INVITED COMMENTARY

What Is the Best Approach to Quantify Myocardial Blood Flow with PET?

In recent years, many approaches have been developed in an attempt to optimize the quantitative measurement of myocardial blood flow (MBF) using agents labeled with positron-emitting radionuclides. These blood flow techniques fall into 2 basic categories: inert freely diffusible tracers (category I) and physiologically retained tracers (category II). The most common category I compound in use for myocardial perfusion is $H_2{}^{15}O$ (*1–3*). Common category II compounds include ^{82}Rb, [^{13}N]ammonia, and [^{62}Cu]PTSM (*4–14*).

All these PET tracers produce MBF estimates that correlate well with microsphere studies in animal models. Unfortunately, each imaging agent and method used to measure the tracer kinetics has properties that are suboptimal for the estimation of MBF. These limitations range from suboptimal physiologic radiotracer characteristics to the limited count-rate and imaging capabilities of modern PET systems. When both tracer kinetic characteristics and the imaging capabilities of PET imaging systems are taken into consideration, one can formulate a list of characteristics of an "ideal" PET MBF radiotracer. These include irreversible trapping in myocardial tissue in direct proportion to myocardial perfusion, rapid clearance from the blood, no recirculating radiolabeled metabolites, and a relatively short physical half-life that facilitates repeated studies.

Radiolabeled microspheres have the potential to meet these criteria but cannot be administered noninvasively. However, the development of commonly used category II PET tracers represents an attempt to produce imaging agents that meet the ideal tracer characteristics. Unfortunately, the retention of the common category II MBF tracers is coupled with energy-dependent trapping mechanisms; thus, these tracers do not accumulate in myocardial tissue in direct proportion to blood flow over the wide dynamic range of perfusion levels that are achieved physiologically. As a consequence, mathematic models must be used to isolate the tracer delivery mechanism from the tracer retention mechanism to accurately quantify MBF. The separation of tracer delivery from retention using these mathematic models and estimation algorithms is sensitive to the signal-to-noise levels of the image data and the relative kinetic properties of tracer delivery, extraction, and retention. The separation of these mechanisms leads to bias and uncertainty in specific processes of interest and, hence, to suboptimal methods for MBF estimation.

van den Hoff et al. (*15*), in this issue of *The Journal of Nuclear Medicine*, have carefully characterized the potential to use [1-^{11}C]acetate as a tracer for the measurement of myocardial perfusion. Although the kinetic properties of [1-^{11}C]acetate do not meet the ideal myocardial perfusion tracer characteristics, uptake and initial retention of the tracer in myocardial tissue is governed primarily by MBF. From the standpoint of blood flow estimation, acetate behaves more like a category II tracer than a category I tracer. In the study by van den Hoff et al., an MBF technique based on [^{13}N]ammonia was used as a gold standard against which the [1-^{11}C]acetate blood flow estimates were evaluated.

Although it is accepted that quantitative MBF methods based on [^{13}N]ammonia kinetics provide good estimates, these techniques themselves are not optimal. Nonetheless, the results presented by van den Hoff et al. (*15*) nicely show the flow-dependent uptake and extraction of [1-^{11}C]acetate. This study also shows that for imaging procedures performed with equal radionuclide doses (1.1 GBq), the uncertainty in the MBF estimate from acetate is smaller than that observed from [^{13}N]ammonia.

Unfortunately, definitive conclusions about the relative quantitative accuracy of acetate versus ammonia MBF estimates are difficult to draw. For equal injected doses, the total amount of ^{13}N decay during 20 min will be approximately 75% of the total amount of ^{11}C decay. In the study by van den Hoff et al. (*15*), the total number of emission events collected from the heart for each study type was not provided. The total number of collected coincidence events from the myocardium was likely greater for the acetate studies, accounting in part for the smaller uncertainty in the blood flow estimates derived from the acetate data. Thus, it is not clear whether the apparent quantitative advantages of acetate MBF estimates were the result of differing image count levels or tracer kinetic properties that are more conducive to isolation of blood flow–dependent model parameters.

The elegant study reported by van den Hoff et al. (*15*), coupled with previous studies that have investigated the estimation of myocardial perfusion with [1-^{11}C]acetate (*16–20*), nicely shows that the kinetic properties of acetate are suitable for estimating MBF. Under the imaging protocols used by van den Hoff et al., the variability in the quantitative estimate of MBF appears smaller for acetate than for ammonia. Whether this apparent improvement in quantitative accuracy will hold up under protocol designs based on other criteria,

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such as equal total emission events from the heart or equal levels of whole-body radiation exposure, is unclear. Nonetheless, this study clearly shows that good MBF estimates can be obtained by fitting a simple compartmental model to regional acetate kinetics. Although the half-life of ^{11}C will not permit perfusion studies to be repeated rapidly in succession, such as is possible with $H_2{}^{15}O$ and ^{82}Rb, studies can likely be repeated over time frames that are similar to those used for [^{13}N]ammonia. Estimation of MBF from a [1-^{11}C]acetate study also has the unique advantage of allowing coupled perfusion and oxidative metabolism estimates from a single tracer administration.

The question of which approach is best for measuring MBF with PET remains difficult to answer. The optimal tracer and imaging protocols for PET imaging of MBF have been debated for many years (*21*). The emergence of [1-^{11}C]acetate as an MBF tracer provides the nuclear medicine community with another option for these studies. The existing MBF methods, including the new acetate methods, use kinetic model parameters related to either tracer uptake (scale of the myocardial tissue curve) or tracer washout (shape of the myocardial tissue curve) as the basis for estimating MBF. In general, the estimation of scale-related parameters is less sensitive to image noise than are the shape parameters of the kinetic model. However, scale parameters are sensitive to bias caused by the limited image resolution (tomograph and cardiac motion), whereas shape parameters are not. Geometric corrections are now routinely used to remove the bias in scale parameters, but these corrections are at the expense of added variance in the MBF estimates. Therefore, the advantage of using a scale parameter over a shape parameter is minimized, and one should carefully consider factors such as image quality, study duration, and study goals when selecting a technique. If biased MBF estimates are acceptable, such as when identifying small changes in perfusion levels may be important, the coefficient of variation will be significantly smaller for scale-related parameters than for shape parameters.

Although appearing to have attractive properties as a tracer for myocardial perfusion, [1-^{11}C]acetate should not be considered an ideal MBF tracer because of the many limitations [1-^{11}C]acetate holds in common with our current MBF tracers. These limitations include a flow-dependent extraction fraction, circulating blood metabolites, the need to use a tracer kinetic model to isolate the uptake and retention or washout components of the tracer kinetics in the heart, and the need to use geometric corrections to remove distortions in quantitative blood flow estimates caused by limited image resolution.

In summary, the study by van den Hoff et al. (*15*) clearly reveals the potential of [1-^{11}C]acetate as an MBF tracer. This study also shows that MBF estimates based on acetate kinetics provide similar, or possibly improved, quantitative accuracy relative to the existing ammonia-based blood flow methods. A significant added advantage of [1-^{11}C]acetate is its ability to simultaneously estimate MBF and oxidative metabolism. Unfortunately, many of the limitations found with the established PET MBF methods exist for acetate as well. Therefore, the search for an ideal MBF tracer continues.

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