Myocardial Blood Flow and Innervation Measures from a Single Scan: An Appealing Concept but a Challenging Paradigm

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The importance of neuronal dysfunction in the progression of heart failure and the utility of cardiac sympathetic imaging for identifying ischemic cardiomyopathy patients who are at high risk of sudden cardiac death is well established. On the basis of the results of the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) multicenter trial, ^{123}I-*meta*-iodobenzylguanidine (^{123}I-MIBG) has received Food and Drug Administration approval for imaging cardiac sympathetic innervation of the heart in the United States (*1,2*). The results validated the independent and incremental prognostic value of delayed heart-to-mediastinum ratio of ^{123}I-MIBG in patients with heart failure beyond left ventricular ejection fraction. Whether cardiac sympathetic imaging will also play an important role in identifying or predicting sustained ventricular tachyarrhythmias in patients with cardiomyopathy and determining those who may benefit from cardioverter-defibrillator implantation is currently under investigation (*3,4*).

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The synthesis of molecular and neuronal radioligands in parallel with recent advances in hybrid PET/CT imaging have made it possible to study and characterize cardiac innervation with position-emitting radiotracers such as ^{11}C-*meta*-hydroxyephedrine (^{11}C-HED) (*5–7*). ^{11}C-HED is taken up by cardiac presynaptic neurons but not metabolized by synaptic degradation enzymes. Similar to the ^{123}I-MIBG planar and SPECT data, decreased ^{11}C-HED PET retention in patients with heart failure has been associated with increased cardiac mortality and the need for cardiac transplantation (*8,9*). Although PET imaging of the cardiac nervous system is advantageous over planar and SPECT techniques because of its superior spatial and temporal resolution, ^{11}C-HED is not Food and Drug Administration–approved. Moreover, widespread clinical use of ^{11}C-HED is limited by its relatively short 20-min half-life and complex production requiring an onsite cyclotron, which makes the entire production costly. Reduced cardiac neural regeneration after myocardial infarction has been theorized to be associated with arrhythmia risk. This was tested in a swine model, in which perfusion was assessed by ^{13}N-ammonia and innervation by ^{11}C-epinephrine 4–12 wk after myocardial infarction induced by balloon occlusion of the left anterior descending artery. Inducible ventricular tachycardia was present in 7 of the 11 animals studied, and in those with inducible ventricular tachycardia, a significantly larger area of perfusion–innervation mismatch was present (*10*). These findings led to the PARAPET (Prediction of Arrhythmic Events with PET) study, which was a prospective, observational clinical trial showing that patients developing sudden cardiac arrest had a significantly larger area of viable but denervated myocardium (*11*).

In this issue of *The Journal of Nuclear Medicine,* Harms et al. explore the possibility of using a single-scan ^{11}C-HED protocol for defining myocardial blood flow (MBF)–innervation mismatch areas in patients with ischemic cardiomyopathy by taking advantage of the underlying tracer kinetic model of ^{11}C-HED (*12*). They hypothesized that the rate of influx of ^{11}C-HED from blood to myocardium (K_1) is proportional to MBF. To study this, they measured MBF with ^{15}O-water and multiplied it by perfusable tissue fraction to mathematically derive transmural MBF (MBF_T), which represents MBF in both infarcted and perfusable tissue. As the authors point out in the "Discussion" section of their paper, direct comparison between K_1 and MBF_T showed that K_1 significantly underestimated MBF_T, and the limited extraction of ^{11}C-HED rules out use of ^{11}C-HED as a tracer of absolute MBF (*12*). This essentially negative study brings up important concepts of radiotracer kinetics and the effect of changes in MBF and biochemistry on radiopharmaceutical biodistribution. Given the fact that blood flow influences in vivo studies but not in vitro studies, it is important to have a measurement of flow changes in each study of biochemistry.

The major challenge in moving from in vitro studies to in vivo imaging is separating the relative importance of delivery, metabolism, and biochemistry to the biodistribution over time. To measure flow, microspheres (considered the gold standard) are replaced by more clinically useful radiotracers whose ideal biodistribution is heavily weighted by flow and therefore not significantly weighted by biochemistry or metabolism (*13*). This requires an extraction fraction close to 1 over the relevant range of MBF so that the blood flow is linear with flow changes, with a slope of 1. The radioligand most often mentioned is ^{15}O-water. Certainly a diffusible tracer such as

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^{15}O-water is ideal, given it does not have possible confounding biochemistry. On the other hand, the interplay between blood flow and metabolism in the extraction and retention of ^{13}N-ammonia is complex. The radioactivity in the tissue after a ^{13}N-ammonia injection is a combination of interstitial and free cellular space and ammonia converted to glutamine. The early extraction phase of freely diffusible ^{13}N-ammonia reflects blood flow, whereas the later slow-turnover phase reflects metabolic trapping of ^{13}N-ammonia, involving predominantly the conversion of ^{13}N-ammonia and glutamic acid to ^{13}N-glutamine mediated by adenosine triphosphate and glutamine synthetase (*14*).

If changes in the biochemistry are the critical metric, and the pharmacokinetics can be determined in a patient-friendly imaging study, the biochemistry can often be measured with a dynamic study or a postvalidation single late scan. This is the case in diseases involving cardiac autonomic dysfunction, such as is known to occur in sudden cardiac death, heart failure, diabetic autonomic neuropathy, and cardiac arrhythmias (*9*). Norepinephrine analogs such as ^{11}C-HED and ^{123}I-MIBG have a rapid uptake in the myocardium but do not bind as irreversibly as the receptor-binding radiotracers. Radioligands for the muscarinic receptor and the β-adrenoceptor designed to measure receptor density are taken up rapidly and retained in the myocardium. They have a microsphere-like biodistribution, although the extraction fraction has not been reported. The β-adrenoceptor ligand CGP 12177 ((−)-4-((*S*)-3-tert-butylamino-2-hydroxypropoxy)$^{-1}$,3-dihydrobenzo-imidazol-2-one) has rapid uptake in the heart and a slow efflux, with an average off-rate of 0.02 min^{-1} (*15*). Since distribution of this ligand in the myocardium is heavily weighted by delivery, in vivo competition studies with high– and medium–specific activity radioligands were required to determine the binding potential and maximum number of binding sites. Delayed images with ^{11}C-HED (30–40 min after injection) and ^{123}I-MIBG (~4 h after injection) showed decreased retention of radioactivity after injection of ^{11}C-HED and ^{123}I-MIBG in heart failure patients. One group has taken the approach of further reducing the rate of delivery and thereby increasing the weighting of the biodistribution compared with that of MBF (*16*). The lead compound, 4-^{18}F-fluoro-*m*-hydroxyphenethylguanidine, has a weaker Michaelis constant with about the same maximum velocity, which was the design goal.

Given that both delivery and biochemistry are key metrics in myocardial innervation, the concept of using a single isotope and a single scanning session to derive both parameters may be appealing but is rather challenging. In the case of ^{11}C-HED, its low extraction fraction in the 40%–50% range limits its use as a tracer of absolute MBF. In the future, the most challenging paradigm will be to develop a radioligand that has maximal sensitivity to flow changes and to biochemical changes. In the meantime, the accuracy of clinical data should not be compromised for the convenience of acquiring single-isotope, single-scan imaging with ^{11}C-HED.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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