EDITORIAL

Assessment of myocardial perfusion with Tc-99m: image is everything

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Despite the multiple imaging modalities that are now available for the diagnosis and assessment of coronary artery disease, radionuclide myocardial perfusion imaging continues to enjoy widespread use due to its combination of diagnostic accuracy and well-established prognostic utility.

After initial research demonstrated the feasibility of perfusion imaging with the metallic cation K-42,[1] Tl-201, another metallic cation, was proposed as a potassium analog for medical use.[2] Extensive research with cell culture, isolated heart and intact animal models showed that thallous ion has a relatively high myocardial extraction, in part via Na-K ATPase, that permits noninvasive assessment of relative regional myocardial blood flow.[3] Experimental models clarified the effect of variable coronary blood flow and myocardial injury on thallium uptake and clearance.[4,5] Moderate tracer washout resulting in ''redistribution'' permitted the differentiation of ischemic from infarcted myocardium with a practical single day imaging protocol,[6] and Tl-201 was approved by the U.S. Food and Drug Administration (FDA) for clinical use in 1977. However, despite widespread clinical use, the relatively long half-life and suboptimal photon energy of Tl-201 for Anger camera imaging led to the search for perfusion agents labeled with Tc-99m.

During the 1980s numerous cationic complexes of Tc-99m were evaluated for use as potential myocardial perfusion agents. The standard assessment involved screening compounds in rodents, evaluation of promising compounds in large animals, with subsequent study in humans of the most promising compounds. Tertbutylisonitrile (TBIN), carboxyisopropyl isonitrile (CPI), trimethylphosphite (TMP), dimethoxyphosphinoethane (POM-POM) and several analogues of dimethylphosphinoethane (DMPE) were synthesized and appeared promising in various experimental animal models.[7-9] However, subsequent evaluation in humans showed these compounds to have poor myocardial retention, delayed blood pool clearance due to binding with blood components, high background lung uptake or high adjacent organ (liver/spleen) uptake.[10-12] Gerundini et al[13] concluded that animal studies were not adequate to evaluate potential Tc-99m-labeled myocardial perfusion compounds. Deutsch et al[14] described 'The Noah's Ark Experiment', an attempt to predict the behavior of Tc-99m complexes using: (1) planar cardiac imaging in multiple animal species to screen new compounds, (2) early imaging studies of promising compounds in human volunteers, (3) biodistribution studies in rodents to refine structure–distribution relationships among structural analogues, and (4) final evaluation of the best candidate compound in human volunteers and patients. With this model of tracer evaluation, imaging assumed an earlier, more prominent role in the development cycle.

In the late 1980s two Tc-99m labelled perfusion agents were studied as myocardial perfusion agents in several experimental models and in human subjects. Teboroxime (TB) is a neutral, lipophlic boronic acid adduct of Tc-99m, and sestamibi (MIBI) is a lipophilic cationic isonitrile complex of Tc-99m.

TB shows the highest myocardial extraction and most accurate estimation of regional myocardial blood flow among the Tc-99m labelled tracers and Tl-201. Myocardial retention of the neutral compound is relatively less affected by myocyte injury, potentially permitting assessment of blood flow despite myocardial infarction.[15,16] While TB shows moderate clearance from isolated cardiac myocytes, the tracer shows rapid clearance in isolated hearts, canine models and patients, in part due to tracer binding to blood components.[17-20] The tracer also shows prominent hepatic uptake.[21]

MIBI shows avid uptake and moderate clearance in isolated myocytes, localizing in cellular mitochondria.[22] However, despite this avid myocardial cellular uptake, the tracer shows only moderate extraction in isolated hearts and canine models due to impaired diffusion of

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the large complex across the capillary endothelial barrier.[23,24] This moderate extraction results in a significant underestimation of hyperemic flow, beyond roughly 2 mL/minute/g, during pharmacologic stress. In patients, a modest coronary flow reserve of 2:1 or higher correlates with the absence of a perfusion defect with MIBI imaging.[25] Like TB, MIBI also shows prominent hepatic uptake.

Both compounds appeared promising, permitted accurate diagnosis of coronary artery disease compared with coronary angiography and were approved by the FDA 2 days apart in December 1990. With the FDA approval of IV dipyridamole that same month, one might have expected the more accurate measurement of hyperemic flow by TB to be an advantage. However, the combination of rapid myocardial clearance and prominent sustained liver uptake required very rapid imaging that was logistically challenging.[26] While some laboratories did evaluate rapid SPECT protocols for TB,[27,28] the tracer's rapid myocardial clearance and prominent hepatic uptake made it appear best suited for rapid planar imaging. Such rapid imaging might permit faster patient throughput, but the longer imaging with MIBI gave higher image quality, well suited to gated SPECT imaging. With the transition to SPECT imaging MIBI achieved wide acceptance. However, the major drawback in image quality for MIBI continued to be prominent, early hepatic uptake that sometimes interfered with assessment of the inferior cardiac wall. Various strategies such as ingestion of a fatty meal, milk, chilled or carbonated water have been suggested to deal with this.

In the 1990s Tc-99m NOET, another neutral, lipophilic compound, appeared promising in various experimental models as a myocardial perfusion agent. However, despite its favorable myocardial extraction and moderate washout, it showed prominent pulmonary uptake and inconsistent image quality in humans.[29,30] It has not been submitted for FDA approval. During the same decade Tc-99m tetrofosmin (TF), a lipophilic cationic phosphine complex, was studied as a potential compound for myocardial perfusion imaging. TF, like MIBI, has moderate myocardial extraction with avid retention in myocyte mitochondria and also shows a plateau in myocardial uptake at levels of coronary flow higher than 2 mL/minute/g.[31,32] Showing utility for the diagnosis of CAD,[33] TF was approved by the FDA in 1996. While a clinical advantage of TF is a somewhat faster hepatic clearance than MIBI, hepatic uptake of TF can still be problematic in some patients.

In this issue of the *Journal of Nuclear Cardiology* Kim et al evaluate Tc-99m-N-MPO (MPO) as a potential myocardial perfusion agent. This nitrido complex[34-37] has some similarities in structure to another complex, Tc-99m-N-DBODC5,[38-41] and is also synthesized with the goal of speeding hepatic clearance while maintaining myocardial image quality. While the discussion above suggests caution in predicting clinical utility from preliminary animal data, the authors have evaluated MPO in different animal species and compare some of their data to those for MIBI. Like MIBI, MPO is a lipophilic cation. Initial cell fractionation data showing similar tracer retention for the two complexes in mitochondria, and serial distribution in rodents showing stable myocardial uptake and low lung uptake, are presented to predict myocardial images similar to MIBI. Serial organ uptake and planar imaging showing rapid hepatic clearance of MPO are presented to predict the feasibility of early myocardial imaging without interference from adjacent organ activity. However, while the images and data show rapid clearance of hepatic activity, prominent splanchnic activity persists. Since the presence of prominent bowel activity adjacent to the heart can sometimes be a challenge for interpretation of clinical myocardial perfusion studies with MIBI or TF, human studies will be important to determine if this is also an issue for MPO.

MIBI and TF achieve good myocardial image quality with excellent myocardial contrast against low background pulmonary tracer uptake. Despite underestimation of hyperemic coronary flow, these tracers accurately detect coronary artery disease. However, prominent early hepatic uptake remains a limitation that delays imaging at rest or after pharmacologic stress, and this can be especially problematic when attenuation correction emphasizes hepatic and splanchnic tracer activity. Despite the clinical success of Tc-99m-based myocardial perfusion imaging, the development of new Tc-99m complexes with favorable kinetics for faster imaging has been slow. It was 13 years between the FDA approval of Tl-201 and approval of the first Tc-99m-labelled myocardial perfusion agents. It has now been 13 years since the last Tc-99m myocardial perfusion agent was approved. If rapid hepatic clearance of new Tc-99m complexes such as MPO is shown to permit high-quality myocardial images together with a clinically significant reduction in imaging delay, this will be a welcome addition to currently approved perfusion agents.

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