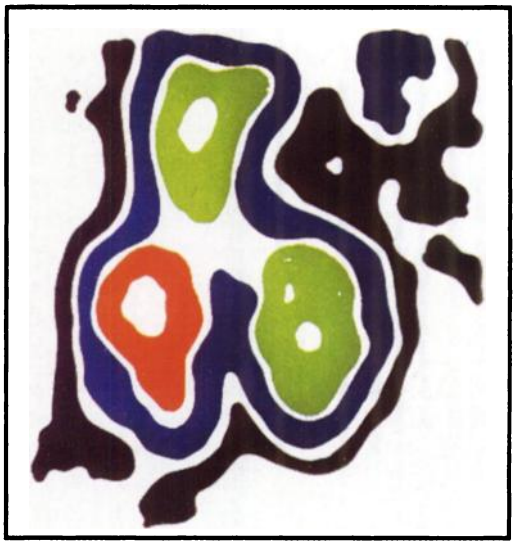
AN UPDATE ON RADIOPHARMACEUTICALS FOR MYOCARDIAL PERFUSION IMAGING

Technetium tracers lead in image resolution and count density

INTEREST IN ^{99m}Tc BASED MYOCARDIAL perfusion imaging agents continues to grow. In addition to the two agents now commercially available, ^{99m}Tc-teboroxime and ^{99m}Tc-sestamibi, clinical trials are well under way for two others, ^{99m}Tc-tetrofosmin and ^{99m}Tc-furifosmin (Q12). These ^{99m}Tc compounds have several advantages over ^{201}Tl. The shorter physical half-life allows for 20-30-mCi injections while maintaining acceptable radiation dosimetry. The consequent substantial increase in photon flux provides images of much higher count density. This factor, combined with less Compton scatter and superior energy resolution compared to ^{201}Tl, provides images with a higher signal-to-noise ratio and better spatial and contrast resolution, potentially resulting in improved sensitivity and inter-observer reproducibility. Moreover, the higher energy of ^{99m}Tc results in somewhat less photon attenuation, affording high quality images in obese patients and a decrease in attenuation artifacts. These factors favorably affect test specificity, potentially limiting the number of unnecessary cardiac catheterizations and thus substantially decreasing health care costs.

Technetium-99m tracer doses are adequate for performing first-pass radionuclide angiocardiography at rest or stress, thereby affording a functional evaluation of both the left and right ventricles in addition to perfusion data with a single radiopharmaceutical injection. Assessment of ventricular function at rest is of considerable prognostic importance in patients with myocardial infarction, cardiomyopathy, and valvular disease. Moreover, exercise left ventricular ejection fraction (LVEF) serves as an extremely valuable indicator of long-term survival and event-free rate in patients with prior infarction. Such combined function/perfusion protocols have been reported for sestamibi and should certainly be feasible with tetrofosmin and Q12, although first-pass studies with teboroxime appear to be limited due to high lung background activity (Williams et al. *J Nucl Med* 1993;34:394- 399).

As a result of the high count density of ^{99m}Tc sestamibi images, planar and SPECT studies can be gated to simultaneously assess resting function and either stress or rest perfusion during a single scan acquisition. This should also be possible with tetrofosmin and Q12, although image acquisition time is probably too short for adequate gated teboroxime images. From gated SPECT studies, wall motion, myocardial thickening, and LVEF can be determined. This additional valuable clinical information may obviate the need for a separate test to assess ventricular function such as echocardiography or equilibrium radionuclide ventriculography in patients undergoing perfusion imaging, thereby decreasing health care cost.



Julie Sturman: *Encore*, 1979, silk screen, another artistic interpretation of a gated blood-pool image.

Additional advantages of the ^{99m}Tc agents are increased flexibility in scheduling and increased laboratory throughput, although some laboratories have found abandonment of the rigid stress/delay ^{201}Tl regimen confusing. Because of very rapid myocardial tracer washout, it has been reported that back-to-back adenosine stress/rest teboroxime SPECT can be accomplished in 30 min using a triple detector camera (Chua et al. *J Nucl Med* 1993;34:1485-1493). In contrast, the other ^{99m}Tc agents remain essentially fixed in the myocardium without substantial washout, enabling a variety of separate-day, single-day, rest/stress, and stress/rest protocols. Although most of these protocols (at least for ^{99m}Tc-sestamibi) have been demonstrated to have comparable diagnostic accuracy for coronary disease, an adequate count density ratio between the stress and rest images must be maintained in order to avoid image "cross talk."

Despite what seem to be obvious advantages of the ^{99m}Tc compounds, market penetration in the United States has not been complete, and many laboratories are reluctant to abandon the tried but not always so true ^{201}Tl. This reluctance has stemmed from practical, financial and theoretical limitations of the two commercially available ^{99m}Tc

agents, which seem to be shared in part by other agents under clinical evaluation. Technetium-99m-teboroxime is best imaged with SPECT, but exceptional technical coordination is required to terminate stress testing, position the patient under the SPECT camera, and complete image acquisition before the tracer washout in the myocardium and excessive accumulation in the liver. Also, some investigators have objected to SPECT imaging of changing tracer distribution in the myocardium and the remainder of the field of view.

With lipophilic compounds such as sestamibi, and to a somewhat lesser degree with tetrofosmin and Q12, excessive liver uptake can create image artifacts, necessitating a delay between injection and imaging. Many facilities possess neither the hardware nor software to perform either first-pass radionuclide angiocardiography or gated SPECT. Small laboratories, particularly those staffed by a single technologist, that rely on unit doses have neither the ability nor time to prepare radiopharmaceutical vials. Moreover, the cost of unit doses of ^{99m}Tc compounds are prohibitive. Although an increasing number of laboratories are successfully employing a single-day stress/rest sestamibi protocol with an appropriate delay between the two studies, some laboratories have found the separate-day protocol inconvenient for patients, the single-day rest/stress protocol objectionable to cardiologists who prefer to perform exercise tests early in the morning, and the dual-isotope (rest Tl/stress sestamibi) protocol difficult to interpret due to the differences in resolution and quality of the two image sets. Although clinical trials have not yet been completed, it is doubtful that either tetrofosmin or Q12 will circumvent these practical objections.

New radiopharmaceutical development has been intensive and has enhanced diagnostic capability, but no "ideal" agent has been developed.

Other clinicians object to ^{99m}Tc agents more for physiologic and theoretical reasons. With the exception of teboroxime, the myocardial extraction of the ^{99m}Tc agents is slower and lower than ^{201}Tl. For instance, in serial planar images in humans, peak myocardial uptake of tetrofosmin was observed to occur at five minutes (Nakajima et al. *J Nucl Med* 1993;34:1478-1484). Theoretically, if peak stress is not maintained during the entire period of tracer extraction, ischemia may be underestimated and test sensitivity may decrease. However, in reported trials comparing sestamibi and ^{201}Tl SPECT, test sensitivities have been comparable.

One of the most intensely discussed and debated topics in cardiology is myocardial viability. For years, ^{201}Tl stress and 4-hr delayed imaging took a beating because of limitations in accurately differentiating scar from ischemia. Persistent defects at 4 hr resulted from one of two factors: either inadequate circulating ^{201}Tl to "fill in" severe stress-induced perfusion defects or chronically hypoperfused regions of myocardium unable to take up ^{201}Tl during the interval from injection to delayed imaging. The ^{99m}Tc agents, which require a separate resting injection, overcome the first problem. However, since the distribution of the ^{99m}Tc agents at rest is proportional to resting blood flow, in areas of stunned or hibernating myocardium or in myocardial regions supplied by severely stenotic coronary arteries, resting regional tracer uptake will be decreased, resulting in overestimation of scar and underestimation of viability. With the introduction of rest/reinjection ^{201}Tl protocols, wherein a "booster dose" of thallium was injected at rest with subsequent imaging at a delayed interval during which time thallium eventually distributed to hypoperfused myocardium, ^{201}Tl became a frontrunner rather than a dark horse in the viability race. In fact, agreement between rest/reinjection ^{201}Tl SPECT and ^{18}FDG PET has been reported to be quite good.

Stress defect reversibility with both ^{99m}Tc-sestamibi and tetrofosmin SPECT has been demonstrated to be less than with stress/rest/reinjection ^{201}Tl SPECT (Nakajima et al. *J Nucl Med* 1993;34:1478-1484 and Dilsizian et al. *Circulation* 994;89:578-587). Also, Dilsizian et al. found that estimation of viability with this thallium protocol correlated better with PET ^{18}FDG uptake. Although the percentage of patients referred for nuclear imaging in whom viability is a real clinical concern is relatively small (approximately 7% in our laboratory), many physicians have been reluctant to abandon ^{201}Tl for this reason. It appears, however, that myocardial viability may be related not only to defect reversibility from stress to rest but also to absolute myocardial tracer uptake, irrespective of the imaging agent. It has been demonstrated that for both ^{201}Tl and ^{99m}Tc-sestamibi, resting defects with more than 60% of maximal myocardial activity improved ventricular function following revascularization, whereas those with less uptake did not (Coleman et al. *Circulation* 1992;86:I-108). Moreover, Dilsizian et al. (see previous reference) found that although 36% of fixed sestamibi defects demonstrated reversibility with ^{201}Tl, concordance between ^{201}Tl and sestamibi with regard to viability increased to 93%, if a 50% threshold criteria for sestamibi defects was used. Thus, approaching myocardial viability from the standpoint of absolute cellular tracer uptake may dispel some hesitancy in using ^{99m}Tc agents. Although the precise role evaluation of wall motion and thickening with gated perfusion SPECT will play in the

assessment of myocardial viability is unknown, it is a promising area of investigation.

Finally, there are developing applications of radiopharmaceuticals which will potentially greatly enhance the role of SPECT in assessing myocardial viability. Preliminary reports suggest that a new agent, ^{99m}Tc-nitroimidazole metabolism (Patel et al. *Circulation* 1992;86(suppl):I-706 [Abstract]. Also, some vendors are attempting to design collimators and modify SPECT cameras to image the 511keV photon of ^{18}FDG. By combining blood flow imaging with a ^{99m}Tc agent with FDG to asses myocardial viability, a technique heretofore confined to a select few PET facilities would be available to many nuclear medicine laboratories. Iodine-123-MIBG, which is gaining popularity in Europe and Japan, may play an important role in selecting therapeutic agents for patients with heart failure and determining patients for which heart transplantation is indicated.

In conclusion, the recent development of new radiopharmaceuticals has been intensive and has enhanced the diagnostic capabilities of cardiovascular nuclear medicine, but no "ideal" agent has been developed. Thus, even in an environment of academic insecurity and cost constraints, radiopharmaceutical development must continue for us to maintain our competitive edge in a managed care environment.

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New Instrumentation for Cardiovascular Nuclear Medicine

Driven by demands for greater diagnostic accuracy, new pharmaceuticals, and competition from other modalities, cardiovascular nuclear medicine has experienced a revolution in instrumentation. SPECT systems designed specifically for cardiac imaging have become common. Corrections for photon attenuation, long promised by scientists, are finally making their way into the marketplace. Multi-headed camera systems (Figure1), digital circuitry in scintillation cameras, and increased computer power have all made these advances possible.

Multi-Headed SPECT Systems

The most obvious benefit of adding more camera heads to a scintillation camera system is the increase in sensitivity that comes from doubling or tripling the crystal area. While camera systems with two heads have been sold for many years, the current revolution in camera design was sparked by the triple-headed systems introduced by Ohio Imaging (now part of Picker International, Cleveland, OH) and Trionix Research Laboratory (Twinsburg, OH) in the late-1980's. Nearly every manufacturer now offers multiple-camera SPECT systems as an integral part of its product line.

The most popular systems are configured with two large field of view rectangular cameras mounted opposite each other (at 180°), increasing throughput of whole body bone imaging by allowing simultaneous acquisition of anterior and posterior images. These systems can also increase throughput for 360° SPECT imaging by halving the imaging time. In practice, the increase in sensitivity may be used to improve the image quality (improved resolution or statistics) rather than throughput.

The increased sensitivity of a second camera at 180° may mean very little for cardiac SPECT, if a 180° orbit (45° right anterior oblique to 45° left posterior oblique) is desired for thallium imaging. Counts collected from the second head would simply not be used. Dual-head SPECT systems with camera heads mounted at right angles (90°) are available from at least four manufacturers. The heart's small size allows the use of smaller camera heads than those necessary for bone imaging.

General Electric Medical System's (Milwaukee, WI) Optima and Elscint's (Hackensack, NJ) CardiaLare cameras designed specifically for cardiac imaging with two rectangular cameras mounted rigidly at 90°. A 180° orbit can be achieved by rotating the gantry (and thus each camera) 90°. Sopha offers the sophycamera DST. In this unique system, two heads are not mounted rigidly but may be set either 90° or 180° with a great deal of flexibility. ADAC's (Milpitas, CA) Vertex™ system also allows SPECT to be performed at 90° or 180° but has the advantage of full-size rectangular heads.

An added benefit of a system configured with two cameras at 90° is the ability to do bi-plane gated blood-pool (MUGA) scans. At the Instrumentation Symposium that followed February's mid-winter SNM meeting, Gordon DuPuey, presi-