

Towards Quantitative Myocardial Perfusion PET in the Clinic

Arman Rahmim, PhD, Abdel K. Tahari, MD, PhD, Thomas H. Schindler, MD

INTRODUCTION

Myocardial perfusion imaging (MPI) with PET provides improved diagnostic quality, certainty, and accuracy over single-photon emission computed tomography imaging [1,2]. The prognostic value in predicting adverse cardiac outcomes has also been demonstrated [3]. In particular, MPI with dynamic PET, in concert with tracer kinetic analysis, provides a powerful means to quantify the tracer transport rate, K_1 , and subsequently, myocardial blood flow (MBF). The ratio of hyperemic to resting MBF, reflecting the myocardial flow reserve (MFR), is commonly applied to noninvasively probe the vasodilatory capacity of the coronary circulation [4].

The noninvasive quantification of MBF and MFR enable expansion of the scope of conventional MPI from the advanced and flow-limiting epicardial coronary artery disease (CAD) to the early stages of atherosclerosis or microvascular dysfunction [5]. This includes 3 functions. First, the identification of early functional and structural abnormalities of the coronary circulation of subclinical CAD. Second, the improved identification and characterization of flow-limiting effects of CAD burden; eg, conventional MPI with a stress-induced regional defect signifies the “culprit” for the most advanced CAD in multivessel disease, whereas flow-limiting effects of the other lesions remain undetected as the radiotracer uptake appears normal. The flow-limiting effects of these remaining lesions may be unmasked by identifying marked reductions of MFRs. In this direction, it has been

suggested that for given CAD lesions $>70\%$ diameter stenosis, reductions in MFR to <1.7 can be assumed to be related, at least in part, to increases in epicardial resistance of CAD lesions [6]. Third, the identification of balanced reduction in MBF or ischemia in all vascular territories where the radiotracer uptake during stress-testing is homogeneous, whereas the MFR is markedly reduced in all 3 major coronary territories (Fig. 1). The ischemic effect, however, should be confirmed by a peak stress transient cavity dilation of the left ventricle (LV) during maximal hyperemic flow increases on gated PET images.

Overall, quantitative MPI with PET has been established as an important diagnostic and prognostic tool to evaluate patients with suspected CAD. MFR is commonly reduced in the presence of cardiovascular risk factors, which can be reversed by preventive medical care and/or lifestyle modifications. Whether the resulting improvements in MFR, reflecting enhanced coronary vasodilator capacity, translate into improved clinical outcome, remains to be clinically evaluated.

CHALLENGES AND SOLUTIONS

Commonly utilized tracers include ^{15}O -water, ^{13}N -ammonia, and ^{82}Rb . Of these, ^{15}O -water has not received US FDA approval and does not enable visualization of myocardial perfusion because of short physical and biological half-lives in the myocardium that result in inadequate count statistics. For this reason, the use of ^{15}O -water is widely limited to research purposes

in the assessment of MFR. Compared with ^{82}Rb (physical half-life 76 seconds), ^{13}N -ammonia has a physical half-life of 9.97 minutes. Furthermore, it has a high first-pass myocardial extraction fraction ($\sim 80\%$) and is trapped in the myocardial cells as ^{13}N -glutamine. Though ^{13}N -ammonia affords excellent count statistics and superior visualization of perfusion and quantification of MBF, it requires an on-site cyclotron (similar to ^{15}O -water), limiting widespread adoption. ^{82}Rb , by contrast, requires a column generator, allowing more widespread use.

The Statistical Challenge

Given the subdivision of the acquired data into dynamic frames, quantitative MPI (particularly for ^{82}Rb) may be challenged by limited statistics. To address this, relatively large injection doses, in particular for ^{82}Rb , can be administered. However, high count rates can give rise to high deadtime and randoms rates in septaless 3-D PET imaging (only option in newer generation scanners), though advances in detector and electronics design continue to address this issue better. In this direction, appropriate dose optimization [7] for a given scanner, acquisition parameters, and even subjects (eg, body size) may be useful.

Flow quantification may also be enhanced using statistical image reconstruction methods, which enables accurate modeling of the physics and the Poisson noise process in PET detection. This, in turn, translates to images of higher quality and quantitative accuracy, including enhanced contrast and signal-to-noise ratio,

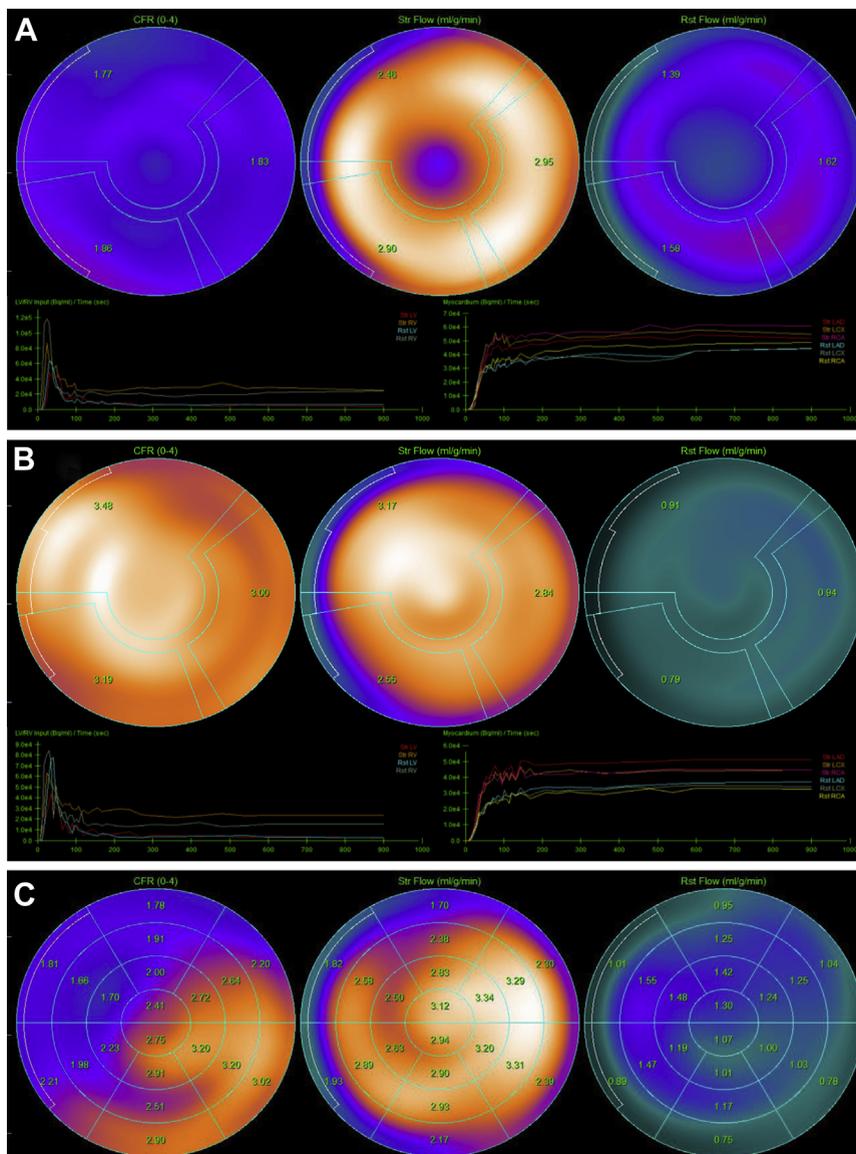


Fig 1. Quantification of myocardial blood flow (MBF) and myocardial flow reserve (MFR) is important. (A) Bull's eye view with regional MBF values for rest (right), stress (middle), and MFR (left). The stress image looks normal except for a possible apical thinning. However, MFR values below 2 point to triple-vessel disease. Compare with (B) with MFR values considerably exceeding 2. In both cases, time-activity curves are depicted in the bottom for myocardial tissue (right) and input (left). (C) Segmental values for MBF and MFR are given in the conventional 20-segment depiction of the left ventricle. CFR = coronary flow reserve; LV = left ventricle; RST = rest; RV = right ventricle; STR = stress.

web 4C/FPO

and improved task performance in observer studies.

The Spatial Resolution Challenge

PET imaging is challenged by finite resolution effects, which are dominated by intercrystal blurring. Photon noncollinearity and position range also can play a role. The resulting undesirable interregional

cross-contamination, ie, the partial volume effect (PVE), is readily observed in visual inspections and can especially affect quantitative estimation.

In the case of quantitative MPI, an attempt to address PVE has been to use additional parameter(s) in the kinetic modeling. This enables enhanced accuracy but can degrade reproducibility. One can also utilize

postreconstruction partial volume correction or reconstruction-based resolution modeling (RM). RM is a very natural approach to tackle PVE, as it models resolution-degrading phenomena within the probabilistic system matrix of the reconstruction algorithm. In fact, RM has been shown to enhance wall to cavity contrast in cardiac imaging [8]. However, RM alters the noise

texture [9], resulting in reduced spatial noise (“roughness”) but potentially degraded reproducibility, and it also results in edge artifacts. Overall, detection task performance is not necessarily enhanced with RM, even if contrast versus noise performance is improved [10], but this needs to be carefully and thoroughly studied.

New Tracer Development

A relatively new tracer, ^{18}F -Flurpiridaz (Lantheus Medical Imaging), is in a phase 3 multicenter trial. It is especially attractive because ^{18}F does not require an on-site cyclotron or generator for production, has a small positron range, and offers better statistics. Furthermore, ^{18}F -Flurpiridaz offers a higher first-pass myocardial extraction fraction (94%) than ^{82}Rb (~60%) and ^{13}N -ammonia (~80%), and, thus, is potentially more able to detect mildly reduced perfusion defects [11].

Shortening Total Scan Time

Compared with rest/stress ^{82}Rb imaging, rest/stress ^{13}N -ammonia and ^{18}F -Flurpiridaz result in considerably longer scan times because of longer half-lives. An alternative to consider is rapid dual-injection single-scan imaging, wherein stress imaging is performed when uptake from rest imaging is still present. This was preliminarily investigated in the contexts of ^{13}N -ammonia and ^{18}F -Flurpiridaz [12,13], though mostly involving simulations. This approach is closely related to the challenging problem of dual-tracer PET imaging, wherein mathematical formulations are developed to separate uptake patterns from 2 different tracers/injections.

EXISTING SOFTWARE AND COMPARISONS

Presently, clinical adoptions include quantification of MBF and MFR reported at the region-of-interest level. To this end, several software packages exist (consult

[14] for a comprehensive table). Each package employs different methods of segmenting the left ventricle and sampling the counts in the myocardium and blood pool to obtain the input and the myocardium time-activity curves. Slomka et al [15] and Tahari et al [16] compared MBF and MFR quantification among different software packages and methods for ^{13}N -ammonia and ^{82}Rb PET, respectively. The first study utilized QPET (Cedars-Sinai), *syngo* MBF (Siemens), and PMOD (PMOD Technologies), whereas the second study utilized Corridor4DM (Invia), FlowQuant (University of Ottawa), and MunichHeart (Technical University of Munich). The first study concluded that different implementations of 1- and 2-compartment models for ^{13}N -ammonia demonstrate excellent correlation in MBF and MFR for each vascular territory, with similar mean MFR values and similar flow values. However, they cautioned that the data were obtained with a single scanner and imaging-reconstruction protocol. The second study, on the other hand, found that quantitative assessment of resting and stress MBF with ^{82}Rb PET was dependent on the software and methods used, whereas MFR appeared to be more comparable. They concluded that follow-up and treatment assessment should be done with the same software and method.

The discrepancies between the software packages are likely due to several factors. Different methodologies of segmenting the myocardium and blood pool and different ways of calculating the input and myocardial time-activity curves may play a role. The spillover is modeled differently in these packages and may lead to differences in quantification of the MBF. The discrepancies may also emanate from fundamentally different tracer

kinetic-modeling approaches and methods for extraction correction of K_1 values to estimate MBF values.

QUANTITATIVE MPI AT THE INDIVIDUAL VOXEL LEVEL

It is entirely plausible that parametric imaging at the individual voxel level can enhance clinical imaging tasks. An example of this would be to enable enhanced visualization and quantification of base-to-apex perfusion gradients [17], which can indicate diffuse coronary arterial narrowing or preclinical CAD. Furthermore, this approach, combined with noninvasive coronary angiography, can potentially enable quantification of the fractional flow reserve via distal/poststenotic flow measurements.

However, a number of challenges have to be first addressed. These include the statistical problem, which especially challenges parametric imaging at the voxel level. Aside from optimizing the injected dose and use of enhanced image reconstructions, as outlined before, more sophisticated kinetic parameter estimation methods will likely be needed; eg, regularized regression typically enables substantial suppression of noise at the cost of some bias.

Another powerful approach is to directly estimate parametric images from the dynamic projection data (4-D reconstruction). This framework enables more accurate handling of the statistical noise and has been recently applied to MPI with PET, demonstrating suppression of noise at matched bias [18,19]. However, it remains to be implemented and validated for routine clinical practice, especially as it requires more sophisticated consideration of interframe motion/drift.

Finally, we note that voxel-level flow quantification could be further aided by appropriate corrections for cardiac and respiratory movements, but this is a challenging area;

ie, 6-D PET imaging incorporating 3 additional dimensions of tracer dynamics, cardiac, and respiratory movements, and it remains to be seen whether the ongoing research will translate to routine clinical applications.

REFERENCES

- Machac J. Cardiac positron emission tomography imaging. *Semin Nucl Med* 2005;35:17-36.
- Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol* 2006;13:24-33.
- Yoshinaga K, Chow BJ, Williams K, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006;48:1029-39.
- Bengel FM, Higuchi T, Javadi MS, Lautamäki R. Cardiac positron emission tomography. *J Am Coll Cardiol* 2009;54:1-15.
- Schindler TH, Schelbert HR, Quercioli A, Dilsizian V. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. *JACC Cardiovasc Imaging* 2010;3:623-40.
- Gould KL, Johnson NP, Bateman TM, Beanlands RS, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol* 2013;62:1639-53.
- Karakatsanis NA, Loudos G, Rahmim A, Nikita KS. Monte-Carlo based characterization of the counting rate (NECR) response for personalized optimization of the administered activity in clinical PET imaging. *Frontiers Biomed Technol* 2014;1:14-34.
- Le Meunier L, Slomka PJ, Dey D, et al. Motion frozen F-18-FDG cardiac PET. *J Nuclear Cardiol* 2011;18:259-66.
- Alessio AM, Rahmim A, Orton CG. Resolution modeling enhances PET imaging (Point/Counterpoint). *Med Phys* 2013;40:120601.
- Rahmim A, Tang J. Noise propagation in resolution modeled PET imaging and its impact on detectability. *Phys Med Biol* 2013;58:6945-68.
- Maddahi J. Properties of an ideal PET perfusion tracer: new PET tracer cases and data. *J Nucl Cardiol* 2012;19:S30-7.
- Rust TC, DiBella EV, McGann CJ, Christian PE, Hoffman JM, Kadras DJ. Rapid dual-injection single-scan ¹³N-ammonia PET for quantification of rest and stress myocardial blood flows. *Phys Med Biol* 2006;51:5347-62.
- Alpert N, Dean Fang YH, Fakhri GE. Single-scan rest/stress imaging (18)F-labeled flow tracers. *Medical Physics* 2012;39:6609-20.
- Saraste A, Kajander S, Han C, Nesterov SV, Knuuti J. PET: Is myocardial flow quantification a clinical reality? *J Nucl Cardiol* 2012;19:1044-59.
- Slomka PJ, Alexanderson E, Jácome R, et al. Comparison of clinical tools for measurements of regional stress and rest myocardial blood flow assessed with ¹³N-ammonia PET/CT. *J Nucl Med* 2012;53:171-81.
- Tahari A, Lee A, Rajaram M, et al. Absolute myocardial flow quantification with (82)Rb PET/CT: comparison of different software packages and methods. *European J Nucl Med Mol Imaging* 2013;41:126-35.
- Gould KL, Nakagawa Y, Nakagawa K, et al. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. *Circulation* 2000;101:1931-9.
- Rakvongthai Y, Ouyang J, Guerin B, Li Q, Alpert NM, El Fakhri G. Direct reconstruction of cardiac PET kinetic parametric images using a preconditioned conjugate gradient approach. *Med Phys* 2013;40:102501.
- Rahmim A, Tang J, Mohy-ud-Din H. Direct 4D parametric imaging in dynamic myocardial perfusion PET. *Frontiers Biomed Technol* 2014;1:4-13.

Arman Rahmim, PhD, is from the Department of Radiology and the Department of Electrical and Computer Engineering, Johns Hopkins University, Baltimore, Maryland. Abdel K. Tahari, MD, PhD, Thomas H. Schindler, MD, and Mahadevappa Mahesh, MS, PhD are from the Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland. **Arman Rahmim, PhD**, Division of Nuclear Medicine, Department of Radiology, Johns Hopkins University School of Medicine, JHOC Bldg Room 3263, 601 N. Caroline St. Baltimore, MD 21287; e-mail: arahmim1@jhmi.edu.