SPECT measurements of myocardial blood flow and flow reserve: from development to implementation

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INTRODUCTION

In the current issue of the Journal,[1] the authors have reported the use of SPECT myocardial perfusion imaging (MPI) to quantitate myocardial blood flow (MBF) and flow reserve. Their data then were used to improve the prognostic value of their SPECT MPI studies. Clinicians have already been introduced to and are becoming more comfortable with the incorporation of blood flow data into PET MPI studies. Therefore, it would be reasonable to review the development of MBF quantitation, and briefly assess some of the evidence that these measurements can contribute to clinical evaluation. The progress that has been made in applying quantitation to SPECT imaging will be reviewed, and the significance of the current paper examined.

MYOCARDIAL BLOOD FLOW

The regulation of MBF is complex, and is characterized by a complex autoregulatory mechanism, in which perfusion is scaled to the metabolic and oxygen demands of the myocardium. Mosher et al. found in experimental animal preparations that if perfusion pressure is increased progressively, coronary blood flow remains remarkably constant through a broad range of mean arterial pressure values.[2] If contractility requirements are increased, blood flow augments to a new plateau. This was felt to be mediated through autonomic vasomotor mechanisms. Gould and Lipscomb subsequently modeled the MBF behavior in coronary arteries with significant stenosis.[3] As stenosis severity increases, resting blood flow remains constant until approximately 85% of the lumen diameter is occluded, and then begins to fall-off. Gould also measured maximal coronary blood flow in response to vasodilation (provided by hypaque dye injection).[4] As stenosis severity increased, the maximal blood flow achieved during vasodilation remained constant until 40%–45% of the lumen was occluded, and then began to diminish. The ratio of vasodilator-to-resting blood flow was termed the myocardial flow reserve (MFR). At approximately 85% stenosis, MFR decreases to 1.0, so no flow augmentation occurs. Gould also demonstrated that regional differences in the degree of coronary occlusion were reflected by distribution of the radiotracers ^{99m}Tc or ^{131}I into the LAD and LCX. When stenosis was $<$ 85%, resting tracer distribution was the same in normal vs. constricted arteries.[4] When stenosis was $>$ 50%, tracer distribution at maximal vasodilator blood flow was visually and quantitatively less, and showed a relative perfusion deficit.

Conventional SPECT imaging has evolved from this principle of utilizing disparities in relative regional perfusion to diagnose obstructive coronary disease.[5] Segments are compared qualitatively or semi-quantitatively to a region in which tracer uptake appears most ''normal.'' Even with semi-quantitative approaches, SPECT diagnosis of CAD depends on comparison of uptake in one region to another, with the assumption that there is a normal control region, as compiled from a file of subjects with low probability of disease. Despite this

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limitation, SPECT MPI achieves a high degree of accuracy. A meta-analysis by McArdle et al. of ^{99m}Tc SPECT studies vs. coronary angiography in a total of 1,755 patients yielded a sensitivity and specificity of 85%.[6] SPECT has also been successful in evaluating cardiac prognosis. Engbers et al. studied 4,057 patients who had CZT SPECT.[7] A normal scan was associated with a 0.2% fatal event rate, and 0.6% overall MACE at 2.7 years. Prognosis varied directly with the extent of the stress perfusion defect. However, diagnostically, using qualitative SPECT with relative perfusion analysis is limited in its ability to identify patients with multi-vessel or left main disease. Lima et al. found that in patients with multi-vessel CAD, combining SPECT perfusion/function studies yielded a multi-vessel pattern of abnormality in only 60%.[8] Only 40% of patients with left main stenosis were detected by SPECT in one study.[9] A review by Travin concluded that there was room for improvement in these results, and that further use of PET imaging with quantitative blood flow determinations should be emphasized.[10]

PHYSICS OF MYOCARDIAL BLOOD FLOW BY PET

The use of quantitative MBF measurements in the clinical setting was originally based on PET imaging. From a physics standpoint, PET has significant advantages over SPECT. PET systems have higher sensitivity and superior spatial resolution and are capable of much higher count rates than conventional SPECT systems. Among the differences between PET imaging and rotating SPECT imagers, PET systems surround a patient's thorax with detectors, and acquire data in a 3D mode. The detectors are sufficiently sensitive that when 2D PET imaging was in the process of being replaced by 3D PET imaging, it became necessary to reduce the amount of injected activity so as not to saturate PET systems' electronics.[11] Because gamma rays emitted from the patient are detected in a 3D fashion with PET systems, there is no problem with sampling radioactive tracer as it changes position and concentration within the patient's body during first-pass transit, whereas for a rotating SPECT system detectors receive gamma rays from one angle at a time as projected onto the 2D detector surfaces. PET systems preferred for MBF assessment are equipped with LSO or LYSO crystals because their 40 nsec decay times affords time-of-flight imaging for optimal spatial resolution, enabling spatial resolution of 4 mm. Conventional rotating SPECT systems equipped with NaI(Tl) crystals have deadtimes of 230 nsec, and because of the necessity of using collimators, have effective tomographic spatial resolution of 9 mm.[12]

Also, corrections for patient self-attenuation are critical for PET imaging. Otherwise, attenuation artifacts confound both visual assessment of myocardial perfusion and invalidate quantitative measurements. Most PET systems now routinely are manufactured with high-end CT units, such that 64-slice CT devices are common. In contrast, few 3D CZT SPECT systems have any CT units, and among rotating conventional SPECT systems, most have no CT systems, while those that do typically have 6- or 8-slice units, not 64-slice units. That is unfortunate, as studies have shown that corrections for attenuation and scatter are important for MBF values derived from conventional rotating SPECT systems.[13]

The accurate physical corrections, high sensitivity and high spatial resolution of PET systems enable collection of time activity curve data in list mode acquisition, from which myocardial distribution of tracer can then be adapted to pharmacokinetic compartmental models, with corrections for partial volume effects and count spillover. Rate constants of compartmental distribution can be calculated, and when these are corrected for the ''fall-off'' in extraction fraction between tracer uptake and MBF, will reflect accurate approximations of global and regional MBF.[14]

VALIDATION OF MBF AS A CLINICAL TOOL

Experimental studies have validated the correspondence between myocardial blood flow and flow reserve quantified in vivo with estimates obtained from kinetic models or retention models. Yoshida et al. used open chest dogs and an electromagnetic flow meter to directly measure show the relation between MFR and ^{82}Rb and ^{13}N-ammonia.[15] Lautamaki et al. used radio-labelled microspheres in a canine model to validate ^{82}Rb measurements of MBF.[16]

Extensive work has been done to validate the reproducibility, accuracy, and prognostic value of MBF and flow reserve, with measurements shown to be reproducible in the short term[17], and vary only within 10% over short time periods.[18] Variation does exist via inter- and intra-observer determinations, and among different algorithms.[19] MBF and flow reserve from ^{82}Rb and ^{13}N-ammonia are comparable.[18] The diagnostic accuracy of MFR and MBF for individual coronary stenosis was tested by Angnostoppoulos et al. in 22 subjects, and found that MFR in coronary territories supplied by arteries with $\leq$ 50% stenosis were identical to normal values (1.9–2.7), while territories supplied by arteries with 70–86% stenosis had MFR of (1.0–1.3)[20] . Using ^{15}O-water in 104 patients, Kajander found that quantitative MFR had a diagnostic accuracy of 92%, vs. 73% for qualitative PET.[21] Fiechter et al. studied

patients with quantitative ^{13}N-ammonia PET and showed that overall per vessel accuracy was 83% vs. 57% for qualitative MPI.[22] In the Pacific Trial, hyperemic MBF had an accuracy equal to that of CTA and FFR, and was superior to that of qualitative SPECT MPI in analyzing individual vessels.[23] The parameter of left ventricular global flow reserve has been used as a parameter to exclude LMCA stenosis and multivessel CAD. Ziadi et al. studied 120 pts with CAD who had ^{82}Rb PET and angiography.[24] Of patients with three vessel CAD, 88% had MFR < 2.0, and MFR was incremental to relative perfusion scores for detecting multi-vessel CAD. Naya et al. studied 290 patients with ^{82}Rb PET. In their series, an MFR value of > 1.93 was 97% accurate in excluding LMCA stenosis or significant multi-vessel CAD at angiography.[25]

Flow reserve is also a significant predictor of cardiac prognosis. Fukushima and Bengal followed 275 patients for one year after ^{82}Rb PET performed for evaluation of possible coronary disease. An MFR below 2.1 was an independent predictor of MACE in patients with and without segmental perfusion defects.[26] Similar data were obtained by Herzog et al. using ^{13}N-ammonia PET imaging in 256 patients.[27] Thomas studied 1,255 pts who had ^{82}Rb PET and followed them for a mean of 3.2 years. There were 454 deaths (36%). The extent of perfusion defect and LV ejection fraction were initially predictors of mortality, but became non-significant when MFR was added into their model. Mortality increased 1.08% for every 0.1 unit decrease in MFR.[28] The prognostic value of PET MFR determinations even remains significant when applied to patients with presumed non-obstructive microvascular CAD. Murthy et al. studied 405 pts who had normal ^{82}Rb PET studies with no evidence of obstructive CAD. MFR < 2.0 was a significant predictor of MACE for both men and women, and was incremental to EF and clinical risk scores[29]. Studies by Gould and Bober indicate that patients with myocardial regions demonstrating severe reduction in flow reserve (< 1.2) have a significantly worsened prognosis. Revascularization of vessels supplying those segments will result in augmentation of myocardial blood flow and improvement in prognosis to that of the control patient groups.[30,31]

DEVELOPMENT OF SPECT MYOCARDIAL BLOOD FLOW AND FLOW RESERVE METHODOLOGY

The preceding discussion demonstrates the value of adding myocardial blood flow and flow reserve quantification to qualitative assessment of myocardial perfusion, specifically for PET imaging. However, the preponderance of nuclear MPI studies performed in the U.S. are with SPECT cameras. The technology remains less expensive and more widely available. Consequently, efforts have been made to develop methods to incorporate quantification of blood flow into the SPECT process.

As reviewed above, significant challenges to developing quantitative SPECT flow included (1) the use of multi-head gamma cameras, whose rotation speed served as an impediment to accurate 3-D reconstruction of tracer time activity curves, and (2) lack of an accepted extraction fraction for SPECT isotopes, preventing the conversion of K1 rate constants to myocardial blood flow. Consequently, early studies simply measured the ^{99m}Tc activity over time in the main or right pulmonary artery at rest and with vasodilator stress, the ratio of which corresponded to MFR, and could be validated by intra-coronary Doppler flow wires.[32] Daniele showed MFR obtained using this method had prognostic value in identifying higher risk groups.[33] Wells et al. provided experimental validation of the use of SPECT quantitation by showing a close correlation, in a model of LAD stenosis, between ^{99m}Tc tracer retention and radiolabelled microspheres.[34] A one-compartment kinetic model, with correction for attenuation, spillover and ^{99m}Tc-based extraction fraction was used.

The diagnostic accuracy of SPECT MBF determinations have been previously evaluated. Ben-Haim performed SPECT in 96 patients, 16 of whom had angiography. MFR was obtained using a one- compartment kinetic model. MFR was lower (1.3 vs. 1.6) in those with abnormal relative perfusion. In the 16 patients with 20 abnormal arteries at angiography, regional MFR was 1.1, vs. 1.3 in normal arteries.[35] Wang et al. emphasized that correction for noise, spillover, count recovery and attenuation was necessary to maintain accuracy for SPECT quantitation,[13] although other authors disputed the need for attenuation correction.[36] Hsu et al. studied 21 patients with and without CAD with dynamic rest/stress SPECT MBF measurements and coronary angiography using a one-compartment model. MFR had the highest diagnostic AUC of 91%, followed by relative perfusion scores of 86%.[37] The accuracy of SPECT MFR vs. angiography and fractional flow reserve was examined by Zavadovsky et al. in 23 patients with stable CAD. MBF values for rest and stress were lower than for PET at 0.36 and 0.67 mL/min/gm. Values for their ratios (i.e., MFR) were more in line with PET values. An abnormal FFR < 0.8 in an individual vessel was detected with a sensitivity of 69% and specificity of 93% by an MFR of < 1.48.[38] Bouallegue et al. reported an 85% accuracy for detecting abnormal FFR in 23 patients with multivessel CAD.[39] Finally, Agostini compared SPECT MBF and MFR (using a CZT system) to both FFR

determinations in 30 patients who also prospectively had blood flow quantification by ^{15}O-water. Flow reserve in all three coronary territories were equivalent on SPECT and PET, and had a 93% overall accuracy in predicting FFR < 0.8.[40] Shrestha et al. performed ^{13}N-ammonia PET and dynamic ^{99m}Tc-tetrofosmin SPECT on 16 patients, and derived expressions for flow dependent extraction and permeability surface area. These expressions were then used to demonstrate a moderate correlation between MBF and flow reserve for the two modalities.[41]

To review, there is now evidence that MBF and MFR by ^{99m}Tc SPECT has been validated experimentally, has reasonable accuracy vs. coronary angiography and FFR, and correlates with measurements obtained by PET. What remains to be determined is whether SPECT MBF and MFR measurements are important prognostically. Only the study of Daniele et al. has reported that flow reserve (and relative perfusion scores) were significant predictors of MACE in a group of 99 patients with suspected CAD referred for SPECT MPI.[33] However, in that study, flow reserve was computed as a retention index from total counts obtained from pulmonary transit of tracer, rather than directly from first-pass myocardial time activity curves.

In the current issue of the Journal, Sun et al. have taken an important first step in demonstrating the prognostic value of SPECT MFR.[1] They defined a unique group of 119 patients who had previous catheterization and had stenosis of ≥ 50 to < 80%, assessed qualitatively by the angiographers. Approximately 60% of the group had multivessel CAD, and the average stenosis severity was 67%. Patients with MI were excluded, and only 8% had previous angioplasty. Subjects underwent rest adenosine-stress SPECT ^{99m}Tc-sestamibi MPI within three months *following* angiography on a SPECT/CT camera with rapidly rotating gantry with correction for isotope decay and photon attenuation. First-pass time activity curves were corrected for spillover and analyzed using a one tissue compartment model with proprietary software. Rate constants K1 and K2 were corrected for ^{99m}Tc-sestamibi extraction fraction to yield blood flow values which were corrected for hemodynamic state. Gated relative perfusion images were performed one hour later. LV ejection fraction, volumes, relative perfusion image scores were calculated, and global and regional MBF and flow reserve were obtained. Follow-up for MACE was performed at an average of 1,408 days for the group. Events occurring within 90 days of the SPECT study were considered to have been guided by the perfusion study, and were not considered as follow-up events.

Their results are significant, but must be viewed in light of the fact that the study subjects represented a low risk group. The mean age was 57, and ejection fraction was 64%. The mean relative perfusion scores were SSS = 1 and SDS = 0. Despite over 3.5 years of average follow-up there were only 18 events, including six revascularizations, 12 admissions for angina or CHF, and no deaths. Their findings were valuable in that global myocardial blood flow was 0.97 mL/min/gm, stress averaged 1.88, and MFR was 2.02, well within the normal ranges for values obtained with other modalities such as PET. Not surprisingly, perfusion defect size or extent of ischemia were not predictive of events, since the values were low. However, global MFR was 1.7 in the patients with events, vs. 2.07 in those without, which was significant, as was the fact that 15/18 patients with events had MFR < 2.0, their defined lower limit of normal. An MFR < 2.0 remained a significant predictor of events for patients with normal scans, and for the few with abnormal relative perfusion (SSS ≥ 4). Other clinical factors such as age, and diabetes were not significant in a multivariate model.

A unique advantage of Sun et al. is their use of a low risk population.[1] This allows the prognostic signal from a mildly reduced MFR to be recognized. In a high risk group, the value of MBF and MFR might be overwhelmed by a reduced LVEF or severe perfusion defects. The drawback of studying a low risk cohort is that there were few events, and no hard events such as death or MI, reducing the statistical power of the data. The second question is whether, in this study in which coronary angiography is the entry procedure, it is reasonable to ascribe all events within 90 days to the SPECT study, and to exclude them from consideration. Other authors include all revascularization events in their analyses to delineate the full impact of the MFR data.[30] It is difficult to determine in Sun et al. how many revascularizations were excluded.[1] One would like to see that data presented, so that readers can make their owns judgement as to whether it affects the conclusion. Notwithstanding those points, Sun et al. have made a valuable contribution to beginning the determination of the prognostic power of MFR derived from SPECT.

What are the next steps? Certainly, multi-center studies, with larger numbers of patients need to be performed to further document the diagnostic and prognostic value of SPECT MFR determinations. Such trials are now ongoing.[42] The studies described above yield a wide range for rest and stress MBF and flow reserve, dependent on methodology. A practical guide unifying the acceptable values and their interpretation will be necessary to achieve clinical acceptance.[43] One concern about promoting the widespread use of MFR in SPECT MPI is that with current methodology, four imaging sessions are required, both for solid state and rotating gantry cameras.[1,39] Laboratory throughput may

therefore be negatively impacted. A recent study suggests that using a rotating gantry camera and commercially available software, the acquisition of static relative perfusion images can directly follow dynamic first pass acquisition of time activity curves, similar to PET studies.[44] The MBF and MFR values they obtained in 173 patients (rest 1.41; stress 3.27; and MFR 2.60) were deemed acceptable. A simplified protocol which is practical and maintains laboratory efficiency will be of critical importance in advancing this technology.

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