Dynamic CZT-SPECT in coronary artery disease: Where are we now?

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Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is an important noninvasive imaging tool for diagnosis, risk stratification and prognostic evaluation in coronary artery disease (CAD).[1] SPECT MPI evaluates the presence, extent and degree of myocardial ischemia and/or infarction usually through visual observation or semi-quantitative parameters. Despite its diagnostic and prognostic values, the relative nature of perfusion images may limit the ability of SPECT to identify patients with high-risk, multivessel CAD.[2,3] These limitations with respect to visual or semi-quantitative assessment of regional myocardial perfusion defects can result in the underestimation or misdiagnosis of ''balanced'' ischemia. In patients with a balanced multivessel CAD or microcirculatory disorders a global reduction in myocardial perfusion can be completely overlooked when assessment is based solely on the relative radiotracer uptake. The underestimation of CAD extent and severity is associated with inadequate discrimination of diffuse nonobstructive and small vessel disease, due to the restrained resolution of traditional sodium-iodine systems. This eventuality can be surmounted by the quantification of myocardial blood flow (MBF) or myocardial perfusion reserve (MPR) using a tracer kinetic method for positron emission tomography (PET).[4–7] PET MPI is a well-validated noninvasive method for the quantification of myocardial perfusion imaging studies, demonstrating an incremental diagnostic and prognostic power of MPR over relative perfusion imaging findings in patients with suspected or known CAD.[8,9] Hence, PET and fractional flow reserve (FFR) are respectively considered gold standards for noninvasive MBF and MPR quantitative measurement[10–12] and invasive assessment of coronary artery stenosis severity.[12,13] However, since the installation of a PET tracer production system involves high costs, this technology is not yet readily available in many areas around the world.[14] The introduction of high-sensitivity dedicated cardiac cadmium-zinc-telluride (CZT) SPECT cameras, allows dynamic acquisition of tomographic images suitable for assessment of radiotracer kinetics and opens up a new era for myocardial flow and flow reserve measurement using SPECT imaging.[15–17] CZT-SPECT can not only achieve low-dose MPI imaging, but also provide parameters for quantitative analysis of absolute MBF through fast dynamic tomography, such as stress or rest MBF and MPR. Quantification of MBF and MPR by list-mode dynamic CZT-SPECT is technically feasible and clinically useful.[18,19] Therefore, MPR is now considered a robust approach that provides incremental value on diagnosis and risk assessment of patients, including those with multivessel disease.[20–23] Ben-Haim et al.[15] showed that global and regional MPR by CZT-SPECT have a good correlation with total perfusion defect. Moreover, in a subgroup of patients with available angiographic data, global MPR correlated inversely with the extent of obstructive CAD. These findings were later confirmed in the WATERDAY study,[24] comparing MBF and MPR from dynamic ^{99m}Tc-sestamibi CZT-SPECT with ^{15}O-water PET and FFR. While stress and rest MBF were significantly overestimated with CZT-SPECT compared to PET, MPR was similar with the two techniques, highlighting that quantification of MBF and MPR by dynamic ^{99m}Tc-sestamibi CZT-SPECT is technically feasible with specific correction for the extraction fraction of ^{99m}Tc-

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sestamibi.[24] These findings support the use of this new technique to guide referrals for invasive coronary angiography or as an optional ''add-on'' investigation after coronary angiography/FFR when the functional severity of stenosis is uncertain or when FFR is contraindicated (i.e., sub-occluded artery).[24] Acampa et al.[25] demonstrated that hyperemic MBF and MPR values obtained by CZT-SPECT are higher than those measured by ^{82}Rb-PET imaging, with a moderate correlation between the two methods. CZT-SPECT showed good diagnostic accuracy for the identification of obstructive CAD. Global and regional MPR were also predictive of the extent of CAD [16] and agreed with the FFR measurements on invasive angiographs.[26] Shirashi et al.[14] reported that MPR using a CZT camera can identify balanced ischemia in patients with a left main or 3-vessel disease. In patients with suspected or known CAD a relationship between MPI findings and both hyperemic MBF and MPR obtained by CZT-SPECT was found.[27] Yet, global MPR resulted independent predictor of CAD and regional MPR was useful for the identification of obstructive CAD in the corresponding coronary artery.[27] Different studies outlined the incremental value of measurements of coronary flow reserve in different categories of patients for both diagnostic and prognostic purposes.[22] Quantitative measurements of coronary vascular function can improve the diagnostic accuracy of MPI. In particular, patients with severe multivessel CAD, where a normal MPI result does not necessarily identify truly low-risk subgroups among high-risk cohorts, usually show a reduced MPR.[16,22] Nkoulou et al.[17] in 28 patients referred to perfusion imaging with either CZT-SPECT and PET for clinical evaluation of CAD showed an overall good correlation between ^{99m}Tc-tetrofosmin CZT-SPECT and ^{13}N-ammonia PET MBF values ($r = 0.62$, $P < .001$). However, MPR values by CZT-SPECT were lower compared to those obtained by ^{13}N-ammonia PET, probably due to higher ^{13}N-ammonia extraction fraction at resting conditions over a larger range of MBF. Nevertheless, in the clinical setting consistent disagreement may still exist between FFR values and absolute MBF and CFR, as determined by PET imaging, possibly due to the variable effects of diffuse coronary atherosclerosis and/or microvascular dysfunction on coronary hemodynamic.[11,12] The disagreement with FFR evaluation becomes even greater when traditional cardiac imaging modalities is considered, with conventional SPECT imaging showing, at best, a moderate accuracy in predicting the outputs of invasive assessment.[28] Notwithstanding the excellent diagnostic value of FFR, it quantifies the pressure gradient across the stenosis, but does not reflect microcirculation. As opposed to FFR, MPR reflects flow in epicardial arteries and microvasculature.[29] It should be stressed that abnormal MPR with insignificant FFR indicates microvascular dysfunction or diffuse CAD. Therefore, FFR and MPR are not equivalent.[28] Moreover, anatomical assessment does not reflect the MPR calculated with CZT-SPECT MPI. It should be noted that multiple 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. de Souza et al.[29] showed that both global MPR and stress MBF were reduced in patients with abnormal perfusion results. Yoshinaga et al.[6] also reported that areas with perfusion defects on ^{99m}Tc-tetrofosmin SPECT demonstrated lower myocardial flow reserve using PET with ^{15}O-labeled water. Besides assessing perfusion, the study conducted by de Souza et al. demonstrated that global MPR is inversely associated with CAD prognostic index (CADPI), a hierarchical index that encompasses all epicardial coronary tree and is related to overall cardiovascular risk.[29] Their results are in close agreement with those described by Taqueti et al.[30] in a similar population of patients who underwent both PET and coronary angiography for the evaluation of known or suspected CAD.

In this scenario, in the current issue of the Journal, Panjer et al.[31] conducted a systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of dynamic CZT-SPECT in CAD compared to quantitative coronary angiogram (CAG), FFR and PET as reference. The authors reviewed and analyzed nine articles reported to perform dynamic CZT-SPECT and within half a year the methodological references coronary angiography with or without FFR, positron emission tomography, magnetic resonance or coronary computer tomography angiography. For the assessment of CZT-SPECT the diagnostic value pooled analysis with a bivariate model was calculated and yielded a sensitivity of 0.79 (95% CI 0.73–0.85) and a specificity of 0.85 (95% CI 0.74–0.92). Diagnostic odds ratio (DOR) was 17.82 (95% CI 8.80–36.08, $P < .001$). Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 3.86 (95% CI 2.76–5.38, $P < .001$) and 0.21 (95% CI 0.13–0.33, $P < .001$), respectively. The results of this systematic review and meta-analysis, emphasize the role of dynamic CZT-SPECT MPI with a good sensitivity and specificity to diagnose CAD as compared to the gold standards. Despite the diagnostic accuracy of CZT-SPECT has already been analyzed in two previous meta-analyses,[32,33] the topic is well argued and adds new appealing information to the current literature. The use of CZT-SPECT systems for the measurement of MPR is very attractive considering that in one examination is possible to obtain perfusion and functional parameters with comparable results to PET imaging. However, what

emerges from this meta-analysis is that the protocol used in the different centers should be more standardized. The included studies use different methodologies, in terms of dose administration, acquisition protocol, CZT cameras, radiotracers and software package used for MPI CZT-SPECT calculation. Furthermore, in each study a different cut-off value for dynamic SPECT MPI was set. Seven studies used as a comparator FFR (77.8%) and two used MPI-PET (22.2%). The definition of stenosis based on FFR was also slightly different. Three studies defined FFR $\leq$ 0.8 (33.3%) and four FFR $<$ 0.8 (44.4%) as significant. For the measurement of MPI acquisition was performed with different types of CZT-SPECT cameras, six studies (66.7%) used Discovery NM 530c (GE Healthcare, Chicago, IL, USA), one study (11.1%) used Discovery NM/CT 570c (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 (11.1%), two studies (22.2%) used ^{201}Tl as radiotracer, and six studies (66.7%) used ^{99m}Tc-labeled tracers. Importantly, different software was used for the MBF quantification and measurement of MPR, including in-house software, with Corridor 4DM (INVIA, Ann Arbor, MI, USA) applied more frequently than others. Moreover, the main limitation of this systematic review and meta-analysis, additional to the typical limitations for this kind of analysis, is a relatively small number of included studies and patients and heterogeneity within comparators. In this view, studies with a larger population and a lower variability between the methodologies, such as different thresholds for MPR, myocardial radiotracer distribution, reconstruction algorithms, and flow model applied, will be needed to demonstrate clearly the additive clinical impact of MBF quantitation on dynamic CZT imaging and to encourage the use of a standard approach in the quantification of MBF and MPR which is expected to become an important tool in routine clinical practice.

Disclosures

V. Cantoni, R. Green, A. D'Antonio and A. Cuocolo declare that they have no financial conflict of interest.

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