Absolute myocardial blood flow vs relative myocardial perfusion: Which one is better?

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Nuclear cardiology provides valuable information in the non-invasive assessment of coronary artery disease (CAD). Initially, single-photon emission computed tomography (SPECT) has been introduced, generating semi-quantitative relative myocardial perfusion imaging (MPI). This approach demonstrates myocardial regions with reduced tracer uptake relative to a normal region and allows assessment of the ischemic burden. Over the past 30 years, SPECT-MPI has become a well-established, widely used method for diagnosis and risk stratification of patients with CAD.[1]

In recent years, positron emission tomography (PET) has been increasingly used in the diagnosis and risk stratification of patients with CAD.[2–4] Compared to SPECT, PET/CT is characterized by higher photon sensitivity, radiotracers with higher extraction fraction, and robust attenuation correction.[2] Therefore, PET/CT provides high quality MPI, and allows dynamic first-pass imaging with quantification of absolute myocardial blood flow.[5–7] The rate of tracer uptake from the arterial blood into the myocardial tissue (k_1) is assessed using time–activity curves and a kinetic model, providing an estimation of absolute myocardial blood flow (MBF), expressed in mL/min/g. The ratio between stress and rest MBF is the myocardial flow reserve (MFR), sometimes referred to as coronary flow reserve (CFR).

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To date, most nuclear cardiac studies are performed using SPECT systems, exceeding the number of PET scanners by more than 10 to 1 ratio.[8] It appears impractical to perform both MPI and quantitative flow to all patients referred for nuclear testing due to system availability and additional work required. The questions are as follows: Are quantitative MBF and MFR measurements superior to relative myocardial perfusion, or do they provide complimentary information for the diagnosis of obstructive CAD? Who are the patients most likely to benefit from the combined assessment of flow and perfusion? Is it possible to perform quantitative flow measurements using SPECT systems as well?

In this issue of the journal, Giubbini et al compared between MPI and MBF among 47 patients who underwent stress–rest PET/CT using N-13 ammonia for clinical evaluation of known or suspected CAD. Using the summed difference score (SDS) for 17 myocardial segments, patients were divided into two groups: with ischemia (SDS $>$ 1) and without ischemia (SDS $\leq$ 1). The investigators demonstrated that average global stress–rest difference of MBF (DMBF) and global CFR were not significantly different among the two patient sub-groups. However, DMBF and CFR per-vascular territory were significantly lower among patients with ischemia compared to those without ischemia. Defining CFR $<$ 2.5, DMBF $<$ 1.1 mL/min/g, and SDS $>$ 1 as abnormal, agreement between regional CFR and MBF versus regional SDS was 56% (79/141) and 69% (97/141), respectively. Noteworthy, among segments without ischemia (SDS $\leq$ 1), 46% had reduced CFR, and 30% had reduced DMBF. Among segments with ischemia, $\sim$30% had normal CFR and DMBF. Thus, discordant results were observed in a considerable number of vascular territories. This study lacks a gold standard of coronary angiography or fractional flow reserve (FFR). Yet, it is important showing the correlation between relative perfusion and quantitative MBF. The study emphasizes the differences between per-

vessel and global flow assessment. The discordant results between flow and perfusion in a considerable number of segments may suggest complementary information that may improve detection of obstructive CAD when the two measurements are combined.

RELATIVE MYOCARDIAL PERFUSION

Multiple studies demonstrated the diagnostic value of SPECT-MPI. Sensitivities of exercise and vasodilator stress in detecting >50% angiographic stenosis (uncorrected for referral bias) were 87% and 89%, respectively, whereas specificities were 73% and 75%, respectively.[9] A recent systematic review and meta-analysis demonstrated that attenuation correction (AC) of SPECT-MPI was associated with substantially improved specificity and subtle increase in sensitivity (83% vs 68%, and 85% vs. 80%, respectively) for CT-based AC vs no AC.[10] The majority of SPECT-MPI examinations (60% to 70%) are performed using exercise testing. The information gained by exercise testing is valuable in the diagnosis and risk stratification of patients with CAD, allows better assessment of the prescan likelihood of obstructive CAD, may assist in the interpretation of equivocal MPI findings, and influence the decision upon the optimal treatment following nuclear testing.

PET-MPI is based on vasodialator stress; thus exercise testing does not confer part of the evaluation. However, this technique offers several important advantages. Bateman et al demonstrated in matched populations of pharmacologic stress that Rb-82 MPI PET was associated with higher accuracy compared to SPECT in detecting obstructive CAD of ≥70% stenosis (89% vs 79%, $P = 0.03$) and ≥50% stenosis (87% vs 71%, $P = 0.003$), respectively.[3] A recent meta-analysis demonstrated that Rb-82 PET had higher area under the ROC curve than SPECT-MPI (0.95 vs 0.90, respectively) in the diagnosis of obstructive CAD with higher accuracy.[4]

The main limitation of MPI, using SPECT or PET, is the need to reference every pixel to a region with maximal tracer uptake. Among patients with extensive CAD, this approach might yield a false negative result due to global hypoperfusion. Relative MPI often demonstrates the most severe hypoperfused region, detecting the culprit coronary artery with the most severe stenosis, missing other territories subtended to less severe stenosis.[11] It should be noted that detection of the coronary artery with the most severe flow-limiting stenosis, accounting for severe perfusion abnormality, is often beneficial in practical clinical settings, particularly before applying invasive treatment. Nevertheless, the diagnostic accuracy of MPI in multivessel CAD is improved when transient ischemic dilation and gated-SPECT variables of left ventricular function are incorporated in MPI interpretation.[12,13]

ABSOLUTE MYOCARDIAL FLOW

Few studies demonstrated higher diagnostic value of quantitative PET/CT flow assessment over relative MPI.[6–8] Using N-13 ammonia adenosine stress, Hajjiri et al[5] found higher diagnostic value for MBF and MFR compared to relative tracer uptake in identifying ≥70% CAD among a small group of 27 patients. MBF (<1.85 mL/min/g) was more sensitive than MFR (<2.0) (81% vs 62%, $P = 0.01$) with similar specificity (85%). The sensitivity of abnormal relative N-13 ammonia uptake (<70% of maximum) was lower (48%) compared to MBF and MFR with comparable specificity (82%). Using Rb-82-PET dipyridamole, Ziadi et al[6] demonstrated that MFR < 2 provided added value to MPI in predicting three vessel CAD, incremental over the summed stress score ($P = 0.005$). Another N-13 ammonia PET/CT study demonstrated higher sensitivity (96% vs 79%, $P < 0.005$) and negative predictive value (89% vs 59%, $P < 0.005$) when MFR (<2.0) was added to MPI compared to MPI alone, respectively, in detecting obstructive CAD (≥50% stenosis).[7] This study was based on 73 patients of whom 53 had angiographic CAD, and 79% of them had multivessel CAD. Of note, 73% of the patients in this study were referred for PET/CT following invasive angiography. Thus, data on the additional value of quantitative PET consist of high proportions of patients with multivessel CAD and following invasive coronary angiography. The present study by Giubbini et al in this issue of the journal was based on patients referred for secondary evaluation to determine the functional significance of known coronary lesions. This included patients with prior revascularization, those with typical angina without coronary stenosis, patients who had equivocal other stress tests, and patients with left ventricular dysfunction. These patient sub-groups were not referred for a primary diagnosis.

Several disadvantages limit PET from widespread clinical use in the diagnosis of CAD. PET/CT scanners are expensive compared to SPECT, and existing PET systems have limited availability for cardiac imaging. PET tracers for flow imaging have very short half-life. The use of N-13 ammonia requires on-site cyclotron. Rb-82 requires on-site generators. PET flow imaging is not reimbursed by many healthcare providers because of high costs. Flourine-18-flurpiridaz is a new PET tracer with longer half-life of 110 minutes which does not require cyclotron on-site; however, data on this radiotracer are preliminary.[14]

DYNAMIC SPECT IMAGING

Dynamic imaging using SPECT technology has gained increasing interest since the introduction of solid-state cadmium–zinc–telluride (CZT) detectors for clinical use. CZT cameras are characterized by high efficient imaging by focus on the heart, and allow dynamic SPECT imaging using list-mode recording, and reconstruction into multiple, successive frames with sufficient temporal resolution. Ben Haim et al[15] demonstrated that dynamic SPECT imaging using a CZT camera coupled with kinetic analysis of myocardial tracer concentration was feasible and reproducible. Using a 2-compartment kinetic model, global myocardial perfusion reserve (MPR) index was calculated as the ratio of stress and rest k_1 values. Global and regional MPR correlated with the semi-quantitative total and regional stress perfusion deficit, respectively. Shiraishi et al demonstrated that MPR index $\leq$1.5 predicted left main or 3-vessel CAD with sensitivity, specificity, and accuracy of 86%, 78%, and 80%, respectively.[16] Both global and regional MPR correlated with angiographic coronary stenosis and invasive FFR among patients with multivessel coronary artery disease.[17] Combining dynamic CZT-SPECT imaging with CT attenuation correction allows assessment of absolute MBF and MFR. In a porcine model, Wells et al[18] demonstrated the feasibility of MBF assessment using a dedicated cardiac CZT camera and CT-based attenuation and scatter correction. Myocardial curves demonstrated good fit to a 1-tissue compartment model, and SPECT-derived flow demonstrated good correlation to microsphere flow measurements. Figure 1 demonstrates representative time–activity curves and k_1 polar maps obtained from attenuation and scatter-corrected images at rest and during dipyridamole stress with LAD occlusion. In a human study,[19] MBF and MFR obtained by CZT-SPECT with CT attenuation correction were compared to those obtained by N-13 ammonia PET. While resting MBF was similar, hyperemic MBF was lower for CZT compared to PET, yielding significantly lower MFR for CZT-SPECT compared to PET. This may relate to the lower extraction fraction of Tc-99m tetrofosmin compared to N-13 ammonia, and may imply that different threshold levels for SPECT and PET should be established. Several technical considerations were tabulated by Liu et al for clinical implementation of quantitative CZT-SPECT.[8] In addition, Tc-99m labeled radiotracers with more favorable kinetics will provide more accurate MBF assessment.

To summarize, MPI provides well-established diagnostic and prognostic value in the assessment of patients with known or suspected CAD. SPECT-MPI has the advantages of widespread availability for cardiac nuclear imaging, and potential to incorporate exercise data in the clinical assessment, whereas the advantage of PET-MPI over SPECT-MPI is better image quality and higher sensitivity. Both SPECT-MPI and PET-MPI underestimate the extent of CAD. The added diagnostic

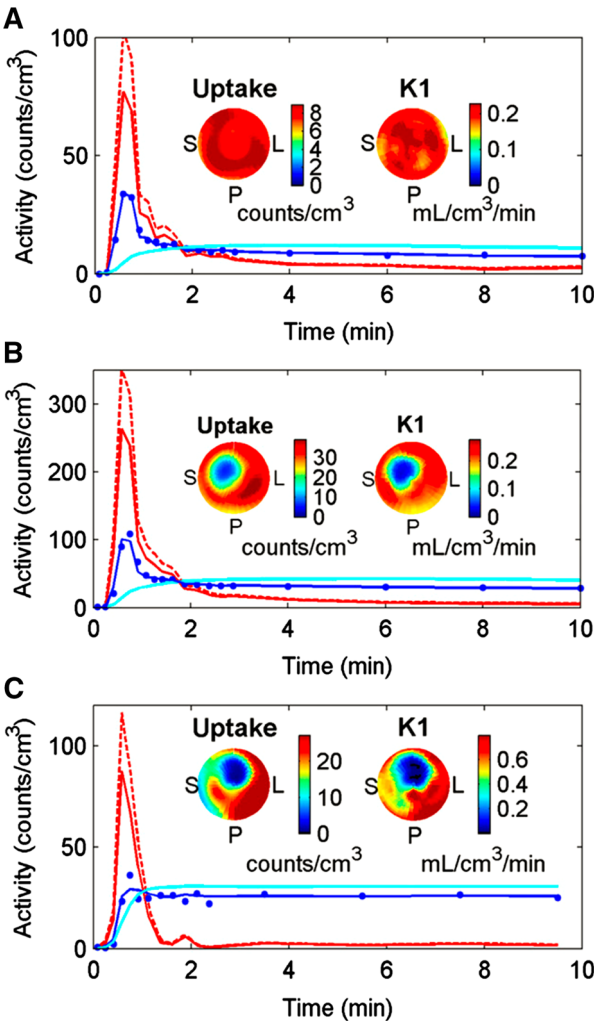

Figure 1. Representative time–activity curves from attenuation and scatter-corrected images at rest for Tc-99m tetrofosmin (**A**) and at stress following subtraction of residual rest uptake for Tc-99m tetrofosmin (**B**) and Tl-201 (**C**). Shown are arterial whole-blood concentrations (*solid red*) measured from region in the left ventricle, plasma concentration or arterial blood curve corrected for tracer-blood binding (*dashed red*), CM fit (*solid blue*) to sampled values (*dots*) from high-count region of myocardium, and resultant estimated pure myocardium tissue curve (*cyan*) after correction for spillover and partial-volume effects. Also shown are uptake and k_1 polar maps. Higher EF of Tl-201 increases k_1 value and myocardim-to-blood contrast, compared with Tc-99m tetrofosmin, but Tl-201 images have increased noise, as reflected by area of reduced uptake in right coronary artery territory of Tl-201 polar map Originally published in JNM[18©] by the Society of Nuclear Medicine and Molecular Imaging, Inc.

value of quantitative PET-MBF and MFR combined with MPI over MPI alone has been assessed in few studies based on relatively small patient populations. Quantitative CZT-MBF has also been suggested to provide incremental diagnostic value to MPI. These studies demonstrated benefit mainly among patients with multi-vessel CAD, or after coronary angiography, rather than for primary diagnosis.[7,8,16,17] Relative perfusion pointing at the most severe coronary flow-limiting lesions combined with absolute flow evaluation detecting additional arteries with flow-limiting stenosis probably provides improved non-invasive functional assessment of high-risk patients with multi-vessel CAD. Further investigations are essential to better define patient sub-groups that will clinically benefit from the combined evaluation.

Disclosures

Tali Sharir is consultant to GE Healthcare. Gil Kovalski is employed by GE Healthcare.

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