EDITORIAL

Measurement of Myocardial Blood Flow by Radiolabeled Tracers

TO THE EDITOR: Noninvasive measurement of myocardial blood flow has been a major focus of research in nuclear cardiology for many years. Recent advances in radiopharmaceutical development of ^{99m}Tc-labeled flow tracers have resulted in alternatives to ^{201}Tl as a perfusion agent. In this issue of the *Journal* Weinstein et al. (*1*) explore differences between the two ^{99m}Tc-labeled compounds (teboroxime and sestamibi) and thallium using the autoradiographic technique on an animal model of complete coronary artery occlusion. In the study, myocardial defects on teboroxime and, to a lesser extent, sestamibi autoradiographs, were more sharply defined and had narrower transition zones than thallium autoradiographs. Thus, teboroxime may provide the most accurate assessment of hypoperfusion of the three tracers.

A number of factors exist that influence ability of a radionuclide tracer to faithfully delineate regional myocardial blood flow. First, the Sapirstein principle (*2*) states that a flow tracer should be avidly extracted by the myocardium. This is a fundamental requirement of any flow marker. It is clear that radiolabeled microspheres are the prime example of a highly extracted (99%) flow tracer. As such, radiolabeled microspheres have served as the gold standard for measuring myocardial blood flow in most animal models. Of the three radiopharmaceuticals Weinstein (*1*) evaluated, teboroxime has been reported to have the highest extraction fraction, followed by thallium and then sestamibi (*3–6*). All three agents have been shown to have good linear correlation with normal physiologic flow levels. However, good linear correlation with flow is a necessary but not sufficient requirement of a good flow tracer. The uptake of a true flow tracer must also have the same increment in uptake against a reference organ flow as the increment in myocardial blood flow using radiolabeled microspheres against the same reference organ flow. That is, the slope of the regression equation of myocardial blood flow, calculated from myocardial uptake of the tracer versus "true" myocardial blood flow using microspheres should be 1.0 (*6,7*). Under these requirements, teboroxime and thallium appear to have slopes of the regression equation versus microsphere-determined myocardial blood flow closer to 1.0 than sestamibi (*6,7*).

The time allowed for uptake of the tracers varies among studies (*2,7,8*). In Weinstein's study, the sestamibi/thallium comparison group had a circulation time of 5 min, while in the teboroxime/thallium comparison group, circulation time of only 2 min was allowed. Other work has used 1.17 min of circulation of these three tracers (*7*). Duration from injection to measurement of tracer uptake may well influence the results. Teboroxime appears to have more rapid uptake than thallium and thallium has more rapid uptake than sestamibi (*3,5,9*). Rapidity of uptake (and rapidity of washout) of these tracers has obvious implications in terms of the duration of ischemia during exercise testing, the timing of imaging postexercise and the duration of the image acquisition to measure peak uptake of these tracers best representing their ability to reflect blood flow. A relatively short duration of ischemia impairs the ability of sestamibi to reflect short-lived maximal flow differences. Lengthening exercise-induced or pharmacologically induced ischemia (or flow heterogeneity) might improve the ability of sestamibi to reflect flow differences as suggested by the findings in the current study (*2*). Conversely, the timing of injection of teboroxime would be critical in allowing maximal ischemia (or maximal flow heterogeneity) to be faithfully recorded by tracer imaging.

Retention of each of the three tracers by the myocardium is different (sestamibi ≫ thallium ≫ teboroxime), (*3,4,9*), thus affecting their capacity for clinical imaging. The speed of image acquisition is critical, especially for teboroxime, but less so for thallium and much less so for sestamibi (*5,10–13*). Teboroxime and thallium will be expected to show evidence of redistribution early after injection (*5,14*).

Finally, results of this study are only applicable for normal and extremely low flow regions. Results cannot be extrapolated to conclude that similar contrast will be present when regions of high flow are contrasted with areas of less severely diminished flow, as is the usual clinical situation encountered in exercise-induced ischemia or pharmacologically induced flow heterogeneity with or without ischemia.

In conclusion, the most important characteristic of a flow tracer is its high first-pass extraction by the myocardium. Of the three currently available single-photon emitting tracers, teboroxime has the highest extraction followed closely by thallium and more distantly by sestamibi. Detection of early coronary artery disease would be expected to improve with flow tracers that exhibit the highest extraction, especially at high flows occurring during provocative stress testing either by exercise or pharmacologic means. Retention of the tracer by the myocardium is of secondary importance and relates mainly to the speed with which the initial tracer uptake can be imaged. This technical aspect of rapid recording of the distribution of the flow tracer is especially challenging for teboroxime but is also important for thallium, given the instrumentation currently available. The timing of the

imaging for these two tracers may significantly affect clinical results obtained and will need to be kept in mind when evaluating future comparisons.

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