INVITED COMMENTARY

^{99m}Tc-N-NOET Imaging for Myocardial Perfusion: Can It Offer More Than We Already Have?

A neutral, lipophilic ^{99m}Tc-labeled compound proposed as a myocardial perfusion imaging agent is ^{99m}Tc-(*N*-ethoxy-*N*-ethyl-dithiocarbamato)nitrido (N-NOET) (*1*). ^{99m}Tc-N-NOET has a high myocardial uptake in humans, with 3% of the injected dose in the heart 5 min after injection (*2*), a high first-pass extraction fraction in canine models (*3*) and in isolated rabbit hearts (*4*), and a myocardial uptake that correlates with myocardial blood flow (*3,5*) over a wide range of flow, with a plateau in ^{99m}Tc-N-NOET uptake only at very high flow rates (>4 $mL \cdot min^{-1} \cdot g^{-1}$ in a canine model), as observed with ^{201}Tl (*5*). ^{99m}Tc-N-NOET exhibits significant redistribution in dog models (*3,6*) and in human clinical studies (*7*). Finally, safety and dosimetry are comparable with that of the other technetium tracers (*2*).

Characteristics that ^{99m}Tc-N-NOET has in common with ^{201}Tl include a high first-pass extraction fraction, a good correlation with coronary blood flow, and a redistribution phenomenon. However, ^{99m}Tc-N-NOET has a more favorable dosimetry, and mechanisms of redistribution (*6*) and myocardial uptake (*8*) are different. In addition, ^{99m}Tc-N-NOET uptake does not reflect myocardial cellular viability but, rather, coronary blood flow, at least in an experimental model of acutely infarcted, reperfused myocardium (*9*).

Compared with currently used technetium complexes (sestamibi and tetrofosmin), ^{99m}Tc-N-NOET has a better myocardial uptake (3% of injected dose vs. 1.2% and 1.5% of injected dose for technetium complexes) and a higher pulmonary uptake (20% of injected dose at rest vs. 1.7% and 2.6%) (*2,10,11*). As far as the heart/lung uptake ratio is concerned, that of ^{99m}Tc-N-NOET is always lower than that of other technetium complexes (*2*). The correlation of technetium complexes' uptake with coronary blood flow shows a plateau at 2–2.5 times the basal flow values for sestamibi and tetrofosmin (*12,13*), whereas this plateau is reached at 3–3.5 times the basal flow values for ^{99m}Tc-N-NOET and ^{201}Tl (*5*). In contrast to sestamibi and tetrofosmin, ^{99m}Tc-N-NOET undergoes a redistribution phenomenon that can be used in clinical practice. Finally, safety and dosimetry are comparable for all 3 technetium complexes (*2*). Known characteristics of ^{99m}Tc-N-NOET are much closer to those of ^{201}Tl than to other technetium complexes; nevertheless, ^{99m}Tc-N-NOET is definitely not a technetium analog of ^{201}Tl.

^{99m}Tc-N-NOET allows imaging of myocardial perfusion abnormalities for very weak variations of coronary flow because of the good correlation of its cardiac uptake with high coronary flow rates. The study by Takehana et al. (*14*) presented in this issue of *The Journal of Nuclear Medicine* is consistent with this observation. Thus, residual critical stenosis can be determined more accurately with ^{99m}Tc-N-NOET than with sestamibi (*14*). This possibility of revealing weak reductions of coronary flow reserve might become useful when perfusion scintigraphy is expected to accurately identify patients with coronary flow reserve abnormalities attributed with coronary atherosclerosis who should benefit from treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Indeed, in current practice, heterogeneity of ^{201}Tl uptake under stress, without any segmentary abnormality, is often observed. In these patients, dyslipidemia, noninsulin-dependent diabetes, or even high blood pressure is always found. A diminution of coronary flow reserve has been reported in such patients even in the absence of significant coronary artery stenosis (*15–17*), and these alterations of endothelial function can be revealed by either PET (*15,17*) or SPECT imaging (*18–20*). Furthermore, we now know that coronary endothelial dysfunction predicts long-term cardiovascular event rates (*21*), but we also know that aggressive cholesterol-lowering therapy with HMG-CoA reductase inhibitors for a period of 2–6 mo improves myocardial perfusion in these patients (*22,23*).

Heterogeneity of perfusion tracer uptake could be an additional semiological criterion, together with the extent and the severity of the segmentary perfusion defects. In this context, ^{99m}Tc-N-NOET, like ^{201}Tl, could become a valuable tool for evaluating this heterogeneity. Therefore, the finalization of mathematic models would be required to quantify these heterogeneity patterns.

Clinical confirmation of the redistribution phenomenon of ^{99m}Tc-N-NOET in a large population of patients will allow the same exploration as ^{201}Tl stress redistribution but with a more favorable dosimetry. The results of the ongoing clinical trials with ^{99m}Tc-N-NOET will, in the near future, tell us whether these expectations are confirmed.

Three aspects of the biologic behavior of ^{99m}Tc-N-NOET require further investigation:

- The heart/lung uptake ratio of ^{99m}Tc-N-NOET is lower than that

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of other technetium tracers or even of ^{201}Tl, although, in our experience, the ^{99m}Tc-N-NOET heart/lung uptake ratio correlates with that of ^{201}Tl. However, this ratio is sufficient to obtain good quality images in most patients (*2,7*). In some cases, pulmonary uptake is detectable, notably at rest. Is this relative pulmonary hyperfixation associated with an increase in pulmonary activity or with a reduction of cardiac activity? Why does it only occur in certain patients? What is its pathophysiologic meaning?

- The cellular uptake mechanisms of ^{99m}Tc-N-NOET have not yet been elucidated. In cultured newborn rat cardiomyocytes, ^{99m}Tc-N-NOET has been shown to bind to cellular membranes, with a particularly high affinity to L-type calcium channels, in a nonenergy-dependent manner (*8*). In contrast, studies on isolated perfused rat hearts (*24*) and in vivo rat hearts (*25*) suggest that ^{99m}Tc-N-NOET might preferably bind to the endothelium.
- Is ^{99m}Tc-N-NOET a tracer of myocardial tissue viability? In a canine experimental model of reperfused acute myocardial infarction, myocardial uptake of ^{99m}Tc-N-NOET reflects the magnitude of flow restoration but not myocardial cellular viability, as does ^{201}Tl (*9*). In this experiment, however, blood flow was normal at the time of ^{99m}Tc-N-NOET injection. As we know, the restoration of normal blood flow allows long-term improvement of myocardial function (stunned myocardium, i.e., myocardial viability in clinical practice). Therefore, we can hypothesize that ^{99m}Tc-N-NOET, a pure tracer of myocardial blood flow, might be a good predictor of clinical viability. However, this point needs to be investigated further.

In summary, ^{99m}Tc-N-NOET is a new tracer of myocardial perfusion. Although it presents, like ^{201}Tl, a redistribution phenomenon, it is not a technetium analog of ^{201}Tl. Moreover, ^{99m}Tc-N-NOET is not equivalent to either sestamibi or tetrofosmin. Perfectly controlled experimental studies, such as those presented by Takehana et al. (*14*), will allow a better understanding of ^{99m}Tc-N-NOET behavior and therefore more precisely define the place it will take among the currently available cardiac perfusion tracers.

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