Relative disagreement among different software packages in PET-flow quantitation: An appeal for consistency

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Positron emission tomography (PET) is increasingly applied to assess myocardial perfusion in conjunction with global and regional myocardial blood flow (MBF) quantitation in mL·g·min in patients with suspected and/or known CAD.[1,2] While the stress-related regional myocardial perfusion defects commonly identify the ''culprit'' or the most-advanced CAD lesion in multivessel disease, the hemodynamic significance of less-severe, intermediate CAD lesions with still homogenous radiotracer uptake may be identified by corresponding regional reductions in hyperemic MBF and/or myocardial flow reserve (MFR = MBF-stress/MBF-rest).[2,3] In this respect, the concurrent assessment of PET-determined MFR has been appreciated to provide not only the additional diagnostic value, but it carries also important prognostic information in patients with subclinical and clinically manifest CAD.[4,5] The reproducibility of such MBF quantitation with PET has been performed mainly in healthy volunteers with and without cardiovascular risk factors.[6] These data have convincingly demonstrated that PET-determined serial MBFs during pharmacologic-stimulated hyperemia and at rest can be employed reliably and are reproducible for quantitation of effects of preventive medical intervention, gastric-bypass-induced weight loss, and/or behavioral interventions related to weight, diet, and physical activity on coronary circulatory dysfunction.[1,7] Subsequently, the reproducibility of PET-flow studies among different software tools was investigated.[8–11] For example, Slomka et al.[8] compared MBF values obtained from three software tools such as QPET, syngo MBF, and PMOD in individuals with or without obstructive CAD. And indeed, the global and regional MBF and MFR values did closely correlate between the three software packages (correlation coefficient r^2 for global values ranging from 0.88 to 0.92 and for regional values from 0.78 to 0.94, respectively), which was reflected by similar mean MFR values (QPET: 3.39 ± 1.22, Syngo MBF: 3.41 ± 0.76, and PMOD: 3.66 ± 1.19, respectively).

In this issue of the Journal of Nuclear Cardiology, Monroy-Gonzalez et al.[12] report that in patients with normal stress-rest PET perfusion images, two out of three comparisons were outside the limits of agreement, while in patients with reversible perfusion deficits suggesting ischemia, comparisons of all software packages of global hyperemic MBFs and MFR were outside the limits of established agreement. In addition, there was an agreement of hyperemic MBFs and MFR mostly only for the LAD distribution. Such observations outline that results of MBF quantitation with different software packages are not necessarily interchangeable. Such observations may contradict the results from Slomka et al.'s study[8] which described quite similar MFR values for each vascular territory except for some disagreement in respect of the RCA distribution due to the influence of high spill-over fraction, a problem familiarly known for ^{13}N-ammonia PET images. PET-flow studies with other positron-emitting radiotracers such as ^{82}Rubidium and ^{15}O-water also yielded a good-to-excellent agreement between the observations made using different software packages.[11,13,14] The reason for these discordant observations may remain uncertain and

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may be related to methodological differences or reorientation, contour detection, left ventricular segmentation, and the sampling of the left ventricle blood pool time activity curve as per the authors' statement.[12] Overall, the contrasting observations in MBF quantitation with different software packages may be surprising at first sight, but they may be reconciled when looking more into the details. For example, there is a distinct variability of individual hyperemic MBF as expressed by the coefficient of variation (COV) ranging 0.49 to 1.34 for hyperemic MBF.[6] In this direction, the calculation of the MFR, which reflects the ratio of hyperemic MBF to MBF at rest, affords a potential advantage of less variability than that for the hyperemic MBFs measured.[15] If a percentage methodological error is made (e.g., positioning of the region of interest for the arterial input function) during hyperemic flows and a similar error is made during rest MBF quantitation, then the errors will cancel out. Thus, when calculating the MFR, any methodological differences among software packages may widely cancel out given the same percentage error is made both during hyperemic vasodilator stress and at rest. For example, in a multicenter trial with a head-to-head comparison of MBF quantitation between gadolinium CMR and ^{13}N-ammonia PET imaging, the MFR between the two modalities correlated well ($r = 0.75$) but not so for hyperemic and rest MBFs ($r = 0.37$ and $r = 0.32$, respectively).[16] The results of the current[12] and other studies[13,17,18] emphasize the relative but significant differences in values of hyperemic MBFs and MFR related to methodological differences of software packages in the quantitation of MBFs and also to a certain observer dependency (e.g., semi-manual segmentation of the left ventricle and positioning of the ROI for the arterial input function). The variability of quantified hyperemic flows can also be appreciated by the range in the standard deviation (SD) of the mean values. This has important clinical implications as the optimal threshold for hyperemic MBFs and MFR to define between normal and abnormal flows may be derived from mean flows values and its SD in healthy volunteers. Abnormal hyperemic MBF and MFR may be present when these flow parameters are ± 2 standard deviations (SDs) below the limits of normal values on the basis of hyperemic MBFs in a healthy study population without cardiovascular risk factors.[1] For example, stress-rest ^{13}N-ammonia PET/CT study in healthy volunteers resulted in a mean hyperemic MBF of 2.37 ± 0.49 mL·min·g and MFR of 3.38 ± 0.67. Consequently, the thresholds to signify reduced hyperemic flow increases (2 SD below the mean) would be 1.39 mL·g·min for hyperemic MBF and 2.04 for the MFR, respectively.[19]

Taken together, Monroy-Gonzalez et al.[12] have to be complemented as their results outline an important issue of a relative but likely clinically important disagreement among software packages in flow quantitations. The observed range of relative discordance[12,13,17] may affect the diagnostic accuracies of hyperemic MBFs and MFR in the identification and characterization of hemodynamic significant downstream effects of epicardial lesions.[20] For this reason, each PET facility should strive for consistency not only in the choice of positron-emitting radiotracer and remaining manual steps in the processing of the MBF quantitation but also in their software package for optimal patient care.

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