Annals of Nuclear Cardiology Vol. 2 No. 1 106-110

FOCUS ISSUE: MBF QUANTIFICATION－REVIEW ARTICLE

The Status and Future of PET Myocardial Blood Flow Quantification Software

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Received: June 3, 2016/Revised manuscript received: July 18, 2016/Accepted: July 28, 2016

Abstract

Myocardial blood flow (MBF) quantification with PET is generally considered a gold standard for the measurement of myocardial perfusion in absolute terms. The resulting values of MBF and myocardial flow reserve (MFR) used to determine the diagnostic path of a patient have a twofold (for MFR) or threefold (for MBF) range in literature, which interferes with establishing meaningful cutoffs—numeric values to tell healthy tissues from sick.

The review discusses software-based causes of variation of the quantification values that can be introduced at various steps of an image analysis—reconstruction, segmentation, quality control, tracer kinetic modelling, and outputting the resulting values. The review discusses possible solutions as well as the future of myocardial blood flow quantification software development.

Keywords: Future of PET, Myocardial flow reserve, Perfusion quantification, PET MPQ, PET software
Ann Nucl Cardiol 2016；2（1）：106-110

Myocardial blood flow (MBF) or myocardial perfusion quantification (MPQ) using PET is generally considered a gold standard for the measurement of myocardial perfusion in absolute terms (1,2). Studies of MPQ produced 'an extensive and technically robust literature, with over 250 papers including almost 15,000 subjects in the past 25 years' as stated by Gould et al in 2013 (3, p.1640). Yet, looking into this literature to exactly see 'how much'—the Latin '*quantus*' of the word 'quantitative'—we might not find the definitive answer. The ubiquitous metric of 'reserve', interchangeably called coronary flow reserve (CFR), or myocardial flow reserve (MFR), or less frequently myocardial perfusion reserve (MPR)—a unitless ratio of myocardial stress to rest flow that helps tell the normally perfused from the ischemic myocardium—has wide variation in the literature for both normal and abnormal hearts.

For normal healthy hearts, its values range from 2.01 ± 0.72 (4) to 5.16 ± 1.64 (5), or even to 6.10 ± 1.64 (6), all studies performed with ^{15}O water PET. In patients with CAD risk factors only, its values range from 1.59 ± 0.41 (7) to 5.11 ± 2.23 (8), studies performed with ^{13}N ammonia and ^{15}O water respectively. In patients with established CAD, the reserve values range from 1.14 ± 0.44 (9) to 3.00 ± 0.76 (10), both studies performed with ^{13}N ammonia. In part, the differences may reflect the physiological variation, and, apparently, the reserve values are higher in normal hearts; however, the dramatic overlap makes definition of meaningful cutoffs—numeric values to tell healthy tissues from sick—not an easy task. These cutoff values for MFR range from 1.44 (11) to 2.74 (12), both studies done with ^{13}N PET, or to 2.5 (13), received with ^{15}O water. Looking at the MFR range one might wonder how the metric, widely used to determine the diagnostic path of a patient, can have such a wide range—almost triple difference between the extremes—its

doi：10.17996/ANC.02.01.106

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cutoffs having a double difference. To understand that, first, we may have to accept that different tracers may behave differently in quantification and may need different cutoff values; second, PET instrumentation can harbor certain sources of precision and accuracy error (14); and, third, we must remember that the basis of all the quantification in PET is the transformation of the measured radioactivity concentration values into milliliters of blood per minute per gram of myocardial tissue (mL/min/g). This process is performed in and with PET software tools, and consists of several steps, each of which can affect the results. These steps are reconstruction, segmentation, quality control, tracer kinetic modelling, and outputting the values. These steps are discussed in this review.

Reconstruction

There are three key reasons for the differences in the input images: (1) temporal sampling, (2) reconstruction methods, and (3) post-filtering. The first problem is under-sampling of the LV blood pool time activity curve (TAC), which can produce inaccurate estimates of MBF and MFR while over-sampling will increase image noise and computational resources (15-17). The solution is to select a sampling protocol of frame durations that sufficiently sample the input function and output function TACs. The second problem is that differences are observed in regional MBF and MFR estimates based on the reconstruction algorithms such as FBP, 3D-OSEM, 3D-OSEM with PSF, 3D-OSEM with TOF, and 3D-OSEM with both PSF and TOF, with the largest differences using TOF (18,19). The currently missing solution is to have empirical corrections to standardize values between the reconstruction methods. The third problem is that greater filtering lead to higher MBF, so the recommendation is to use minimal filtering (20).

Segmentation

Segmentation precedes modelling and informs the computer where the myocardium of the left ventricle (LV) and the blood in its cavity are. The first step performed by all software tools is to reorient the images from transverse into a standard cardiac orientation. These software tools differ in their approaches to segmentations by algorithms involved and by automaticity of the process. Carimas and MunichHeart demand a human operator to start the process by manual definition of the LV axes; UW-QPP and PMOD automatically find the mid-line of the myocardial wall and then iteratively select the edges of the myocardium (the EPI/ENDO method in PMOD); ImagenQ implements wavelet-based edge detection, while Corridor4DM automatically segments using the original 4DM algorithm incorporating gradient operators and weighted spline interpolators (21). QPET performs fully automated segmentation based on widely used QPS algorithm, with manual override of the localization, masking region and valve plane if required (22). To our knowledge there are no studies comparing all the algorithms together. Another cause of difference might come from the impact of a human operator—usually even the automatic tools leave the operator a possibility to adjust the result of the segmentation and so to add variation. This human-based variation may yet be unavoidable, as one cannot entirely rely on the currently existing segmentation algorithms in all the cases, especially in cases of ^{15}O water.

To further complicate segmentation, three more problems can alter the results: (1) blood pool ROI definition, (2) RV activity spillover, and (3) tissue sampling differences between rest and stress series. The first problem that may affect consistency of MBF estimates is in possibility of different placements of the blood pool ROI—in the LV cavity, LV base, left atrium, or outflow tract—as well as its size and shape across various software packages. A recent study has demonstrated the effects of ROI placement on MBF and CFR (23) but further studies are necessary to standardize the optimal placement. The second problem of the spillover of the RV blood pool can affect the tissue TACs and MBF estimates can be solved by modelling RV spillover (24,25). Yet, not all software tools consistently implement it. The third problem is differences in the basal valve plane location in the LV surfaces for stress and rest series that affects global and regional MFR based on tissue sampling of different regions. The alignment of rest and stress myocardial surfaces is a problem as well. The solution—to synchronize stress and rest series basal valve planes—is not widely implemented (26).

Quality control

The problems at this step are (1) motion in a blood pool phase and (2) manual motion correction. The first problem is patient motion that is prevalent in dynamic PET—up to 62% of datasets with majority 45% in the axial direction and it affects mean estimates of MBF up to 250% (27). Indeed, existing software (e.g. Munich Heart and syngo.MBF) have options for motion correction, but seem to focus only on the tissue uptake phase and have not been fully evaluated in the literature. The solution is to perform motion correction either manually or automatically with shifting of individual frames relative to a reference summed tissue image. The second problem is lack of automated motion correction since manual motion correction is time consuming and introduces user variability. Clinically viable solutions are still being developed but are not yet commercially ready. The solution is to develop automated motion correction for all phases of the dynamic sequence.

Tracer kinetic modelling

Once segmented and polar map sampled, the TACs can be calculated and quantified by an appropriate tracer kinetic model. Here, as well, there are many options implemented in software tools. For ^{82}Rb, there are at least four models—Retention, 1-tissue compartment model (1TCM), 2-tissue compartment model (2TCM), and Axially Distributed—implemented in at least ten software tools (28), and the values they provided in the mentioned study differed substantially—up to 2.3 times (ibid.).

The models conventionally used are compartmental models. The differences between these models highlight the trade-off between model accuracy and precision which in practice means that estimates provided by more complex and realistic models like Axially distributed (29) and 2TCM will generally have higher variance than those of the simpler 1TCMs (30). The Retention model is the simplest of these models that assumes washout can be neglected. It is defined as the ratio of the average late tissue activity over the total early blood pool activity within a predefined time interval, which requires consistent tracer arrival time into LV blood pool (31). The above models all assume that the LV blood pool TAC is a true signal, which is not the case due to partial volume effects. For large LV blood pool ROIs placed in the LV cavity, the tissue activity will spillover into the blood pool. This is seen in the tail of the blood TAC where the activity does not seem to clear the blood. Two proposed solutions are to implement dual-spillover correction (32,33) or place a smaller ROI in the left atrium outside LV cavity (23).

Outputting the values

The main problem at this step is the MBF variability due to various Renkin-Crone models—the RC K1-to-MBF relationship is fitted specific to the type of data, PET scanner (2D, 3D), reconstruction method (PGC, PSF, TOF) and method of segmentation for TAC sampling. MBF threshold related to outcomes are RC model dependent (34). The proposed solution by the authors is to generate unique RC models for each camera and flow model or better yet focus on MFR which tends to cancel out biases in MBF.

Quid deinde? [What next? (*Latin*)]

Summarizing the reviewed status of the PET MBF software and the existing problems, authors see three possible ways of further development of PET MPQ. The first way is the one advocated by Gould et al., which was summarized in an all-star state-of-the-art 2013 paper—'each PET facility has to establish its own flow values causing ischemia" (3, p.1646). It is indeed possible to build an all-inclusive custom system from a PET scanner to the analysis software, which will provide the robust results in that facility; yet, it undoubtedly leads to compartmentalization of nuclear cardiology as it prevents communication of results between the facilities as well as the possibility to pool the results from several centers.

The second way, pursued by deKemp et al. (35), Tahari et al. (36), Dunet et al. (37), as well as the authors of this review (28,38), is to find a common denominator for the existing tools. In practice, it means the following: we doubt that it is currently feasible to single out 'the one' software solution, make everyone let go the tools they have been using for years already and switch to that one tool. What is feasible, however, is to test all the tools on common datasets, find out where each of the tools stands in respect to the rest and use these results in pooling and communicating the data. We are performing it for all the nuclear cardiology tracers.

Nonetheless, this way we see as a temporary substitute and consider the third way the most likely future. The third way is to support emergence and perfection of the software and the underpinning algorithms—of reorientation, segmentation, motion correction, etc.—which would ultimately lead to the survival of the fittest tools for PET MPQ that in the long run will converge on the most accurate and precise values. Nobody can guarantee though that in the same long run the survivors, which will measure myocardial blood flow accurately and sparingly, will be the software tools analyzing images of PET.

Acknowledgments

The authors acknowledge Adam Alessio (USA), Ioana Florea (Switzerland), and Xiao-Bo Pan (UK) for their help in preparing the review.

Sources of funding

None

Conflicts of interest

B.C. Lee and J.B Moody are both employees of INVIA; other authors declare that they have no conflicts of interest to report.

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The 11th Congress of Asian Society of Cardiovascular Imaging ASCI 2017 in Kyoto

Date: June 1 (Thu) – 3 (Sat), 2017

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We would like to cordially invite you to join the 11th Congress of Asian Society of Cardiovascular Imaging (ASCI) which will be held in Westin Miyako Hotel in Kyoto, Japan from June 1st to 3rd, 2017 (Thursday to Saturday). Our theme is “Cardiac Imaging - Innovation and Partnership for Patients”.

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We look forward to your participation and invite you to enjoy the ASCI 2017 meeting and the charms of Kyoto with us.

Sincerely yours,

Hajime Sakuma, MD, PhD, FAHA
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