SPECT quantification of myocardial blood flow: Another step toward widespread availability

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INTRODUCTION

Myocardial blood flow (MBF) quantification with positron emission tomography (PET) has emerged as a clinically robust method for both cardiovascular risk stratification and to assess for the presence of flow-limiting coronary artery disease (CAD) and coronary microvascular disease.^{1–3} However, application of this technology to large populations has been limited by cost of both the PET system and positron-emitting radiotracers, requiring either an onsite cyclotron or monthly purchase of an expensive generator.

Thus, efforts have been made to develop methodologies to assess MBF quantification using single photon emission computed tomography (SPECT) technology. In particular, cadmium zinc telluride (CZT)-based SPECT scanners allow for the ability to do fully sampled concurrent stationary imaging, like PET (Table 1). And while CZT solid-state detectors buy energy resolution and allows compact detectors, it is the geometry of these systems that enables the fast dynamics required for MBF measurements. In particular, the ability to acquire all needed projections without motion (hence, PET-like) is what allows for the short time frames used in the

dynamic analysis. Additionally, SPECT-based MBF quantification uses commercially available radiotracers which are widely available and relatively inexpensive. Several groups have reported their experience using SPECT for MBF quantification,^{4–6} including a handful studies that have compared MBF results head-to-head between SPECT and PET in the same population (Table 2).^{7–11}

In their recent manuscript “Quantification of myocardial perfusion reserve with CZT-SPECT: comparisons with rubidium PET,” Acampa et al. compare the performance of D-SPECT with rubidium-82 PET.¹¹ They report that MBF and myocardial flow reserve (MFR) measured by CZT-SPECT correlate moderately well compared to PET (Pearson correlation ~ 0.5) in 25 patients referred for clinical evaluation. They show that CZT-SPECT performance is comparable to PET with an Area Under ROC Curve (AUC) of 0.83 and 0.84, respectively. Additionally, they identify a regional cutoff for CZT-SPECT MFR of 2.1 which provides 92% sensitivity in diagnosing CAD compared with 100% for cardiac PET. This work is an important contribution to efforts to bring MBF quantification to SPECT and thus make it more widely available. It also highlights several challenges and issues that must be considered along the way.

First, the role of MBF and MFR serves dual purposes. Although MFR is reported to help with the diagnosis of CAD, this has not been well-validated clinically. More specifically, though the correlation between MFR and coronary artery stenosis is well established in research environments, where a specific ROI in the territory of a perfusion defect is selected for MFR quantification,^{12,13} the ability of MFR to diagnose CAD using clinical software is not well established. One potential reason for this is that commercially available

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Table 1. Comparison of SPECT systems currently available

SPECT scanners	Planar resolution	Fast dynamics	Attenuation correction
Conventional SPECT	~ 13 mm	No	Yes*
Spectrum Dynamics D-SPECT™	~ 23 mm	Yes	No
C-SPECT High Res	~ 13 mm	Yes	Yes
C-SPECT High Sens	~ 28 mm	Yes	Yes
GE Healthcare Discovery™ NM 530c	~ 19 mm	Yes	No
GE Healthcare Discovery™ NM/CT 570c	~ 19 mm	Yes	Yes
Spectrum Dynamics VERITON-CT	15–23 mm**	Yes‡	Yes
GE Healthcare NM/CT 870 CZT	~ 13 mm	No §	Yes

Planar spatial resolutions are estimated by us based on the public literature and do not include the effect of resolution modeling in reconstruction, which typically improves resolution by a factor of 2. The column of fast dynamics indicates if motion is required for SPECT or if motion-free fast dynamic imaging can be performed. The last column shows if there is a hardware-based system for attenuation correction, such as a CT or transmission source

*Attenuation correction is available but optional with conventional SPECT systems

**There is high uncertainty in our estimate of the VERITON resolution because collimator parameters have not been published and available performance measurements in the literature¹⁶ do give the size of the field of view over which each camera head is swiveled

‡system is in principle capable of fast dynamics

§ General-purpose solid-state systems are rotating cameras and, thus, fast dynamic imaging is currently not feasible

software, such as FlowQuant (University of Ottawa, Canada) and Corridor-4DM (Invia, Ann Arbor, Michigan), uses pre-determined regions to represent coronary territories. These may or may not correlate well with the territories perfused by the culprit vessel for a given patient, depending on patient-specific anatomy. Similarly, significant stenosis in a given branch may give significant focal alternations in MFR which are then diluted by high MFR in the rest of the software-defined coronary territory. Algorithms that implement the 17-segment myocardial model or that focus on regional flow quantification of perfusion deficits on static images may help overcome this limitation, and most of these software packages do provide the former measurements, though studies are needed to understand how to interpret segmental MBF and MFR. On the other hand, in the absence of flow-limiting epicardial CAD, MBF is a direct measurement of the coronary microvasculature and MFR reflects coronary microvascular function. Thus, MBF is a robust quantitative tool to evaluate coronary microvascular disease. Several studies have shown that resting MBF and MFR are well correlated with cardiovascular outcomes in a variety of patient populations without CAD.³

Second, limiting bias in patient selection is crucial in establishing the effectiveness of SPECT in comparison with PET and understanding what limitations need to be addressed. While knowing that SPECT MBF may not be feasible in all patients due to size and weight restrictions, it seems that the least bias would come from

cohorts where PET was performed prospectively on patients being evaluated for MBF by SPECT (or vice versa) rather than only obtaining PET MBF when the SPECT result was inconclusive or technically limited in some other way.

Third, the authors determined that the correlation between PET and SPECT was only around 0.5. This may be partly due to use of different software. Whereas Corridor-4DM was used for SPECT MBF quantification, PET dynamic data were quantified using FlowQuant. This is a limitation of the study as using different software for MBF quantification can introduce as much as 13% variability.¹⁴ This modest correlation may also be due to the measurement uncertainty in both SPECT and PET as well as differences in the tracer characteristics and the hardware. In particular, SPECT MBF in the right coronary artery (RCA) territory was lower, which may be from diaphragmatic attenuation, extracardiac uptake, or the worsening resolution for SPECT for regions further from the collimator; this last explanation may apply in reverse to PET since its RCA values are relatively higher as PET scanners have degraded resolution for regions further from the center due to depth of interaction in the crystals.

Fourth, as we move to improved quantification for SPECT MBF, it will also be important to account for scatter and attenuation for more accurate SPECT reconstructions and to model accurately the mixing between the myocardium and the blood pool. While careful phantom and patient studies will be needed to do this

Table 2. Summary of myocardial blood flow quantification comparison between CZT-based SPECT and PET in patients with known or suspected coronary artery disease

Author Year	N	SPECT system	PET tracer	Vasodilator	Software	Rest MBF (mL/min/ g)	r	Stress MBF (mL/min/ g)	r	MFR	r
Nkoulou 2016 ⁷	28	NM 570c	¹³ N- ammonia	Adenosine	PMOD	0.89 [0.77- 1.00]	0.51	1.11 [1.00- 1.26]	0.30	1.32 [1.13- 1.52]	N/A
Wells 2017 ⁸	31	NM 530c	⁸² Rb & ammonia	Dipyridamole	FlowQ	0.92 [0.78- 1.06]	0.85**	2.06 [1.48- 2.56]	0.85**	2.36 [1.57- 2.71]	N/A
Agostini 2018 ⁹	30	D-SPECT	¹⁵ O-water	Regadenoson	4DM	1.15 ± 0.31	0.83**	3.18 ± 0.95	0.83**	2.84 ± 0.69	0.75
Giubbini 2019 ¹⁰	54	NM 530c	¹³ N- ammonia	Regadenoson	4DM	1.02 ± 0.22	N/A	2.66 ± 0.92	0.48†	2.64 ± 0.81	0.50†
Acampa 2020 ¹¹	25	D-SPECT	⁸² Rb	Dipyridamole	4DM FlowQ	1.14 ± 0.40† 0.77 ± 0.24‡ 0.76 ± 0.19	N/A	2.36 ± 1.09† 1.62 ± 0.68‡ 1.87 ± 0.45	0.59‡	2.18 ± 0.96† 2.22 ± 0.97‡ 2.52 ± 0.56	0.52‡
						0.99 ± 0.3	N/A	2.40 ± 0.9	0.44	2.44 ± 0.7	0.56
						1.08 ± 0.4		1.94 ± 0.7		1.99 ± 0.7	

MBF = myocardial blood flow (SPECT results in top row and PET results in bottom row)

MFR = myocardial flow reserve (SPECT results in top row and PET results in bottom row)

r = correlation coefficient

Flow results are provided either median [with interquartile range] or mean ± standard deviation

*Only mean residual difference reported for both rest and stress MBF

**Only correlation for combined rest and stress MBF reported

† Non-attenuation-corrected SPECT results

‡ Attenuation-corrected SPECT results

well, we know intuitively and from animal work¹⁵ that the mixing from the blood pool into the myocardium is not zero; underestimating this parameter will tend to reduce the results of MBF measurement. To go further, in clinical SPECT where the resolution can vary substantially over the heart and where the patient anatomy can vary significantly as well, it may be important to consider methods for region-specific and patient-specific mixing parameters. In agreement, Wells and collaborators observed that corrections for motion and tracer binding improved global MBF correlation and precision compared to PET MBF.⁸ On the other hand, somewhat equivocal results have been found regarding the importance of attenuation correction on MBF quantification with SPECT.^{8,10}

Fifth, the authors identified a noteworthy difference in hyperemic MBF measured between the modalities. Hyperemic MBF was higher for CZT-SPECT, despite the known lower extraction fraction of sestamibi at higher flow rates than its PET-counterpart, which should, theoretically, result in lower hyperemic MBF values. However, prior studies are in agreement with Acampa, for example, Agostini⁹ and Giubbini,¹⁰ both observed higher hyperemic MBF with SPECT, a finding that remains incompletely elucidated (Table 2). To help compare PET and SPECT in the future, it would lead to more reproducible results to explicitly state what corrections are done and how they are done. For example, there is a need to compensate for existing myocardial uptake when multiple injections and scans are performed for positioning, rest, and stress, respectively. Further, the software not only calculates MBF, but implicitly calculates K1. If both values or the mapping curve is given, future studies that improve our understanding of the flow-dependent extraction fraction will be able to update these MBF values.

Future work in establishing MBF imaging with SPECT will need to include the development of accurate methods to quantify mixing parameters, the validation of current models and assumptions used for PET in SPECT imaging, and additional understanding of the interaction between hardware, software, and patient selection. As SPECT technologies continue to advance, studies such as this comparing SPECT with PET for MBF quantification will be crucial in making state-of-the-art cardiovascular risk stratification and diagnostic modalities available to larger segments of the population.

References

1. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG and Di Carli MF. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;129:2518-27.

2. Klein R, Beanlands RSB and deKemp RA. Quantification of myocardial blood flow and flow reserve: Technical aspects. *J Nucl Cardiol* 2010;17:555-70.
3. Guerraty MA, Rao HS, Anjan VY, Szapary H, Mankoff DA, Pryma DA, Rader DJ and Dubroff JG. The role of resting myocardial blood flow and myocardial blood flow reserve as a predictor of major adverse cardiovascular outcomes. *PLoS ONE* 2020;15:e0228931.
4. Ben-Haim S, Murthy VL, Breault C, Allie R, Sitek A, Roth N, Fantony J, Moore SC, Park MA, Kijewski M, Haroon A, Slomka P, Erlandsson K, Baavour R, Zilberstien Y, Bomanji J and Di Carli MF. Quantification of myocardial perfusion reserve using dynamic SPECT imaging in humans: A feasibility study. *J Nucl Med* 2013;54:873-79.
5. Klein R, Hung GU, Wu TC, Huang WS, Li D, deKemp RA and Hsu B. Feasibility and operator variability of myocardial blood flow and reserve measurements with (9)(9m)Tc-sestamibi quantitative dynamic SPECT/CT imaging. *J Nucl Cardiol*. 2014;21:1075-88.
6. Gullberg GT, Di Bella EV and Sinusas AJ. Estimation of coronary flow reserve: Can SPECT compete with other modalities? *J Nucl Cardiol* 2001;8:620-5.
7. Nkoulou R, Fuchs TA, Pazhenkottil AP, Kuest SM, Ghadri JR, Stehli J, Fiechter M, Herzog BA, Gaemperli O, Buchel RR and Kaufmann PA. Absolute Myocardial Blood Flow and Flow Reserve Assessed by Gated SPECT with Cadmium-Zinc-Telluride Detectors Using 99mTc-Tetrofosmin: Head-to-Head Comparison with 13N-Ammonia PET. *J Nucl Med* 2016;57:1887-92.
8. Wells RG, Marvin B, Poirier M, Renaud J, deKemp RA and Ruddy TD. Optimization of SPECT Measurement of Myocardial Blood Flow with Corrections for Attenuation, Motion, and Blood Binding Compared with PET. *J Nucl Med* 2017;58:2013-19.
9. Agostini D, Roule V, Nganoa C, Roth N, Baavour R, Parienti JJ, Beygui F and Manrique A. First validation of myocardial flow reserve assessed by dynamic (99m)Tc-sestamibi CZT-SPECT camera: head to head comparison with (15)O-water PET and fractional flow reserve in patients with suspected coronary artery disease. The WATERDAY study. *Eur J Nucl Med Mol Imaging* 2018;45:1079-90.
10. Giubbini R, Bertoli M, Durmo R, Bonacina M, Peli A, Faggiano I, Albano D, Milan E, Stern E, Paghera B, Rodella C, Cerudelli E, Gazzilli M, Dondi F, Bertagna F and Camoni L. Comparison between N(13)NH3-PET and (99m)Tc-Tetrofosmin-CZT SPECT in the evaluation of absolute myocardial blood flow and flow reserve. *J Nucl Cardiol* 2019.
11. Acampa W, Zampella E, Assante R, Genova A, De Simini G, Mannarino T, D'Antonio A, Gaudieri V, Nappi C, Buongiorno P, Mainolfi CG, Petretta M and Cuocolo A. Quantification of myocardial perfusion reserve by CZT-SPECT: A head to head comparison with (82)Rubidium PET imaging. *J Nucl Cardiol* 2020.
12. Di Carli M, Czernin J, Hoh CK, Gerbaudo VH, Brunken RC, Huang SC, Phelps ME and Schelbert HR. Relation among stenosis severity, myocardial blood flow, and flow reserve in patients with coronary artery disease. *Circulation* 1995;91:1944-51.
13. Beanlands RS, Muzik O, Melon P, Sutor R, Sawada S, Muller D, Bondie D, Hutchins GD and Schwaiger M. Noninvasive quantification of regional myocardial flow reserve in patients with coronary atherosclerosis using nitrogen-13 ammonia positron emission tomography. Determination of extent of altered vascular reactivity. *J Am Coll Cardiol* 1995;26:1465-75.
14. Nesterov SV, Deshayes E, Sciagra R, Settimo L, Declercq JM, Pan XB, Yoshinaga K, Katoh C, Slomka PJ, Germano G, Han C, Aalto V, Alessio AM, Ficaro EP, Lee BC, Nekolla SG, Gwet KL,

- deKemp RA, Klein R, Dickson J, Case JA, Bateman T, Prior JO and Knuuti JM. Quantification of myocardial blood flow in absolute terms using (82)Rb PET imaging: the RUBY-10 Study. *JACC Cardiovasc Imaging* 2014;7:1119-27.
15. Guerraty MA, Johnson LC, Blankemeyer E, Rader DJ, Moore SC and Metzler SD. Development and feasibility of quantitative dynamic cardiac imaging for mice using muSPECT. *J Nucl Cardiol* 2020.
16. Desmonts C, Bouthiba MA, Enilorac B, Nganoa C, Agostini D and Aide N. Evaluation of a new multipurpose whole-body CzT-based camera: comparison with a dual-head Anger camera and first clinical images. *EJNMMI Phys* 2020;7:18.

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