

SPECT quantification of myocardial blood flow: A journey of a thousand miles begins with a single step (Lao Tzu, Chinese philosopher, 604-531 BC)

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There is increasing evidence for the incremental diagnostic and prognostic value of myocardial blood flow (MBF) quantification over conventional relative myocardial perfusion imaging (MPI). Measurement of stress and rest MBF on an absolute scale (mL/min/g) together with the derived ratio of stress/rest flow reserve (MFR) can help to avoid the accepted under-estimation of the extent and severity of disease observed using conventional relative-scale MPI. Improved detection of multi-vessel and micro-vascular disease has been demonstrated with stress MBF and MFR imaging, mainly using dynamic PET with ⁸²Rb or ¹³N-ammonia tracers. Despite these significant advantages, PET imaging is not as widely available as SPECT, which remains the clinical work-horse in nuclear cardiology for the diagnosis and management of patients with obstructive coronary artery disease (CAD).

Recently, dynamic SPECT imaging has been reported using dedicated cardiac systems with new solid-state CZT detector technologies,¹ and using conventional NaI gamma-camera systems with fast detector rotation and regularized iterative image reconstruction.^{2–5} These important advances have opened the door to investigate the potential for quantification of MBF using SPECT. While there remain some technical

challenges to overcome such as lower scanner efficiency, correction of residual rest activity, and lower tracer extraction using technetium-based SPECT tracers versus rubidium or ammonia PET, there is also an important change in clinical workflow required: shifting from conventional post-injection rest and post-stress imaging to first-pass dynamic imaging during tracer injection, while the patient is on the SPECT scanner bed.

In this issue of the Journal, Sciammarella and colleagues present initial clinical findings from a small pilot study evaluating dynamic SPECT myocardial blood flow (MBF) imaging compared to early- and standard-timing SPECT myocardial perfusion imaging (MPI) in 15 patients with suspected or known CAD.⁶ Their study takes advantage of a unique ‘4D reconstruction’ method for dynamic SPECT imaging, specially developed in-house for cardiac perfusion imaging.⁴ This type of advanced parametric image reconstruction represents the measured data as a combination of pre-defined time-activity curves (also called shape or basis functions) for every voxel in the field of view. While there is not yet an accepted ‘standard basis’ for 4D image reconstruction, the authors have shown promising results using their chosen shape functions in several earlier simulation and human studies.^{3–5} If these shape functions can provide a good fit to the measured dynamic data, then the modeled tracer distribution or ‘parametric images’ can be visualized post hoc at any time point from the start to end of the scan. This has the potential to allow visualization of tracer uptake in very short time intervals (i.e., 5 seconds in the present study) but with the image quality and count statistics derived from the much longer dynamic scan. Using this technology, the authors were able to retrospectively select an optimal time point from the dynamic acquisition that minimized extra-cardiac interference. They compared this ‘early’ parametric

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image, visualized at approximately 10 minutes after injection of ^{99m}Tc-tetrofosmin, versus the standard pharmacological stress MPI acquired at 25 to 40 minutes post injection. They also compared interpretations of these MPI results to those based on the quantitative MFR estimates derived from the dynamic first-pass data.

The novelty of the clinical imaging protocol and dynamic SPECT image reconstruction methods notwithstanding, the study has some important methodological limitations that should be considered in the interpretation. Most importantly, they reported a very small sample of patients (*n* = 15) with selective and arguably sub-optimal measurements of invasive coronary angiography (ICA): 11 of 15 patients with ICA up to 2 years after SPECT, and 10 of these with reported stress SPECT MBF and MFR values in the expected physiological range. It may be tempting to accept the reported high specificity and low sensitivity values of the MPI results (using early or standard timing) in this small cohort. However, these values are exactly opposite to what would be expected in a cohort of patients using ICA as the gold standard for obstructive CAD, where the measured specificity is typically reduced due to post-test referral bias. As shown in Table 1, these results should be ‘taken with a grain of salt,’ as none of the measured sensitivity or specificity values are significantly different between methods, and most of the values are not different from the chance rate of 50%. A much larger sample size is needed to make meaningful measurements of diagnostic performance.

The study does present some supportive data (Figure 1) that are consistent with previous observations using cardiac PET, i.e., a 40 or 50% reduction in stress MBF or flow reserve in coronary vessels with versus without obstructive disease (stenosis ≥70%). However, it should be noted that in 2 of the 6 vessels reported with obstructive disease, it appears that MFR or stress MBF values were above the typical normal cut-off values of 2.0 and 1.5, respectively. The values from one of the 7 patients with obstructive disease were not reported, as they were deemed to be ‘outliers’ above the normal

physiological range [personal communication]. The average values of stress MBF (2.4 mL/min/g) and MFR (3.5) across all 30 vessels were substantially higher than those typically reported using ⁸²Rb or ¹³N-ammonia PET in patients with known or suspected CAD. The reported values are more similar to the normal reference range obtained in young healthy subjects without CAD, as summarized in the recent position paper on clinical quantification of MBF published jointly by the J Nucl Cardiol and J Nucl Med.⁷ Together, these results suggest that additional verification and/or adjustment of the tracer extraction correction function or 4D SPECT image reconstruction methods may be required, to ensure that ^{99m}Tc-tetrofosmin SPECT measurements of MBF and MFR are comparable to the clinical standard values obtained using ⁸²Rb or ¹³N-ammonia PET.

The encouraging results of this small feasibility study suggest that a similar one-day imaging protocol may be able to provide both absolute MBF and relative MPI data using ^{99m}Tc-tetrofosmin with 20-minute dynamic scans at rest and stress, analogous to the well-established dynamic PET imaging protocols. Spillover and scatter of tracer uptake from adjacent organs into the myocardium will be critical to understand and/or correct in such ‘early-MPI’ data. If a one-day rest + stress or stress + rest imaging protocol is anticipated, it will also be important to correct the second scan for residual tracer activity from the first scan to maintain quantitative accuracy. Unfortunately, there was no comparison of image quality or extra-cardiac uptake presented in the study by Sciammarella; the authors noted only that ‘optimum contrast’ was typically observed in the 4D reconstructed images at 8 to 12 minutes post injection.

Following this initial step toward clinical implementation, the use of similar accelerated protocols should be evaluated in larger clinical research studies (including healthy normal subjects) to allow a robust assessment of image quality, sensitivity, and specificity for the detection of i. obstructive CAD, ii. reversible ‘ischemic’ perfusion defects, and iii. impaired stress MBF and MFR. For example, a similar protocol has

Table 1. 95% Confidence Limits for identification of obstructive CAD (stenosis > 70% on invasive coronary angiography) based on the results reported by Sciammarella et al⁴

Performance (<i>n</i> = 11 patients)*	Stress MPI early (10–12 minutes static)	Stress MPI standard (25–40 minutes gated)	Stress/Rest MFR (0–20 minutes dynamic)
Sensitivity	5–85% (2/5 patients)	5–85% (2/5 patients)	28–99% (4/5 patients)
Specificity	54–100% (6/6 patients)	36–99% (5/6 patients)	54–100% (6/6 patients)

*No significant differences in sensitivity or specificity between methods (*p* > .2)

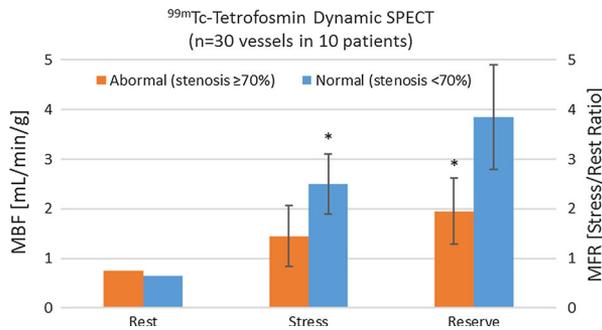


Figure 1. Reported stress MBF and MFR (Reserve) were significantly reduced in vessels with versus without obstructive CAD ($*p < .001$). Rest MBF values were derived from the stress MBF and MFR values reported in 10 of the 11 patients with angiographic evaluation of CAD.

been evaluated recently for combined MBF and MPI using ^{99m}Tc-sestamibi with a fast-rotational NaI SPECT scanner and dietary or pharmacologic suppression of early liver uptake, also with promising initial results.⁸

References

- Wells RG, Marvin B, Poirier M, Renaud JM, deKemp RA, Ruddy TD. Optimization of SPECT measurement of myocardial blood flow with corrections for attenuation, motion, and blood-binding compared to PET. *J Nucl Med* 2017
- Hsu B, Chen FC, Wu TC, Huang WS, Hou PN, Chen CC, Hung GU. Quantitation of myocardial blood flow and myocardial flow reserve with ^{99m}Tc-sestamibi dynamic SPECT/CT to enhance detection of coronary artery disease. *Eur J Nucl Med Mol Imaging* 2014;41:2294-306.
- Gullberg GT, Reutter BW, Sitek A, Maltz JS, Budinger TF. Dynamic single photon emission computed tomography—basic principles and cardiac applications. *Phys Med Biol* 2010;55:R111-91.
- Shrestha UM, Seo Y, Botvinick EH, Gullberg GT. Image reconstruction in higher dimensions: Myocardial perfusion imaging of tracer dynamics with cardiac motion due to deformation and respiration. *Phys Med Biol* 2015;60:8275-301.
- Shrestha U, Sciammarella M, Alhassen F, Yeghiazarians Y, Ellin J, Verdin E, Boyle A, Seo Y, Botvinick EH, Gullberg GT. Measurement of absolute myocardial blood flow in humans using dynamic cardiac SPECT and ^{99m}Tc-tetrofosmin: Method and validation. *J Nucl Cardiol* 2017;24:268-77.
- Sciammarella M, Shrestha UM, Seo Y, Gullberg GT, Botvinick EH. A combined static-dynamic single-dose imaging protocol to compare quantitative dynamic SPECT with static conventional SPECT. *J Nucl Cardiol* 2017
- Murthy VL, Bateman TM, Beanlands RS, Berman DS, Borges-Neto S, Chareonthaitawee P, Cerqueira MD, deKemp RA, DePuey EG, Dilsizian V, Dorbala S, Ficaro EP, Garcia EV, Gewirtz H, Heller GV, Lewin H, Mann A, Malhotra S, Ruddy TD, Schindler TH, Schwartz RG, Slomka PJ, Soman P, Di Carli MF. Clinical quantification of myocardial blood flow using positron emission tomography. Joint Position Paper of the Cardiovascular Council (CVC) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) & the American Society of Nuclear Cardiology (ASNC). *J Nucl Med and J Nucl Cardiol* 2017
- Hsu B, Hu LH, Yang BH, Chen LC, Chen YK, Ting CH, Hung GU, Huang WS, Wu TC. SPECT myocardial blood flow quantitation toward clinical use: a comparative study with ¹³N-Ammonia PET myocardial blood flow quantitation. *Eur J Nucl Med Mol Imaging* 2017;44:117-28.