Creeping towards broader clinical application of PET myocardial blood flow quantification

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Received Jun 21, 2018; accepted Jun 21, 2018
doi:10.1007/s12350-019-01651-w

See related article, pp. 719–728.

The value of an imaging test is assessed according to diagnostic accuracy, improved risk stratification, and downstream management implications. In clinical practice, the enthusiasm for incorporating measurements of absolute myocardial blood flow (MBF) with dynamic cardiac PET is based on the excellent performance within these categories. Specifically, myocardial flow reserve (MFR) has consistently provided incremental risk stratification beyond gated and relative perfusion variables.[1,2] More recently, PET MBF has also been used to diagnose and predict adverse events related to coronary microvascular dysfunction.[3,4] In addition, visual interpretation of both SPECT and PET uses normalized or relative perfusion images that are limited by artifacts and less accurate in the presence of balanced or severe diffuse disease. Finally, preserved MFR can exclude high-risk CAD and may therefore aid in appropriate patient selection for subsequent invasive testing.[5,6]

In part due to the added value of MBF measurements, rest-stress myocardial perfusion PET may be a preferred, first-line test in certain clinical scenarios.[7] Despite all of these favorable characteristics, and having been performed for over 30 years, the technique has been limited to research applications and is employed at a limited number of hospital based, predominately academic medical centers where it may not be included in the final report. The majority of published data are predominantly retrospective and from single-centers.[6] As MBF assessments have become more widespread, potential factors to consider and pitfalls in data acquisition and analysis have been highlighted and are summarized in Table 1.[8] Indeed, even before attempting to ascribe value to an imaging test, the implicit assumption is that the test is highly accurate with robust reproducibility. Given the number of options, factors to consider, and the potential errors that can be introduced, agreement on what to measure and normal values have not been defined.

In the current issue, Koenders et al[9] address a basic and important point related to accuracy and reproducibility, myocardial creep. Within this context, myocardial creep refers to altered myocardial blood flow measurements due to changes in diaphragmatic position after vasodilator administration. Specifically, the authors defined myocardial creep as misalignment of at least one-third of the width of the left ventricle in 2 time frames including filling of the left ventricle during the first pass phase. If myocardial creep was identified, manual re-alignment of the contours was performed, and the outcome was a difference in MBF or MFR of at least 10% between corrected and uncorrected scans.

According to this definition, in this retrospective cohort study of 104 patients, approximately half demonstrated myocardial creep during the stress acquisition. Although the magnitude of motion was not quantified, the high prevalence of visually significant creep is an obstacle in applying MBF in clinical practice. As the authors demonstrate, myocardial creep is especially a concern in the RCA distribution where misalignment can lead to inappropriate counts in the inferior wall when the signal is actually from the left ventricular cavity. Their results are consistent with this observation where the mean stress MBF in the RCA distribution decreased from 4.0 to 2.7 mL/min/g.

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J Nucl Cardiol 2019;26:735–7.
1071-3581/$34.00

Table 1. Technical factors affecting MBF quantitative accuracy

Technical factor	Impact
I. Scanner	
A. Spatial resolution	Spillover/partial volume errors
B. Data corrections (deadtime, randoms, scatter)	Quantitative errors
C. Detector saturation	Quantitative errors; reproducibility depends on infusion technique
D. Time-of-flight (TOF) capability	Image quality difference between scanners
II. Technique	
A. Infusion characteristics	Bolus vs sustained infusion, bolus peak depends on age of Rb-82 generator and IV line quality, possible double-peaks
B. Timing (relative to scan start)	Potential for missed bolus or inconsistency
C. CT acquisition (breath-hold, free-breathing)	Attenuation-related quantitative errors and artifacts
D. Protocol (single CT for both rest/stress versus separate CTs)	Attenuation-related quantitative errors and artifacts
III. Image generation	
A. Reconstruction algorithm and parameters	Noise characteristics, convergence errors, potential bias in MBF
B. Dynamic framing	Timing of frames may affect MBF
C. PET/CT registration (capability and quality of registration correction)	Attenuation-related quantitative errors and artifacts
D. Motion correction (real-time, or post-processing)	Attenuation-related quantitative errors and artifacts
IV. MBF analysis	
A. Software selection	Vendor-dependent MBF results
B. Motion correction (frame-by-frame)	Availability of tools to inspect and correct (automated, manual, both, or neither?)
C. MBF algorithm	Differences between flow-extraction models, errors at high flow
D. Blood pool ROI definition	Quantitative errors

Even though Koenders et al do not provide data regarding subsequent testing and adverse events, the high incidence and magnitude of myocardial creep could certainly impact diagnostic accuracy. Therefore, routine quality control in a rest-stress MBF assessment should include inspection of time activity curves and frame-by-frame inspection of dynamic data.[10] In this regard, MBF analysis software must provide user-friendly tools for frame-by-frame inspection and correction of patient motion. As the authors highlight, increased signal in the RCA distribution compared to the LAD and LCX on the first pass phase of the time activity curve is compatible with differential spillover from the left ventricle because myocardial uptake has not yet occurred. Similarly, during the first pass phase, spillover from the left ventricle into the automatically drawn myocardial contour may be observed in the inferior wall.

Overall, Koenders et al and others have made a valuable contribution to the literature highlighting the importance of blood pool phase patient motion during MBF measurements.[11,12] Recently, Memmott et al have shown that patient motion is more common with adenosine compared to regadenoson and hypothesized that patient motion may be most pronounced at termination of the adenosine infusion.[11] In addition, Lee et al demonstrated that blood phase motion in the inferior direction resulted in mean MBF and MFR errors of 29-44% in the RCA territory,[12] results consistent with the current manuscript.

Within a broader context, these papers all highlight the importance of technical considerations in measuring and reporting MBF measurements, especially as it relates to clinical reporting in different labs and the inclusion of MBF assessments within multi-center

clinical trials.[10] Accordingly, it is worth emphasizing the best-case scenario for test–retest variability and highlighting sources of methodological variation. In a single-center study, Kitkungvan et al demonstrated that the coefficient of variance for serial studies performed minutes apart was approximately 10% and was 20% for studies performed days apart.[13] This precision of ± 20% reflects both methodological and biological variability, and importantly, defines probability bounds in which clinical decisions could be made with certainty.

This methodological variation of 10% represents an ideal scenario with uniform protocols and equipment performed at a single center. Putting aside the choice of radiopharmaceutical and vasodilator, which will also effect MBF measurements,[14] what technical aspects will further influence this methodological variation? In general, considerations relate to the following domains: scanner parameters, radiopharmaceutical administration, methods of attenuation and motion correction, image reconstruction, and MBF analysis (Table 1). Given the equipment and software options and technical demands of the technique, professional medical societies and laboratory accreditation bodies need to provide measurement standardization and quality control guidance on how to perform absolute PET MBF measurements. The work by Koenders et al highlights just one of the important variables influencing measurements.

Disclosure

Paul C. Cremer, Frank P. DiFilippo, and Manuel D. Cerqueira have nothing to disclose.

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