Incremental prognostic value of coronary flow reserve assessed with single-photon emission computed tomography

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See related article, pp. 612–619

The diagnostic and prognostic values of stress myocardial perfusion imaging (MPI) is well established with SPECT¹⁻¹² and more recently with PET or PET-CT imaging.¹³⁻¹⁵ Conventional MPI identifies local reductions in perfusion relative to the best ventricular wall, where the maximum value is presumed to be normal. However, this technique is known to underestimate the extent or severity of multi-vessel coronary disease, when the maximum value does not represent normally perfused myocardium.^{16,17} In contrast, myocardial perfusion measured on an absolute scale (mL/min/g) permits the assessment of stress-to-rest perfusion or vasodilator reserve without the assumption of a normal reference region, first demonstrated with PET imaging by Gould et al¹⁸ In this way, the stress perfusion scan is interpreted relative to the individual's normal resting state, using the patient as their own control. The clinical value of absolute perfusion or myocardial blood flow (MBF) measurements has been reported extensively using dynamic PET imaging with ¹⁵O-water and ¹³N-ammonia in patient populations such as diabetes, hypertension, hyperlipidemia, smoking, syndrome X, non-compaction, takotsubo, hypertrophic, and dilated cardiomyopathies. The impact of invasive fractional flow reserve (FFR) imaging to direct PCI and improve patient outcome has recently been reported using FFR

measurements in a prospective randomized controlled trial.¹⁹

However, there is limited data available on the value of *non-invasive* myocardial flow reserve (MFR) imaging to improve patient management, or predict future clinical events, compared to conventional MPI. This is partly due to the limited availability of ¹³N-ammonia and ¹⁵O-water PET, which require a local cyclotron for tracer production. Tio et al²⁰ recently reported on the prognostic value of ¹³N-ammonia PET flow reserve imaging in patients with known coronary artery disease and LV dysfunction who did not undergo revascularization. This study showed that MFR was a stronger predictor of cardiac death compared to LVEF in this population (HR 4.1 vs 2.8; 7 years median follow-up), but did not assess the incremental value compared to standard MPI. Herzog demonstrated similar findings that impaired MFR (ratio < 2) was an independent predictor of cardiac death (HR 2.9; 5.5 years mean follow-up) using ¹³N-ammonia PET in a wider unselected population.²¹ This study also showed the incremental prognostic value of MFR over standard MPI in patients with known or suspected CAD, more typical of the clinical population referred for assessment of myocardial ischemia. In patients with normal MPI, impaired MFR was an independent predictor of cardiac death (3.1 vs 0.5%) and major adverse cardiac events (MACE; 6.3 vs 1.4%) within a period of 3 years. In patients with abnormal MPI, impaired MFR also predicted an increased rate of disease progression, even beyond 3 years. A larger patient series, followed for a shorter time, has recently confirmed the incremental prognostic value of generator-produced ⁸²Rb PET MFR to predict death or myocardial infarction (death + MI; HR $\geq$ 3.3) and MACE (HR $\geq$ 2.4; 1-year median follow-up) in patients with normal *or* abnormal stress MPI.²²

The current study by Stephania et al²³ builds on these previous findings using ^{99m}Tc-SPECT, which is more widely available as the clinical standard for MPI. The authors use first-pass planar imaging followed by conventional SPECT MPI to estimate a retention index of MBF and corresponding global flow reserve. They

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J Nucl Cardiol 2011;18:541–3.

1071-3581/\$34.00

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doi:10.1007/s12350-011-9408-6

showed that in patients with normal MPI, reduced global flow reserve was associated with higher annual rates of major adverse cardiac events (5.2% vs 0.7%; 5.8 years mean follow-up) consistent with previous PET studies.

Some differences between the SPECT and PET results may be attributed to important variations in the flow reserve imaging methodologies, and affect the ability to incorporate routine MFR measurements into the clinical practice of MPI. This study reported a substantially higher rate of abnormal MFR (65%) in patients with normal MPI, compared to the previous PET studies (24%-31%). This is likely due to the use of a retention index instead of absolute MBF for flow reserve estimation, as illustrated in Figure 1. If the tracer retention rate is measured in mL/min/g, then quantitative estimates of MBF and flow reserve can be derived by correcting for the retention fraction which decreases non-linearly with MBF. However, this correction is not possible when tracer retention is measured in arbitrary units (a.u.). The tracer retention fraction decreases progressively with increasing blood flow, therefore some underestimation in flow reserve will occur using a retention index approach. Since this study used a retention reserve cutoff value <2 as abnormal, this may explain the relatively high rate of abnormal flow reserve findings. This suggests that more than half the patients classified as abnormal by SPECT may have been considered normal using PET flow methods, possibly accounting for the slightly lower event rate of 5.2%/year in this study compared to 6.3% in the study by Herzog. It also suggests a more strict definition of normal MFR in this study, explaining the very low event rate of 0.7%/year compared to 1.4% by Herzog, in patients with normal MPI and MFR combined. Therefore, a lower cutoff value for identification of impaired reserve should be considered in studies using retention index estimates of MBF.

This study did not adjust resting MBF values for changes in heart-rate-pressure-product (RPP). This is consistent with previous PET prognosis studies, which have not demonstrated an independent effect of resting blood pressure or RPP on patient outcomes. Normal resting MBF is known to decrease with the age-dependent increase in blood pressure and heart rate.²⁴ Therefore, it is common with PET to adjust resting flow values to a reference heart-rate-pressure-product (RPP) before calculating MFR_{ADJ} for investigation of disease-specific pathologies. However, it is possible that the effect of hypertension to increase resting MBF and reduce MFR with increasing age may be a contributing factor to the increased rate of cardiac events predicted by impaired flow reserve.

Translation of a new diagnostic test such as flow reserve quantification into a routine clinical tool requires

Figure 1. Myocardial flow reserve (MFR) and stress/rest retention ratio (S/R) illustrated for typical rest and stress flow values (1 and 2 mL/min/g, respectively). Myocardial flow reserve is underestimated by measurements of tracer retention index in arbitrary units (a.u.).

several key features. These include: (i) reproducibility and validation in animal models and in humans, (ii) availability of both the tracer and imaging technology, (iii) ease of implementation in clinical practice, (iv) proven added value for diagnostic or prognostic application and/or impact on therapy decisions and patient outcomes. Despite some methodological variations in the flow reserve studies reported to date, there is now increasing evidence using both SPECT and PET techniques, to suggest that a “warranty period” of 2 years (e.g., $<2\%$ risk of death + MI) following normal MPI may be extended to >3 years or shortened to <1 year according to the corresponding MFR results. The small study sample size used in the present investigation (99 patients), as well as in previous retrospective PET prognosis studies, highlights the need for additional prospective evaluation studies in larger populations to confirm the positive impact of routine MFR combined with MPI imaging on patient management and clinical outcomes. In particular, it will be important to discriminate between patients with impaired flow reserve due to multi-vessel obstructive coronary artery disease vs those with micro-vascular disease, to select the most appropriate and effective therapy for each.

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