Toward improved standardization of PET myocardial blood flow

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Quantification of myocardial blood flow (MBF) is becoming part of standard clinical practice in most centers performing cardiac PET imaging, as the added diagnostic and prognostic value is now well established and widely accepted. Despite (or perhaps because of) the rapid development and clinical adoption of PET MBF over the past few years, there remains an impressive variability in the imaging methods employed in the reported literature. For new centers starting a cardiac PET program, there are a number of choices to be made toward establishing a robust clinical service. Comparison between published methods and results can be difficult because of real (or perceived) differences in methodology and nomenclature. ***Improved standardization of reporting in the physical science and clinical research literature will help to streamline the clinical implementation and improve the reliability of PET (and eventually SPECT) MBF imaging.***

NOMENCLATURE

In vivo tissue perfusion refers to the flow rate (mL/min) of whole blood traversing the arterial to venous capillary network within a certain mass (g) of total extravascular and vascular tissue (wet weight). Measurements of myocardial tissue perfusion follow this convention with units accurately expressed as $mL \cdot min^{-1} \cdot g^{-1}$ and commonly reported in the PET literature as MBF [mL/min/g]. ***The ratio of stress rest MBF has thus been coined as myocardial flow reserve (MFR) and is the term recommended for clinical reporting in recent PET guidelines***.[1] While other terms have been used in the multimodality cardiac imaging literature including myocardial blood flow reserve, myocardial perfusion reserve, their use is less common and may be discouraged to help promote standardization in the context of PET imaging. The term coronary flow reserve has also been used in the PET literature, but some may argue this term better describes the volumetric flow rate (mL/min) of blood in an epicardial coronary artery as measured using invasive coronary catheter based methods for example.

TRACER KINETICS

PET is fortunate to include the accepted primary- or gold-standard for MBF measurements by which all non-invasive imaging methods are compared, i.e., the clearance of O-15-water which is (almost) ***freely diffusible*** across capillary and cell membranes, with first-pass extraction fraction $E \approx 1$.[2] Despite this physiological property which is ideal for MBF quantification, O-15-water is not retained in the myocardial tissues and does not enable conventional perfusion imaging. O-15-water has been used widely as the in vivo standard to validate MBF imaging methods for other PET tracers including N-13-ammonia and Rb-82. However, there are some important considerations when comparing these other tracers to O-15-water MBF (F) values when derived from the washout-rate ($F = \rho\ k_2\ E^{-1}$) and/or the uptake-rate ($F = K_1\ PTF^{-1}\ E^{-1}$) where ρ is the partition coefficient and PTF is the perfusable tissue fraction.[3]

A constant distribution volume of water in myocardial tissue (partition coefficient) is typically assumed as $\rho = 0.91$ [mL/g] ''…determined as the ratio of the water content in the myocardium (0.78 g water/g tissue) to that in the blood (0.86 g water/mL blood for a hematocrit of about 0.45).''[3] Therefore, in cases where the partition coefficient is altered by pathophysiological conditions such as myocardial edema, scar, cardiomyopathy, or even by age and sex where normal blood hematocrit is different between men and women, then the gold-standard water PET values may change accordingly.

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The water PTF is similar in principle to the partial-volume recovery coefficient (RC) used in tracer kinetic models of the ***retained tracers*** such as Rb-82, N-13-ammonia, and F-18-flurpiridaz. The values of PTF (and RC) will change with myocardial wall-thickness, wall-motion, and PET image resolution for example. In contrast to water where the regional values of PTF are actually measured ($K_1\ \rho\ k_2^{-1}$) in response to the geometric factors above, the values of RC used in the retained tracer kinetic models are typically assumed constant based on calibration or simulation, or the values are estimated based on strategic ROI placement where the tissue fraction (RC) and vascular fraction (f_V) total is assumed equal to one ($RC = 1 - f_V$).[4] If these assumptions of constant wall-thickness, wall-motion, image resolution or ROI placement are violated as a consequence of pathophysiology or imaging protocol when using the retained tracers, then the resulting MBF values may be altered, and should be interpreted accordingly. ***Discussing the validity of such assumptions is an important part of research study reporting, as these published papers may be used eventually to inform and guide clinical management.***

PET INSTRUMENTATION

MBF quantification requires accurate imaging of the first-pass transit of injected activity from the venous circulation to the right heart cavities, through the lungs to the left heart cavities, and then to the systemic circulation including the myocardium. Despite the successful transition from 2D to 3D PET over the past three decades, driven mainly by dose-reduction for whole-body F-18-FDG indications in oncology, some technical challenges still remain for accurate first-pass imaging in the heart.[5] Current PET scanner instrumentation and industry performance standards[6,7] have been developed mainly to optimize diagnostic image quality during the late tracer retention (or tissue) phase following blood-pool clearance, e.g., 60 min following FDG injection. However, accurate cine-dynamic imaging of tracer activity during the first-pass transit through the lungs and heart is challenging due to the rapidly changing biodistribution and associated corrections for randoms, scatter, cascade gammas (for Rb-82), and detector dead-time, in addition to attenuation correction and blurring effects that are changing with cardiac contractile, respiratory, and patient body motion. While weight-based dosing is recommended to help standardize myocardial perfusion image (MPI) quality during the tissue phase, higher injected activities in larger patients can result in more uncertainty in these correction factors and may bias the resulting MBF estimates. While some methods have been developed to characterize the accuracy of first-pass cardiac imaging[8,9] these have not yet been integrated into the PET industry-standard performance assessments. ***Improved communication among PET imaging scientists, scanner manufacturers and standards organizations should help to advance the development and implementation of industry standards necessary to ensure accurate first-pass cardiac imaging.***

QUALIFYING STANDARDS

Adoption of advanced imaging methods such as MBF quantification into clinical practice requires the publication of robust evidence documenting the diagnostic and/or prognostic value. There is an extensive body of literature on the clinical value of MBF PET imaging, however, most studies have been single-center retrospective reviews. A critical requirement for high quality prospective multi-center trials, is the establishment of qualifying standards for accurate measurement of MBF. While quantitative imaging standards have been developed to support prospective PET trials in oncology[10] and neurology,[11] no common standards have yet been proposed for clinical implementation or prospective multi-center trials demonstrating the value of cardiac PET MBF imaging. The American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging both have published guidelines for conventional stress myocardial perfusion imaging (MPI), but these do not include standardized protocol recommendations for quantitative MBF imaging. Recently, the European Association of Nuclear Medicine (EANM) has published guidelines for PET/CT quantitative myocardial perfusion imaging[12] with general descriptions of nomenclature and proposed schema for clinical reporting, but ***no specific standards are provided for testing the accuracy or precision of measured MBF values.***

QIBA PET MBF PROFILE

The Radiological Society of North America in 2007 established the Quantitative Imaging Biomarker Alliance (QIBA) with the goal ''to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice.''[13] QIBA provides a well-described formalism to develop imaging 'profiles' that define the precision and bias of a 'measurand' such as MBF to support interpretation of a single-patient scan or a change between serial scans over time.[14] These profiles are focused primarily on definition of the measurand properties, i.e., ***'what' is to be measured***, with a secondary focus on the methods or technical considerations of ***'how' to obtain the measurements***

which satisfy those properties. The PET MBF profile includes specific 'claims' for performance based on a review and meta-analysis of the extensive test-retest literature which defines the 'within-subject coefficient of variation' of a single measurement, wCV ≈ 15% for stress and rest MBF. The profile also contains a detailed description of requirements for an imaging center to achieve 'conformance' with the claims. There are more than 20 QIBA profiles in various stages of development including the PET MBF Profile which is aiming to be released for public comment (Stage 1) later in 2023. The author encourages those who may be interested to participate in these developments to review the information available on the QIBA website.[13] ***By engaging the leading experts in our field, we can help to ensure that PET MBF methods and applications continue to develop and to reach their full potential for clinical care.***

Disclosures

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