The potential of regional myocardial blood flow measurement with SPECT

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Myocardial perfusion imaging (MPI) with SPECT has been widely used for the diagnosis and risk stratification of patients with coronary artery disease (CAD) for over 30 years. Its utilization is supported by numerous large studies validating its diagnostic accuracy and prognostic value.¹ However, SPECT MPI is limited as a relative perfusion imaging technique and this has been further emphasized by recent advances in PET MPI and absolute myocardial blood flow (MBF) quantification.² Relative imaging relies on the assumption that areas with the highest tracer uptake are perfused by non-obstructed coronary arteries and are normal.³ Thus, relative MPI can be associated with underestimation of CAD severity and extent, especially in cases of multivessel disease.⁴ In that context, MBF quantification could enhance the diagnostic performance of SPECT MPI, as well as to provide incremental prognostic value over relative perfusion imaging alone.

Assessment of MBF with PET has been validated with different tracers and is currently routinely used in the clinical setting with various commercially available software programs.⁵ Accurate MBF quantification requires a dynamic acquisition to assess the tracer first-pass circulation in the myocardium, which is readily possible with current PET systems. Unfortunately, PET cameras are not widely available and SPECT remains

the work-horse of nuclear cardiology. Although feasible,⁶ quantification of MBF is suboptimal with conventional NaI SPECT systems as they have low count sensitivity and poor temporal resolution. The advent of new SPECT systems with solid state cadmium-zinc-telluride (CZT) detectors and a non-rotating gantry design such as the Discovery NM 530c/570c (GE Healthcare) and the D-SPECT Cardio (Spectrum Dynamics) systems can circumvent many of the conventional angler camera limitations, with higher sensitivity and allowing improved temporal and spatial resolution. The first preclinical validation of MBF assessment with a CZT camera was performed in pigs and compared to microspheres.⁷ The authors showed that MBF quantification with both ^{99m}Tc-labeled tetrofosmin and sestamibi tracers and ²⁰¹Tl was possible. As well, several studies have shown the feasibility of MBF quantification with SPECT in humans.^{6,8–12}

In this issue of the *Journal of Nuclear Cardiology*®, Zavadovsky et al.¹³ report the diagnostic accuracy of regional MBF, coronary flow reserve (CFR), and flow difference (Stress MBF-Rest MBF) assessed with a CZT camera for detection of obstructive CAD identified with invasive coronary angiography and fractional flow reserve (FFR). Twenty-three patients underwent same day rest-stress dynamic imaging with ^{99m}Tc-sestamibi on a Discovery NM/CT 570c camera with stress injection (9 MBq·kg⁻¹) performed 45 minutes after rest injection (3 MBq·kg⁻¹), followed by coronary angiography within 7 days. Importantly, FFR was measured in all stenotic arteries when technically possible, allowing combined anatomical (% stenosis) and functional (FFR) per-vessel analysis. Global and regional MBF was quantified using a net retention model without correction for extraction fraction.¹⁴ The authors report significant correlations between regional MBF ($r = 0.63$), CFR ($r = 0.66$), and flow difference ($r = 0.73$) vs FFR values.

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In regions with CFR below 1.48, FFR was significantly reduced in 90% of cases and in regions with preserved CFR, FFR was normal in 78% of cases. Of interest, these flow parameters better predicted the presence of impaired FFR compared to conventional semi-quantitative perfusion parameters derived from relative perfusion images. These results support those of Miyagawa et al.¹⁵ who showed a significant correlation ($r = 0.62$) between FFR and regional CFR index in a larger population.

The average global rest (0.36 , range 0.33 – 0.54 $\text{mL}^{-1}\cdot\text{minute}^{-1}\cdot\text{g}^{-1}$) and stress MBF (0.67 , range 0.55 – 0.81 $\text{mL}^{-1}\cdot\text{minute}^{-1}\cdot\text{g}^{-1}$) values reported are strikingly decreased compared to those reported by other studies using either PET or SPECT (Figure 1), and well below the physiological range. The authors attribute those low flow values to the tracer kinetic properties of $^{99\text{m}}\text{Tc}$ -sestamibi. The extraction fraction of sestamibi decreases with increasing MBF.¹⁴ Appropriate extraction fraction correction in the model will permit accurate measurement of MBF with more physiologic values,^{7,9,12} particularly for stress MBF. However, the lack of extraction fraction correction does not explain the low rest flows which may be due to inaccurate scaling of the integrated myocardial uptake and the arterial input data. Notably, the CFR measurements are more reasonable which may reflect cancelation of this scaling factor when using the ratio of stress and rest flows.

Despite this limitation of low rest and stress MBF values, this study presents interesting results that are a welcome addition to the body of literature demonstrating the feasibility and possible role of MBF quantification with SPECT. One of the most remarkable findings of this study is that among ten patients with normal relative perfusion images (sum rest score and sum stress score ≤ 3), 6 (60%) patients had significant

CAD on angiography including multivessel disease in 3 (30%) of subjects. In these six patients, mean global stress MBF was significantly lower than patients without significant CAD. Thus, measurement of global stress MBF could improve sensitivity of SPECT MPI, especially in the context of multivessel CAD.

Prior to wider clinical implementation, standardization of MBF quantification is desirable for clinical care and multicenter studies. While some studies use extraction fraction parameters of other tracers such as ammonia to calculate index of MBF,⁸ others rely on ratios of K1 values avoiding extraction fraction correction.¹⁵ SPECT MBF measurements with extraction fraction correction correlate well with PET measurements using a 1-tissue-compartment model¹² and a retention model,⁹ suggesting that this approach with extraction fraction correction is optimal. Multicenter studies assessing the diagnostic performance and the prognostic utility of SPECT MBF are also necessary to determine its incremental value relative to relative perfusion imaging. Supplemental technical and professional reimbursement will be necessary to offset the increased time required for acquisition, processing, and interpretation and much easier to justify with additional clinical value. SPECT measurement of MBF has much potential which now needs to be realized.

Disclosure

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Figure 1. Representative samples of rest MBF, stress MBF, and CFR for PET (blue)^{16–20} and SPECT (black)^{6,9–11} in various populations with and without CAD. The rest and stress MBF obtained by Zavadvovsky et al. (red) appear lower compared to other studies especially for stress MBF.

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