EDITORIAL

Novel SPECT perfusion imaging agents with improved myocardial or liver kinetics: Experimental studies and the need for clinical evaluation

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Myocardial nuclear perfusion imaging represents the most extensively used non-invasive diagnostic and prognostic tool for coronary artery disease. As reviewed in an excellent editorial by Dahlberg,[1] the suboptimal physical characteristics of the historical agent Tl-201 have prompted the development of Tc-99 m-labeled myocardial perfusion imaging agents with more favorable emission energy and dosimetry. For a number of reasons that were addressed in the abovementioned editorial, and despite excellent myocardial extraction and encouraging clinical results, the neutral and lipophilic tracers TcN-NOET and Tc-TEBOROXIME have not reached routine clinical use.[1] On the other hand, the cationic and lipophilic tracer Tc-MIBI has been extensively studied experimentally[2-10] and has reached wide clinical acceptance for a number of years. However, in addition to suboptimal myocardial extraction in comparison to that of Tl-201 due to the roll-off phenomenon leading to underestimation of myocardial perfusion at high flow rates,[7] Tc-MIBI also presents a modest heart-to-liver activity ratio which is comparable or lower than that of Tl-201 and which might be responsible for misinterpretation of myocardial perfusion in the inferior or inferoapical left ventricular wall.[11,12] In the clinical setting however, despite these different biological, physical, and imaging characteristics, both Tl-201 and Tc-MIBI have comparable diagnostic accuracies for detecting coronary artery disease, as confirmed in the large randomized ROBUST study.[12] Similarly, the prognostic power of nuclear perfusion imaging—i.e., its ability for predicting future coronary events—has been demonstrated in a large number of high-quality studies and in thousands of patients, whatever the tracer used.[13]

Tc-TETROFOSMIN is another cationic and lipophilic tracer of myocardial perfusion that was approved for clinical use 6 years after Tc-MIBI. The cellular uptake mechanisms of both tracers consist in mitochondrial accumulation due to the negative mitochondrial membrane potential and the positive charge associated with the lipophilicity of the tracers. Although Tc-TETROFOSMIN presents a flow-extraction curve similar to that of Tc-MIBI,[14] the heart-to-liver ratio of the tracer turned out to be significantly higher than that of Tc-MIBI in the clinical setting.[15] The more favorable liver kinetics of Tc-TETROFOSMIN resulted in a lower number of poor quality scans than observed with Tc-MIBI in daily practice,[16] a result which however did not lead to differences in sensitivity, specificity, and diagnostic accuracy between the two tracers.[17]

As described below, a number of experimental studies including the paper by Liu et al[18] in this issue of the *Journal* have addressed the issue of developing new myocardial perfusion imaging agents with improved myocardial and/or liver kinetics in comparison with those of Tc-MIBI. Although these studies often yielded encouraging experimental results, the current literature clearly lacks clinical data confirming the improved kinetics of these novel agents over Tc-MIBI.

7′-Z-[125I]-iodorotenone (ZIROT) is a neutral and lipophilic inhibitor (IC50 = 0.25 nmol/L) of complex I of the mitochondrial transport electron chain. Biodistribution experiments in rodents indicated that ZIROT heart-to-liver ratio was significantly higher than that of Tc-MIBI and similar to that of Tc-TETROFOSMIN.[19] Experiments performed on isolated, erythrocytes-, and albumin-perfused rabbit hearts indicated a much higher extraction of ZIROT (84 ± 5%) when compared with that of Tc-MIBI (48 ± 10%).[20] The superiority of ZIROT flow vs extraction relationship over Tc-MIBI was confirmed in a canine model of critical coronary

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stenosis,[21] in which ZIROT also outperformed the values of Thallium-201 myocardial extraction as measured previously in similar experimental conditions. Interestingly, a [^{18}F]-labeled rotenone also demonstrated an initial extraction fraction similar to that of Thallium-201 in isolated, erythrocytes-, and albumin-perfused rabbit hearts.[22] Despite these experimental results suggesting that the excellent extraction fraction of radiolabeled rotenone may provide a mean for the absolute quantification of myocardial blood flow, no clinical data are yet available with such tracers. This situation may possibly be due to the need for iodine radiolabeling as far as SPECT imaging is concerned.

The agents Tc-N-MPO, Tc-15C5PNP, and Tc-DBODC5 mentioned below belong to a class of cationic perfusion imaging agents composed of two different bidentate ligands that have been synthesized in order to optimize the balance between myocardial extraction and liver uptake.[23] Along the same line, it should be mentioned that Bolzati et al[24] recently published the synthesis and biological evaluation of a new series of bidentate ligands from which two potentially promising candidates have been selected for further experimental evaluation.

Tc-N-MPO is a mono-cationic tracer that accumulates in the mitochondrial fraction to the same extent as Tc-MIBI as demonstrated by a myocardial subcellular distribution study following intravenous injection of the tracers to rats.[25] Biodistribution experiments performed in the same experimental model indicated that Tc-99 m-N-MPO heart-to-liver ratio was much higher than that of Tc-MIBI at all time points, and slightly and transiently higher than that of the novel perfusion imaging agent Tc-DBODC5 (see below).[26] The likely mechanism for fast liver clearance of Tc-N-MPO in rats is an efficient recognition of the tracer by the MDR transport function of hepatocytes.[25] Additional studies in guinea pigs led to somewhat disappointing results with similar Tc-N-MPO and Tc-MIBI myocardial and liver activities resulting in a modest and transiently significant advantage of Tc-N-MPO over Tc-MIBI with respect to heart-to-liver ratio.[26] Finally, a recent study indicated a heart-to-liver ratio of 1.2 ± 0.1 in a canine model.[27] Again, no clinical data are yet available regarding the myocardial and liver kinetics of Tc-N-MPO in patients.

In this issue of the *Journal*, Liu et al[18] performed experimental cardiac imaging in rats using the cationic tracer Tc-15C5-PNP and compared the results with those obtained using Tc-MIBI. He et al[28] initially described the biodistribution of Tc-15C5-PNP in 2006. Surprisingly, the heart-to-liver ratios that were obtained from biodistribution experiments by He et al were significantly higher than those observed by Liu et al despite similar experimental conditions (9.5 ± 3.0 vs 3.3 ± 0.3 at 60 minutes post-tracer injection, respectively). In any case, in vivo SPECT acquisitions revealed perfusion images of similar quality with both tracers and an objectively lower liver activity when using Tc-15C5-PNP as compared with Tc-MIBI.

Finally, Tc-DBODC5 probably is the agent that has undergone the most extensive experimental evaluation. Biodistribution studies in rats indicated an excellent heart-to-liver ratio for Tc-DBODC5 of 18.4 ± 2.0 at 60 minutes post-injection to be compared with values of

Table 1. Experimental and clinical heart-to-liver ratios of clinically used and currently evaluated myocardial perfusion imaging agents

	Heart-to-liver ratio		
		Clinical	
Tracer	Experimental	Rest	Exercise/stress
Tc-MIBI	2.6 ± 0.2[29]	0.6 ± 0.1[11]	1.8 ± 0.3[11]
Tc-MIBI (guinea pig)	3.8 ± 0.4[26]	0.6 ± 0.1[11]	1.8 ± 0.3[11]
Tc-TETROFOSMIN	5.8 ± 0.7[29]	1.2 ± 0.8[15]	3.1 ± 3.0[15]
Tc-DBODC5	18.4 ± 2.0[29]	0.7 ± 0.1[31]	1.3 ± 0.3[31]
Tc-N-MPO	24.3 ± 4.9[26]	N/A	N/A
Tc-N-MPO (guinea pig)	5.4 ± 0.7[26]	N/A	N/A
Tc-N-MPO (dog)	1.2 ± 0.1[27]	N/A	N/A
Tc-15C5PNP	3.3 ± 0.3[18]	N/A	N/A
ZIROT	2.4 ± 0.2[19]	N/A	N/A

Experimental and clinical values were determined at 60 minutes post-tracer injection.
Experimental heart-to-liver ratios were obtained from biodistribution experiments in rats otherwise indicated.
References are superscripted.

5.8 ± 0.7 and 2.6 ± 0.2 for Tc-TETROFOSMIN and Tc-MIBI, respectively.[29] Canine studies also demonstrated an advantage for Tc-DBODC5 over Tc-MIBI with regards to heart-to-liver ratio, but to a lesser extent than that observed in rodent experiments.[30] Results from a phase I clinical study are available for Tc-DBODC5.[31] The heart-to-liver ratio from patients injected with the tracer reached approximately 0.7 and 1.3 under rest and stress conditions, respectively. These values are similar to those that were observed in Tc-MIBI phase I clinical study,[11] and slightly lower than those observed for Tc-TETROFOSMIN.[15] The above data are summarized in Table 1.

In conclusion, a number of tracers with improved myocardial and/or liver kinetics have been evaluated experimentally over the last years with the aim of enhancing the quality of perfusion images currently acquired using Tc-MIBI or Tc-TETROFOSMIN. The only phase I clinical study performed using Tc-DBODC5 failed to reproduce the encouraging experimental results that were initially observed with the tracer. The clinical evaluation of experimentally validated novel perfusion imaging agents is therefore promptly needed to determine whether or not the favorable results observed in the experimental setting will translate into improved clinical kinetics.

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