Editorial

How Can the Assessment of Myocardial Flow Reserve by Nuclear Medicine Change the Interpretation of Myocardial Perfusion Scintigraphy?

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Myocardial perfusion scintigraphy (MPS) with single-photon emission computed tomography (SPECT) is important for the diagnosis and prognostic evaluation in patients with coronary artery disease (CAD).[1] MPS evaluates the presence, extent and degree of myocardial ischemia and/or infarction, usually through visual observation or semi-quantitative parameters. Despite its proven diagnostic and prognostic values, the relative nature of perfusion imaging may limit SPECT ability to identify patients with high-risk multivessel CAD.[2] Limitations regarding visual or semi-quantitative assessment of regional myocardial perfusion defects may result in underestimation or misdiagnosis due to "balanced" ischemia.

This limitation can be addressed by quantifying myocardial blood flow (MBF) or myocardial flow reserve (MFR) using tracer kinetics in positron emission tomography (PET).[3,4] PET is a well-validated non-invasive method for quantification of myocardial perfusion, demonstrating an incremental diagnostic and prognostic power compared to MPS in patients with suspected or known CAD.[5,6] PET then is considered the gold standard for non-invasive quantification of MBF and MFR.[7-9] However, the production of PET tracers is costly and the technology is not yet available in many countries.

The introduction of high-sensitivity cadmium-zinc-teluride (CZT) cameras for cardiology tests allows the dynamic acquisition of tomographic images to evaluate radiotracer kinetics, and opens a new era for measuring MBF and MFR.[10]

Quantification of MBF and MFR using dynamic CZT-SPECT in list mode is technically feasible and clinically useful.[11,12] The WATERDAY study[13] compared MBF and MFR obtained with 99mTc-sestamibi in CZT-SPECT with those obtained in a ^{15}O-water PET and fractional flow reserve (FFR). While stress and rest MBF were significantly overestimated with CZT-SPECT compared to PET, MFR was similar between the two techniques, which means that the quantification of MBF and MFR by dynamic 99mTc-sestamibi CZT-SPECT is clinically useful.[13] Acampa et al.[14] demonstrated that CZT-SPECT values are higher than those measured by 82Rb-PET imaging, with a moderate correlation between the two methods. CZT-SPECT showed good diagnostic accuracy for identifying obstructive CAD. Different studies have outlined the incremental value of MFR measurements in different categories of patients for diagnosis or prognosis.[14] In patients with multivessel CAD, where normal myocardial perfusion imaging (MPI) may not necessarily identify truly low-risk subgroups among high-risk cohorts, they often show reduced MFR.[14]

Despite the excellent diagnostic value of FFR, which quantifies pressure gradient through stenosis, it does not reflect microcirculation abnormalities. Unlike FFR, myocardial perfusion reserve (MPR) reflects flow in epicardial arteries and microvasculature. Therefore, FFR and MPR are not equivalent.[16]

It should be noted that several factors can affect the hemodynamic flow response to luminal stenosis, including lesion geometry and location and the presence of collateral vessels, impacting overall regional flow. In a study by our group, De Souza et al.[17] showed that both global MPR and MBF stress were reduced in patients with abnormal perfusion. In addition to assessing perfusion, this study demonstrated that overall MPR is inversely associated with CAD prognostic index (CADPI), a hierarchical index that includes the entire epicardial coronary tree and is related to overall cardiovascular risk.[17]

In this scenario, Panjer et al.[18] performed a systematic review and meta-analysis with the objective of evaluating the diagnostic accuracy of dynamic CZT-SPECT in coronary artery disease (CAD) compared to FFR and PET as a reference. To assess CZT-SPECT, the analysis yielded 0.79 sensitivity (95% CI 0.73–0.85) and 0.85 specificity (95% CI 0.74–0.92). Diagnostic odds ratio was 17.82 (95% CI 8.80–36.08, P \ 0.001). Positive likelihood ratio and negative likelihood ratio were 3.86 (95% CI 2.76–5.38, P<0.001) and 0.21 (95% CI 0.13–0.33, P<0.001), respectively. The results of this systematic review and meta-analysis emphasize the role of dynamic CZT-SPECT MPI with good sensitivity and specificity for diagnosing CAD compared to gold standards. The use of CZT-SPECT systems for measuring MPR is very attractive considering that in just one scan it is possible to obtain perfusion and functional parameters with results comparable to PET. However, what emerges from this meta-analysis is that the protocol used in different centers should be better standardized. The included studies use different methodologies in terms of dose administration, acquisition protocol, CZT cameras, radiotracers and software package used. Furthermore, in each study a different cutoff value was defined for the dynamic SPECT MPI. Seven studies compared with FFR and two used PET. To measure acquisition, MPI was performed with different types of CZT-SPECT cameras. Six studies used Discovery NM 530c (GE Healthcare, Chicago, IL, USA), one study (11.1%) used Discovery NM/CT 570c

Keywords

Coronary artery disease; Scintigraphy; Diagnosis.

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DOI: https://doi.org/10.36660/abcimg.2023363i

(Alcyone technology, GE Healthcare, Haifa, Israel) and two studies (22.2%) used D-SPECT (Spectrum Dynamics, Palo Alto, California). Dual isotope administration was used in one study. Two studies used 201Tl as a radiotracer, and six studies (66.7%) used 99mTc-labeled markers. Different software was used for MBF quantification and MFR measurement, including internal software, with 4DM Corridor (INVIA, Ann Arbor, MI, USA) applied more often than others. Furthermore, the main limitation of this systematic review and meta-analysis, in addition to the typical limitations for this type of analysis, is the relatively small number of included studies and patients and inter-comparison heterogeneity.[19] In this regard, studies with a larger population and smaller variability between methodologies, such as different thresholds for MFR, myocardial radiotracer distribution, different reconstruction algorithms and applied flow models will be necessary to clearly demonstrate the additional clinical impact of MBF with CZT.

Myocardial flow reserve assessment using CZT can be useful in many clinical situations, as shown by PET (Table 1).

One of the main uses was demonstrated in the extremely high sensitivity to detect multivascular disease, as in the study by DiCarli et al., where normal MFR on PET virtually excluded the possibility of this event.[20] MFR evaluation by CZT-SPECT also allows for this increase in accuracy.[21]

The possibility of identifying microvascular disease as the cause of angina is useful for reducing investigation costs but also very important as a determinant of prognosis. MFR, both on PET and on CZT-SPECT, is a non-invasive modality for confirming this phenomenon.[22]

In preparation for pharmacological stress with dipyridamole or adenosine, abstinence from caffeine for at least 24 hours is recommended. However, when this preparation is not carried out properly, vasodilator response may be compromised and, consequently, induction of flow disparity. In traditional scintigraphy, this cannot be identified and may result in a "false-negative" result, but this inadequate response is detected by MFR evaluation.[23]

As more studies are published, leading to better standardization of MBF and MFR quantification by CZT-SPECT, it will become an important tool in the clinical practice of ischemic cardiomyopathies, adding to our understanding of this disease.

Table 1 – In which situations can myocardial flow reserve make a difference?

1) Patients with little ischemia who may have multivessel CAD.
2) Perfusion defects, but with artifact.
3) Normal perfusion but at high risk for CAD.
4) Identification of microvascular disease.
5) Determine vaso-stressor effectiveness.

Author Contributions

Writing of the manuscript: Lima RSL.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Mastrocola LE, Amorim BJ, Vitola JV, Brandão SCS, Grossman GB, Lima RSL, et al. Update of the Brazilian Guideline on Nuclear Cardiology - 2020. Arq Bras Cardiol. 2020;114(2):325-29. doi: 10.36660/abc.20200087.
2. Lima RS, Watson DD, Goode AR, Siadaty MS, Ragosta M, Beller GA, et al. Incremental Value of Combined Perfusion and Function Over Perfusion Alone by Gated SPECT Myocardial Perfusion Imaging for Detection of Severe Three-Vessel Coronary Artery Disease. J Am Coll Cardiol. 2003;42(1):64-70. doi: 10.1016/s0735-1097(03)00562-x.
3. Muzik O, Duvernoy C, Beanlands RS, Sawada S, Dayanikli F, Wolfe ER Jr, et al. Assessment of Diagnostic Performance of Quantitative Flow Measurements in Normal Subjects and Patients with Angiographically Documented Coronary Artery Disease by Means of Nitrogen-13 Ammonia and Positron Emission Tomography. J Am Coll Cardiol. 1998;31(3):534-40. doi: 10.1016/s0735-1097(97)00526-3.
4. Parkash R, de Kemp RA, Ruddy TD, Kitsikis A, Hart R, Beauchesne L, et al. Potential Utility of Rubidium 82 PET Quantification in Patients with 3-Vessel Coronary Artery Disease. J Nucl Cardiol. 2004;11(4):440-9. doi: 10.1016/j.nuclcard.2004.04.005.
5. Zampella E, Acampa W, Assante R, Nappi C, Gaudieri V, Mainolfi CG, et al. Combined Evaluation of Regional Coronary Artery Calcium and Myocardial Perfusion by 82Rb PET/CT in the Identification of Obstructive Coronary Artery Disease. Eur J Nucl Med Mol Imaging. 2018;45(4):521-29. doi: 10.1007/s00259-018-3935-1.
6. Assante R, Acampa W, Zampella E, Arumugam P, Nappi C, Gaudieri V, et al. Prognostic Value of Atherosclerotic Burden and Coronary Vascular Function in Patients with Suspected Coronary Artery Disease. Eur J Nucl Med Mol Imaging. 2017;44(13):2290-98. doi: 10.1007/s00259-017-3800-7.
7. Johnson NP, Gould KL, Di Carli MF, Taqueti VR. Invasive FFR and Noninvasive CFR in the Evaluation of Ischemia: What Is the Future? J Am Coll Cardiol. 2016;67(23):2772-88. doi: 10.1016/j.jacc.2016.03.584.
8. Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA, et al. Quantitative Assessment of Myocardial Perfusion in the Detection of Significant Coronary Artery Disease: Cutoff Values and Diagnostic Accuracy of Quantitative [(15)O]H2O PET Imaging. J Am Coll Cardiol. 2014;64(14):1464-75. doi: 10.1016/j.jacc.2014.05.069.

9. Kajander SA, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, et al. Clinical Value of Absolute Quantification of Myocardial Perfusion with (15)O-Water in Coronary Artery Disease. Circ Cardiovasc Imaging. 2011;4(6):678-84. doi: 10.1161/CIRCIMAGING.110.960732.

10. Wells RG, Timmins R, Klein R, Lockwood J, Marvin B, deKemp RA, et al. Dynamic SPECT Measurement of Absolute Myocardial Blood Flow in a Porcine Model. J Nucl Med. 2014;55(10):1685-91. doi: 10.2967/jnumed.114.139782.

11. Esteves FP, Raggi P, Folks RD, Keidar Z, Askew JW, Rispler S, et al. Novel Solid-State-Detector Dedicated Cardiac Camera for Fast Myocardial Perfusion Imaging: Multicenter Comparison with Standard Dual Detector Cameras. J Nucl Cardiol. 2009;16(6):927-34. doi: 10.1007/s12350-009-9137-2.

12. Bocher M, Blevis IM, Tsukerman L, Shrem Y, Kovalski G, Volokh L. A Fast Cardiac Gamma Camera with Dynamic SPECT Capabilities: Design, System Validation and Future Potential. Eur J Nucl Med Mol Imaging. 2010;37(10):1887-902. doi: 10.1007/s00259-010-1488-z.

13. Agostini D, Roule V, Nganoa C, Roth N, Baavour R, Parienti JJ, et al. First Validation of Myocardial Flow Reserve Assessed by Dynamic 99mTc-Sestamibi CZT-SPECT Camera: Head to Head Comparison with 15O-Water PET and Fractional Flow Reserve in Patients with Suspected Coronary Artery Disease. The WATERDAY study. Eur J Nucl Med Mol Imaging. 2018;45(7):1079-90. doi: 10.1007/s00259-018-3958-7.

14. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, et al. Improved Cardiac Risk Assessment with Noninvasive Measures of Coronary Flow Reserve. Circulation. 2011;124(20):2215-24. doi: 10.1161/CIRCULATIONAHA.111.050427.

15. Acampa W, Zampella E, Assante R, Genova A, De Simini G, Mannarino T, et al. Quantification of Myocardial Perfusion Reserve by CZT-SPECT: A Head to Head Comparison with 82Rubidium PET Imaging. J Nucl Cardiol. 2021;28(6):2827-39. doi: 10.1007/s12350-020-02129-w

16. Zavadovsky KV, Mochula AV, Boshchenko AA, Vrublevsky AV, Baev AE, Krylov AL, et al. Absolute Myocardial Blood Flows Derived by Dynamic CZT Scan vs Invasive Fractional Flow Reserve: Correlation and accuracy. J Nucl Cardiol. 2021;28(1):249-59. doi: 10.1007/s12350-019-01678-z.

17. Souza ACDAH, Gonçalves BKD, Tedeschi AL, Lima RSL. Quantification of Myocardial Flow Reserve Using a Gamma Camera with Solid-State Cadmium-Zinc-Telluride Detectors: Relation to Angiographic Coronary Artery Disease. J Nucl Cardiol. 2021;28(3):876-84. doi: 10.1007/s12350-019-01775-z.

18. Panjer M, Dobrolinska M, Wagenaar NRL, Slart RHJA. Diagnostic Accuracy of Dynamic CZT-SPECT in Coronary Artery Disease. A Systematic Review and Meta-Analysis. J Nucl Cardiol. 2022;29(4):1686-97. doi: 10.1007/s12350-021-02721-8.

19. Cantoni V, Green R, D'Antonio A, Cuocolo A. Dynamic CZT-SPECT in Coronary Artery Disease: Where are we Now? J Nucl Cardiol. 2022;29(4):1698-701. doi: 10.1007/s12350-021-02752-1.

20. Naya M, Murthy VL, Taqueti VR, Foster CR, Klein J, Garber M, et al. Preserved Coronary Flow Reserve Effectively Excludes High-Risk Coronary Artery Disease on Angiography. J Nucl Med. 2014;55(2):248-55. doi: 10.2967/jnumed.113.121442.

21. Souza ACDAH, Gonçalves BKD, Tedeschi A, Lima RSL. Quantification of Coronary Flow Reserve with CZT Gamma Camera in the Evaluation of Multivessel Coronary Disease. Arq Bras Cardiol. 2018;111(4):635-37. doi: 10.5935/abc.20180196.

22. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, et al. International Standardization of Diagnostic Criteria for Microvascular Angina. Int J Cardiol. 2018;250:16-20. doi: 10.1016/j.ijcard.2017.08.068.

23. Bateman TM, Heller GV, Beanlands R, Calnon DA, Case J, deKemp R, et al. Practical Guide for Interpreting and Reporting Cardiac PET Measurements of Myocardial Blood Flow: An Information Statement from the American Society of Nuclear Cardiology, and the Society of Nuclear Medicine and Molecular Imaging. J Nucl Med. 2021;62(11):1599-615. doi: 10.2967/jnumed.121.261989.