening on gated SPECT.

Use of Perfusion Imaging to Assess Myocardial Viability

Differentiating myocardium that is alive but not contracting normally from scarred myocardium in patients with coronary artery disease and left ventricular dysfunction is extremely important clinically, particularly when considering a patient for a revascularization procedure. Ischemia of the myocardium resulting from a temporary reduction in coronary flow causes left ventricular dysfunction, and this can be either brief or more prolonged following repeated episodes of ischemia. This type of dysfunction is called stunning. Alternatively, contraction of the heart muscle may decrease chronically if blood flow is reduced at rest. This condition is called hibernation (*63,64*). Myocardial perfusion imaging has been found to be an important tool for identifying dysfunctional but viable myocardium (*65*).

For many years it was believed that a redistributing thallium defect meant ischemia/viability, while a fixed defect meant scarred/nonviable tissue. However, it was also observed a number of years ago that many segments with fixed thallium defects, suggesting scar, showed improved tracer uptake, indicating that they were viable, after coronary angioplasty (*66*). Subsequent studies have shown that by either quantitating defect severity or by performing late, 24-hr imaging, one could

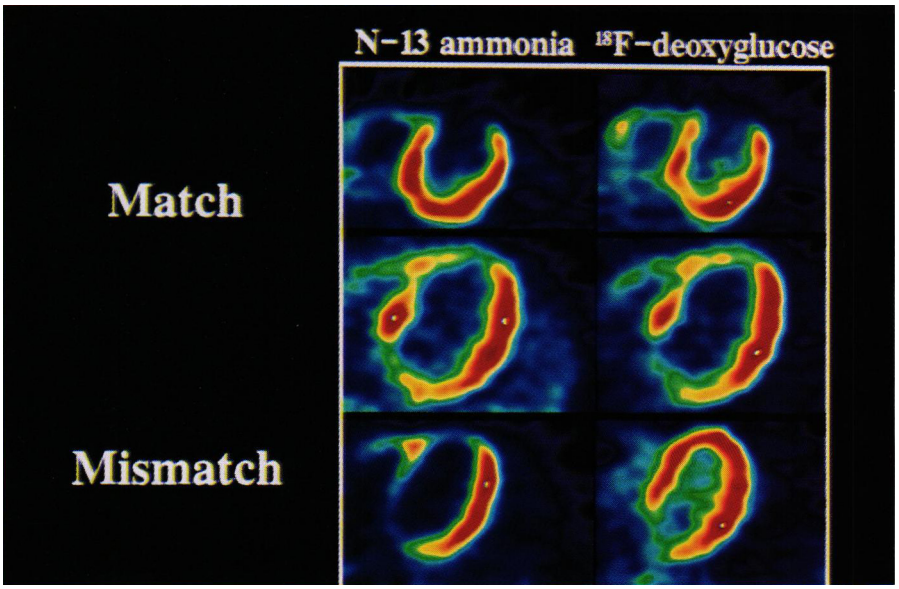

FIGURE 2. PET imaging. The top row shows transaxial slices of a matched apical defect with reduction of both ^{13}N-ammonia uptake and ^{18}F-deoxyglucose uptake in a patient with a myocardial infarction. The middle row shows mild reduction in uptake of both ^{13}N-ammonia and ^{18}F-deoxyglucose in the septum of a patient with a nontransmural infarction. The bottom row shows reduced blood flow (decreased ^{13}N-ammonia uptake) in the septum and apex (left), but with preserved ^{18}F-deoxyglucose uptake (right). This "mismatch" pattern denotes myocardium that has reduced blood flow but is metabolically active and therefore alive. (Figure courtesy Jamshid Maddahi.)

identify myocardium that is alive and will improve functionally following revascularization (*67,68*).

Positron emission tomography (PET) permits imaging of radioisotopes attached to metabolic tracers, such as ^{18}F-deoxyglucose (^{18}FDG), a glucose analog, or ^{11}C-palmitate, a fatty acid analog. Uptake and retention of these substances by myocardial cells indicate preserved cellular metabolism, and thus cellular viability (*69,70*). Examples of PET imaging are shown in Figure 2. However, PET is an expensive technology and is not widely available. In 1990, Dilsizian and colleagues described the technique of thallium reinjection, in other words, administering a second injection of ^{201}Tl following acquisition of the standard 4-hr delayed images with re-imaging. In a study of 100 patients, 49% of fixed defects were seen to improve or normalize following thallium reinjection, and this defect reversibility correlated well with improvement in wall motion following coronary angioplasty (*4*). Bonow et al. subsequently demonstrated a good correlation between thallium reinjection and ^{18}FDG PET imaging for differentiating viable from nonviable myocardium (*71*). An alternative thallium reinjection protocol which can significantly shorten the total test time is to reinject thallium immediately following completion of the initial scan and reimage 3–4 hr later. Van-Eck Schmidt and colleagues have shown that this protocol is equally sensitive as the NIH protocol for detecting defect reversibility (*72*).

When the clinical question is limited to viability, and not exercise induced ischemia, rest-redistribution thallium imaging may be performed (*73*). Quantitative analysis to assess defect severity makes rest-redistribution thallium imaging comparable to stress-redistribution-reinjection imaging regarding myocardial viability and concordant with results of PET imaging (*74*).

Because ^{99m}Tc-sestamibi does not show clinically significant redistribution of tracer after initial uptake, there was concern that sestamibi would provide limited information regarding myocardial viability (*75,76*). However, Udelson et al., using quantitative analysis, demonstrated that rest sestamibi activity paralleled rest-redistribution thallium activity and that both radioisotopes were able to differentiate viable from nonviable myocardium and predict wall motion improvement after revascularization (*77*). Preliminary experience suggests that the additional information provided by wall motion analysis from gated sestamibi imaging will further enhance this agent's usefulness in assessing myocardial viability.

An interesting method of combining the best attributes of ^{201}Tl with ^{99m}Tc-sestamibi was reported by Berman et al. in a study of dual isotope imaging (*78*). In this technique rest thallium imaging is followed immediately by stress sestamibi imaging. This protocol is highly accurate for detecting coronary artery disease and correlates well with rest sestamibi for assessment of defect reversibility. Repeat thallium imaging on the next day may enhance the detection of myocardial viability.

FUTURE TRENDS

The technetium-labeled perfusion tracers now allow both function and perfusion to be measured with a single tracer injection. The only technology that allows function to be measured at the moment of peak stress is first-pass radionuclide angiography. Presently this additional acquisition can only be performed using a multicrystal scintillation camera which represents add-on technology. The detectors of new generation SPECT cameras are being designed to achieve higher count rates into the range for statistically accurate first-pass acquisitions and constructed to be positioned for data acquisition during exercise. Whether or not exercise first-pass studies will become widely performed will depend on the results from centers such as Cedars-Sinai, where large databases of patients who have undergone simultaneous perfusion and function are being acquired. Preliminary reports suggest that in patients with moderate defect size and severity, the incremental prognostic value of the exercise left ventricular ejection fraction (LVEF) is greatest (*79*). Whether this incremental value is

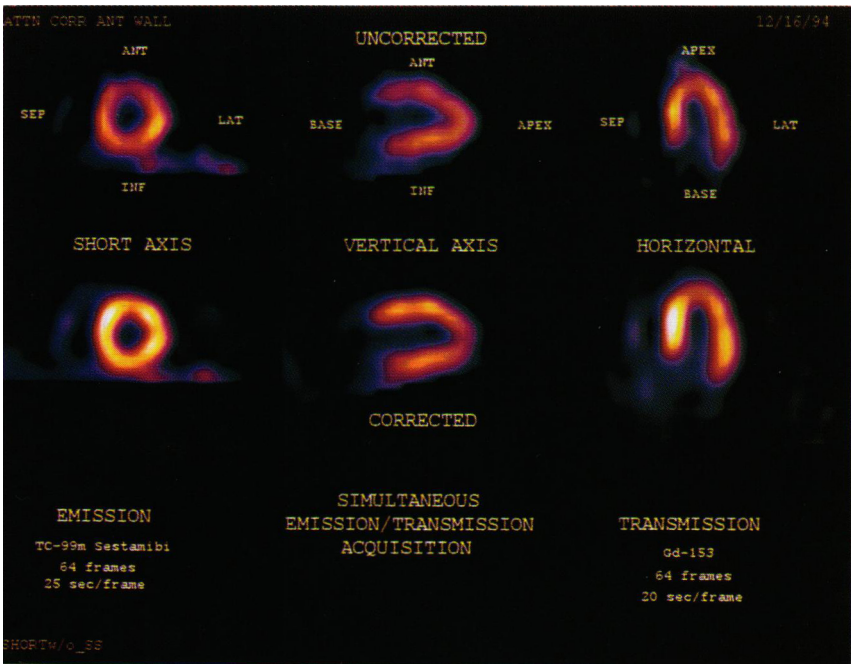

FIGURE 3. The use of emission/transmission (E/T) imaging to correct for breast attenuation artifact. The top row contains the uncorrected images and shows a defect in the anterior wall. Following attenuation correction in the bottom row of images, the defect is no longer visualized, demonstrating it to be an artifact of soft tissue attenuation. (Figure courtesy Robert C. Hendel.)

great enough to push this more labor-intensive technology into widespread clinical use remains to be seen. Meanwhile, gated tomography will continue to develop including refinements of algorithms to measure resting LVEF using geometric models and quantitative wall motion analysis, and the acquisitions will be more routinely performed.

Assessment of coronary metabolism using single-photon agents will continue to develop including the technology for coincidence counting using positron emitters and conventional detectors. The positron emitter that will probably find the widest clinical use will be ^{18}FDG which has a 110-min half-life, allowing transportation from regional cyclotrons to individual users. Fatty acid uptake and retention represents another approach to evaluating changes in myocardial metabolism induced by ischemia. The fatty acid analog which is easiest to image is ^{123}I-methyl iodophenyl pentadecanoic acid (BMIPP) (*80*). Although this tracer has been evaluated extensively in Japan and Europe, at present it is not available clinically in the U.S.

Emission/transmission (E/T) imaging to correct for soft tissue attenuation will have the greatest potential impact on clinical cardiac nuclear technology. The use of E/T imaging to correct for breast attenuation artifact is illustrated in Figure 3. Although two camera manufacturers now have FDA approval for E/T imaging (Picker for a triple detector system, ADAC for a right angle mounted dual detector system), the results of large multicenter studies to evaluate this technology have not yet been reported or published. It is possible that further refinements need to be made in software to prevent over- or under-correction of the data. When these problems have been worked out, E/T imaging could represent a major step forward for single-photon imaging, especially in the evaluation of women. Further refinement of the technology in addition to better defining which patient group, such as women, will benefit from which type of specific technology will occur.

In search of the perfect perfusion tracer, new radioisotope compounds will continue to be developed. In addition, tracers that do what no available tracers do, such as image acutely ischemic or hypoxic tissue in a hot spot manner, will be sought. The nitroheterocycles are agents in this category and are still in investigational stages of development (*81*).

Finally, there is the potential for identifying active atherosclerotic plaques by labeling various components of the plaque such as platelets, lipid rich foam cells or proliferating smooth muscle cells (*82,83*). If plaques with active morphology which will advance to rupture or restenosis can be identified noninvasively using radionuclides, then the final piece in the diagnostic puzzle of atherosclerosis will fall into place. It may be possible to identify patients with atherosclerotic lesions of diameter stenosis too low to be seen as perfusion defects on stress imaging, but with the potential for producing an unstable ischemic syndrome in the near future. Work in this area is still in the early stages.

SUMMARY

The concepts and methodology to perform stress perfusion imaging and gated blood pool scintigraphy were first described about 25 years ago. This new technology represented a major step forward in the practice of diagnostic cardiology because for the first time myocardial perfusion and left ventricular function could be assessed noninvasively. Single-photon myocardial perfusion imaging continues to be the only widely available noninvasive method to assess coronary perfusion and, therefore, has wide application in the evaluation of patients with coronary heart disease. Nuclear cardiac imaging technology has advanced from planar to tomographic imaging and the introduction of technetium-based perfusion imaging agents has improved image quality and allowed for assessment of both

perfusion and left ventricular function with a single radiotracer injection. The use of pharmacologic stress agents increased the utility of the tests to include patients who are unable to exercise. Prospective and retrospective database studies have demonstrated the prognostic value of stress perfusion studies, both for identifying patients at high risk for reduced event-free survival as well as for identifying patients at low risk for cardiac events. Future directions for the technology include further development of emission/transmission tomography for soft tissue attenuation correction, development of single-photon agents to evaluate myocardial metabolism as well as modifications of conventional gamma cameras to image positron-emitting agents, and further development of radiopharmaceuticals to image myocardial ischemia and to image active atherosclerotic plaques.

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