INVITED COMMENTARY

Quantification in SPECT Cardiac Imaging

Nuclear medicine is a unique imaging modality that can provide myocardial images reflecting fundamental biophysiologic functions in vivo, such as perfusion, the metabolism of several substrates, and the binding potential of particular receptors. The article by Schaefer et al. (*1*) in this issue of *The Journal of Nuclear Medicine* is a timely reminder that these physiologic functions are not necessarily given directly by the myocardial distribution of the radiolabeled tracer measured by SPECT or PET devices. Appropriate methodology may need to be applied to extract the physiologic function of interest independent from other factors that contribute to the in vivo distribution of radiotracers.

Radiolabeled microspheres are considered the gold standard for quantification of regional myocardial blood flow, because their distribution is proportional to tissue perfusion and because quantitative flow values can be obtained simply from the radioactivity concentration in the tissue divided by the integration of the arterial input function. However, physical microsphere measurements are limited to animal experimentation because of their invasive nature. For clinical studies, most SPECT flow tracers are designed to mimic microspheres through a relatively high first-pass extraction fraction and retention in the tissue by high chemical affinity (or a large tissue-to-blood partition coefficient or distribution volume). However, the fixation of these tracers is often imperfect, and tracers can clear from the tissue during the study. This clearance causes the regional radioactivity concentration to change over time and to no longer entirely reflect flow in delayed images. Retention of the tracer can also be affected by the pathology of the tissue. Although the assumption of microsphere-like behavior may be valid in normal tissue, it may not necessarily hold in abnormal myocardial regions.

Change of tracer distribution over time is well demonstrated by ^{201}Tl. It is a potassium analog that accumulates in myocardial cells associated with Na^+/K^+ adenosine triphosphatase. Because of a high transcapillary extraction fraction, it is rapidly taken into the myocardial tissue, and initial regional uptake predominantly reflects regional blood flow. ^{201}Tl clears rapidly from arterial blood, reducing delivery of tracer to the myocardium. When an equilibrium is reached between myocardial and blood ^{201}Tl concentrations, the myocardial concentration of ^{201}Tl no longer reflects flow but reflects the ability of the myocardium to retain ^{201}Tl and is related to the number of myocytes with maintained membrane potential in a given volume unit (*2*). The kinetics of ^{201}Tl in myocardial tissue were extensively studied in the 1970s and early 1980s and are, in fact, indirectly applied to clinical studies. In normal myocardium, there is a rapid initial uptake reflecting normal flow, followed by slow clearance toward equilibrium. For ischemic myocardium, with maintained cell potential, initial uptake is low as a result of low flow, and uptake continues toward the same equilibrium as for normal myocardium (redistribution). In infarcted areas, reduced flow causes a reduced initial uptake, and loss of cell membrane potential causes loss of ability to retain ^{201}Tl and increased clearance rate, indicating a complete defect. Areas could also have maintained flow with reduced membrane potential, in which the very initial uptake is normal but rapid clearance causes a reduced equilibrium tracer concentration (reverse redistribution). Clinical diagnosis thus involves qualitative (visual) analysis of the early and delayed images. The early images taken at 15–20 min assess flow, and the delayed images taken at 3–24 h identify viable myocardium. Regional myocardial blood flow and distribution volume (the Na^+/K^+ potential) can potentially be quantitatively assessed from a series of dynamic scans with ^{201}Tl. Recent studies have revealed that both regional blood flow and distribution volume can be quantitatively estimated using quantitative reconstruction including appropriate correction strategies for attenuation and scatter and application of a kinetic mathematic model (*2*,*3*).

Despite a relatively long history of cardiac SPECT imaging, only limited attempts have been made to extract quantitative physiologic parameters. The limited number of attempts is largely attributed to the limited sensitivity and resolution of SPECT devices, compared with PET devices, and the complexity of attenuation and scatter correction for SPECT, particularly in the heterogeneous thorax. These limitations of SPECT are also reflected in SPECT radiotracer development. Most tracers do not achieve a transcapillary extraction (first-pass extraction fraction) high enough to support uptake linearly coupled to the true flow, though linear coupling is essential for absolute quantification over a wide physiologic range. Emphasis has instead been placed on tracers whose uptake remains relatively constant over the long imaging times typically associated with SPECT and that provide good contrast between the myocardium and adjacent structures (e.g., liver) by allowing delayed imaging when some of the background activity has diminished. Tracers such as ^{99m}Tc-teboroxime have properties well suited to measuring perfusion (*4*–*6*) but, because of fast clearance requiring rapid SPECT, have not found widespread use. In addition, general use of filtered back-

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projection reconstruction with 180° of data collection to improve the qualitative image appearance does not lend itself well to quantitative studies.

^{99m}Tc-tetrofosmin is a lipophilic cation whose accumulation in tissue is attributed to the Na^+/H^+ ion channel and to cellular and mitochondrial membrane potential. It was expected that ^{99m}Tc-tetrofosmin would have reasonably high transcapillary extraction at rest and that the extracted ^{99m}Tc-tetrofosmin would stay in tissue. If so, the accumulation rate of ^{99m}Tc-tetrofosmin in tissue should have been identical to the supply rate of this tracer into the capillary bed and therefore should have represented regional flow (*7*). However, ^{99m}Tc-tetrofosmin uptake can be modified by using Na^+/H^+ antiporter and mitochondrial uncoupler, suggesting that ^{99m}Tc-tetrofosmin uptake can be influenced by membrane potential and mitochondrial integrity (*8–11*). It was also demonstrated that myocardial ^{99m}Tc-tetrofosmin washed out from the myocardium significantly during the study, even from normal myocardium at rest (*12–14*). The clearance of myocardial ^{99m}Tc-tetrofosmin became greater in reperfused myocardium (*15*). These findings suggest that, at least at an equilibrium state, the myocardial ^{99m}Tc-tetrofosmin concentration is influenced not only by myocardial flow but also by energy-dependent processes.

Schaefer et al. (*1*) investigated regional myocardial blood flow with $H_2{}^{15}O$ PET in regions that had reduced ^{99m}Tc-tetrofosmin uptake with preserved ^{18}F-FDG uptake, namely metabolism–perfusion mismatch myocardium (MPMM). This study made apparent the preservation of myocardial blood flow in MPMM identified by significantly decreased ^{99m}Tc-tetrofosmin uptake. The hypothesis was then posed that, like ^{201}Tl, alteration of the energy-dependent cellular membrane potential could occur in clinical situations in regions of MPMM despite preserved resting blood flow and that this was responsible for the reduced uptake of ^{99m}Tc-tetrofosmin. A claim was therefore made that the flow–metabolism mismatch can be significantly overestimated if ^{99m}Tc-tetrofosmin is used as a flow tracer. This explanation is reasonable and quite likely. As long as the trapping mechanism is related to the membrane potential and mitochondrial integrity, alteration in energy-related processes can contribute to the reduction of the equilibrium concentration of ^{99m}Tc-tetrofosmin in tissue.

SPECT images were acquired approximately 1 h after ^{99m}Tc-tetrofosmin administration in the study of Schaefer et al. (*1*). This timing was empirically determined to provide better contrast in the myocardium relative to liver than do timings that produce linearity between the tracer concentration and the true flow (*13*). SPECT scans acquired earlier after tracer administration, when clearance of ^{99m}Tc-tetrofosmin is less significant, would probably have been more suited for providing images proportional to the perfusion. This highlights the importance of understanding the kinetic behavior of the tracer. Although the assumption of microsphere-like behavior may be reasonable for early imaging times in normal myocardium, as demonstrated by this study in comparison with $H_2{}^{15}O$ studies, delayed imaging in, particularly, the MPMM regions no longer reflects only regional perfusion. Rather than concluding that ^{99m}Tc-tetrofosmin overestimates MPMM regions, one should take the findings as an opportunity to elucidate additional information about the underlying processes. Vanoverschelde et al. (*16*) demonstrated that resting blood flow could be normal in hibernating myocardium of patients with chronic myocardial infarction in which coronary flow reserve was reduced. Similar mechanisms may be involved in the MPMM regions in this study.

Quantitative kinetic studies are well established in PET, providing physiologic parameter estimates, such as flow, from dynamic data using mathematic model-based analysis. As referenced by Schaefer et al. (*1*), regional myocardial blood flow can readily be quantified by the kinetic analysis for $H_2{}^{15}O$ PET, including a correction for the partial-volume effect and a determination of the distribution volume of water (or water-perfusable tissue fraction) (*17*), and even the spillover from blood activity (*18*). Although much less common, estimation of absolute physiologic parameters in the myocardium is also feasible with SPECT and has been successfully applied to dynamic ^{201}Tl SPECT (*2*), allowing separation of flow from equilibrium retention (volume of distribution) of ^{201}Tl in the myocardium. Similar methodology could also be applied to ^{99m}Tc-tetrofosmin SPECT. Sequential imaging (a dynamic scan) after the ^{99m}Tc-tetrofosmin administration should provide exact kinetics and would be informative, as the radioactivity concentration at an extremely early phase might be as high as in normal areas and then would clear more rapidly in MPMM. A mathematic model–based kinetic analysis could be useful for estimating both flow and the effects of membrane potential and mitochondrial integrity simultaneously.

However, estimation of physiologic parameters places requirements in addition to those of current standard clinical protocols on the collection and processing of SPECT data. It is essential that the regional radioactivity concentration be quantified accurately at every temporal period in each myocardial tissue element and, thus, that accurate corrections be made for the effects of attenuation and scatter. Although attenuation correction techniques are well established, care has to be taken in the choice of scatter correction algorithms to maintain quantitative accuracy and avoid artifacts (*2,19*). Partial-volume effects caused by limited spatial resolution also need to be addressed, as does the additional blurring introduced by cardiac and respiratory motion.

A camera capable of performing dynamic SPECT is required, and the short frame times and relatively poor sensitivity of SPECT require methodology capable of handling the noisy data. Some of these demands can be reduced by using simplified techniques, such as a lookup-table technique (*3,20–23*), provided that appro-

priate validation studies are performed first. An important further requirement for flow measurement, particularly when coronary flow reserve is assessed, is a tracer with uptake that is linearly related to the true flow. Several studies have demonstrated that ^{99m}Tc-tetrofosmin is less than ideal, with uptake significantly underestimated and saturated at high flows (*13*,*24*), mostly because of the limited extraction fraction of this tracer.

The power of radiotracer imaging techniques, such as PET and SPECT, lies in their ability to trace physiologic processes and biochemical pathways. Use of dynamic tracer information is well established in PET for quantifying particular physiologic and biochemical processes of interest. The limited sensitivity and resolution of SPECT, and the traditional lack of quantitative studies with SPECT because of limitations on the correction of attenuation and scatter, have popularized SPECT tracers with relatively slow kinetics that allow qualitative images of, for example, perfusion to be obtained by static SPECT. Furthermore, imaging and processing protocols have frequently been tailored to improve the perceived quality of the images, such as by delaying acquisition to allow clearance of tracer from adjacent liver. However, tracer uptake at a given time is rarely governed by only a single process such as flow but rather is governed by several mechanisms, including blood flow, transport mechanisms across capillaries and cell membranes, and binding and retention in cells. With the exception of early and delayed redistribution imaging of ^{201}Tl, little advantage has been taken of the potential additional information obtainable from following the time course of tracer in the tissue. As demonstrated by the study of Schaefer et al. (*1*), uptake and retention mechanisms, particularly in abnormal regions, cannot be ignored even for tracers designed for static SPECT imaging.

Rather than being seen as a disadvantage, these mechanisms should be taken as an opportunity, through suitable quantitative imaging protocols and model application, to extract additional information from the tracer study and gain a better understanding of the underlying processes. The feasibility of clinically practical quantification with SPECT has been demonstrated both in the heart (*2*–*6*) and in other regions (*20*,*22*,*25*). This feasibility may, in turn, result in placement of less emphasis on developing SPECT tracers and improving "static image" appearance and more emphasis on characterizing particular physiologic and biochemical processes of interest, an area that is uniquely suited to radiotracers.

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