Time-of-flight in cardiac PET/TC: What do we know and what we should know?

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Coronary arteries disease (CAD) is the most common cause of death in the world, and an accurate diagnosis can be made by combining the diagnostic results of different invasive and noninvasive techniques. Among the latter, molecular imaging has gained growing importance, and above all, positron emission tomography (PET), combined with computed tomography (CT), has shown increasing diagnostic accuracy in detecting small and low perfusion areas in the myocardial wall.¹ This was possible thanks to the cardiac-dedicated PET radiotracers (for example, Rubidium-82 chloride, ⁸²Rb), but also to the last generation of correction techniques available for the acquisition of the emission data and in the reconstruction process of myocardial images.

Time-of-flight (TOF) technology allows for the identification of positron annihilation location with greater accuracy than non-TOF detection, resulting in a reduction of the spatial uncertainty and thus, in lowering the image noise. Accordingly, an advantage of TOF is the improvement of lesion contrast and the related signal-to-noise ratio, finally resulting in a superior overall image quality.²

Effects on PET images related to the finite spatial resolution of the PET scanners are referred to as partial volume effect (PVE) and result in a quantitative bias when small objects are investigated.³ The PVE-correction algorithms available on the last generation of PET

systems belong to the resolution modeling (RM) technique that incorporates the point spread function (PSF) of the system used in the forward and backward projection matrix of the iterative process. However, although the application of PSF modeling has demonstrated to improve image quality of Fluorine-18 fluorodeoxyglucose ([¹⁸F]FDG) studies, there is no consensus on the actual benefits derived on quantitation, as the noise propagation related to RM is far from being fully characterized.⁴

Several papers have studied the impact of TOF technology and PSF modeling on the detectability of hot lesions in oncological imaging with [¹⁸F]FDG,⁵ but their effects in the presence of cold lesions or low-uptake regions, such as those of myocardial imaging, are far from being fully explored. Moreover, the study of perfusion (and/or viability) of the myocardium is further complicated by the organ motion and by the heterogeneity of radiotracer distribution and tissue density in the human torso.

A further step toward the assessment of these issues in PET cardiac studies was recently achieved by Dasari et al.⁶ In a group of obese patients, the authors studied the individual and combined effects of TOF and PSF on ⁸²Rb myocardial perfusion images as a function of different anatomic features: gender, body mass index (BMI), cross-sectional body area in the scanner field of view, and left-ventricular myocardial volume.

In accordance with a previous published study,⁷ TOF confirmed the gain in uniformity of the radiotracer distribution, showing in particular an increased uptake of about 10% in the septal segments of the myocardial wall. However, the element of originality of the study of Dasari et al is that the increased uptake at septal level is more pronounced for patients with large cross-sectional area and for female (due to breast attenuation). On the contrary, PSF modeling had only a slight effect on image quality, increasing the overall perfusion uptake irrespective of patient gender and anatomic features.

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The perfusion semiquantitative analysis reported in this study showed somehow surprising results: the summed stress (SSS) and rest (SRS) scores were, on average, significantly smaller for TOF with respect to non-TOF reconstructions. These results would indicate a reduction in the appearance of the defects in TOF images that could affect the risk stratification of the patients with regard to cardiac event-free survival. Consequently, some patients with a severe disease after a non-TOF PET study could be moved to a less-severe category if TOF reconstruction is used.

Thus, does TOF improve the uniformity of the PET cardiac images, and, at the same time, reduce the appearance of the perfusion defects particularly in obese patients?

How much benefit might be derived from TOF technology in the myocardial perfusion studies is still unclear and needs to be better understood.

TOF AND PSF VERSUS CONVERGENCE OF ITERATIVE ALGORITHM IN CARDIAC STUDIES

TOF demonstrated its superiority in the contrast recovery of hot lesion and in the better visualization of cold areas in studies performed on both anthropomorphic phantoms and on [^{18}F]FDG patients.⁴ The evidence was that TOF provides overall significant improvement in image uniformity and increased convergence rate of the iterative algorithm compared to non-TOF technology, which requires approximately three times more iterations than TOF to reach the true activity distribution in the reconstructed images. This issue is of particular importance in nuclear cardiology, as the basic task is to determine the presence or the absence of ipo-perfused regions in the myocardial wall: for a normal patient, a uniform tracer distribution in the myocardial wall has to be translated into a set of uniform images of the left-ventricular signal. However, the convergence is a nonlinear process and behaves differently depending on the different radiotracer concentrations present in the field of view, as areas with lower uptake (such as the perfusion defects) converge slower than those with higher uptake.⁸ Heart orientation, breast size and location, and the presence of fluid in lung could also affect the image uniformity due to the incomplete convergence of iterative algorithm in the corresponding areas of the PET images.

The synergic effect of PSF when coupled to TOF has been reported in the literature for both [^{18}F]FDG patients (8,1) and phantom (9,1). The authors agree in the contrast improvement of cold defects, although at a different level on different PET/CT scanners.⁹

The PSF modeling is obtained by an analytical approach,¹⁰ via Monte Carlo simulations¹¹ or by measured datasets,¹² depending on the model of PET scanner. Anyway, in contrast with TOF, PSF model included in the iterative algorithm degrades the performances slowing the convergence of the iterative algorithm.⁷

Moreover, the study of Dasari et al used an approximate PSF modeling as the PSF of ^{18}F was used for ^{82}Rb exams. The effect of PSF modeling on ^{82}Rb imaging could be in principle different from that on ^{18}F , due to the higher energy of the positron emitted by ^{82}Rb (1535 keV) with respect to ^{18}F (635 keV). This could explain the small increase in perfusion uptake in almost all heart segments (averaging 1.5%), with no statistical significance for any segment when PSF modeling is applied.

Few other papers studied the effect of PSF on ^{82}Rb imaging, but they are all related to blood flow and myocardial flow reserves in patients.^{13–15} Anyway, they all show equivalency or superiority of TOF-only PET imaging.

TOF AND PET/TC MISALIGNMENT ARTIFACTS

Misalignment between PET and CT images is known to generate artifactual defects in PET images due to inaccurate attenuation correction (AC). This is more critical in cardiac studies where, in addition to the patient movements, heart beat and respiratory motion can produce an involuntary spatial mismatch between PET and CT. This could result in an unrealistic increased or decreased cardiac uptake corresponding to over- or under-attenuation correction of the emission data.

It was observed in a phantom study that the mismatch between PET and CT is more evident for non-TOF than TOF images. TOF reconstruction is less sensitive to mismatched attenuation correction, erroneous normalization, and poorly estimated scatter correction, as TOF provides additional information of the origin of each detected event. The mismatched artifacts can be also observed in patients, but with a lower intensity.²

Dasari et al suggest indeed that the increase in septal wall perfusion when TOF is used could be attributable to inconsistencies in scatter correction that can be more critical for areas that are located centrally in the body, as is the case in respect of the septal wall.

The justification for the superiority of TOF images lies in the fact that in the iterative algorithm, the quantitative contribution coming from TOF has superior weight to that coming from the AC based on CT, when the mismatch between PET and CT images is small

(quantitation errors < 10% for 5 mm misalignment).¹⁶ When PET/CT misalignment is greater than 5 mm, the use of reconstruction algorithms—different from the traditional ordered subsets expectation maximization (OSEM) used by Dasari et al—has been proposed. The maximum likelihood attenuation and activity (MLAA) algorithm in the paper of Presotto et al¹⁷ is a feasible and robust technique to avoid large mismatch artifacts in TOF PET cardiac studies, provided that a CT of the patient is available.

TOF AND OVERWEIGHT PATIENTS

The larger the cross-sectional area present in the field of view, the stronger the attenuation and scatter phenomena of the emission data and the higher the probability of mismatch between PET and CT images. The category of obese patients with CAD would clearly benefit from the above-described potentialities of TOF. Moreover, with TOF, the gain of signal-to-noise ratio generally increases with the increasing patient size.

⁸²Rb is widely used for PET myocardial perfusion study thanks to its high sensitivity,¹⁸ and its distribution in the myocardial wall of obese patients was recently investigated by comparing TOF and non-TOF images reconstructed with a variable number of iterations.⁷ It has been demonstrated that nonconvergence (insufficient number of iterations) of non-TOF reconstruction is very important in obese patients and may result in artifactual nonuniformity distribution of the perfusion radiotracer with consequent both false-positive and false-negative interpretation. This was more important for the myocardial regions located near the lungs and the breast, where the tissue density is far from being uniform.

TOF AND PERFUSION QUANTIFICATION RESULTS

Surprisingly, the results of Dasari et al would indicate a reduction in the appearance of the perfusion defects in TOF-PET imaging with significant decreases between 2.4 and 3.0 for both SRS and SSS. This could affect risk stratification for CAD, moving some of patients to a less-severe category. On the contrary, SRS and SSS were largely unchanged when PSF modeling was applied.

In line with the above considerations, a possible explanation is related to the incomplete convergence of non-TOF reconstruction in the study of Dasari, so one may wonder how the perfusion would be modified by increasing the numbers of iterations. In fact, all the iterative reconstruction types (non-TOF, TOF, and TOF + PSF) were performed with four iterations, 21

subsets, and an 8-mm full-width at half-maximum (FWHM) 3D Gaussian post-reconstruction filter.

Moreover, SSS and SRS are based on the evaluation of the differences between the patient-specific distribution of myocardial perfusion and the corresponding mean in normal patients as a function of normal variability. Both the mean and variability of normal distribution uptake depend on a number of factors, including the reconstruction algorithm used and the correction techniques applied. When a nonspecific normal database is used, misestimation in the evaluation of perfusion scores is reported in the literature.^{19,20} Thus, the quantitative approach is a robust tool for patient-risk assessment, provided that specific normal database are used. Dasari et al did not mention which normal databases were used in the study.

A VIEW TO THE FUTURE

All the observations we reported claim that further knowledge ought to be gained on the correct use of TOF and non-TOF technologies in PET studies of myocardial perfusion. New experiments under controlled conditions with known clinical distributions of ⁸²Rb, i.e., with appropriate anthropomorphic phantoms with different anatomic features, should be performed with a to better understand the potential false-positive or false-negative interpretation when convergence of the iterative reconstruction is not reached. Moreover, further clinical studies should be performed in order to evaluate the effects of TOF and PSF on SSS and SRS results with respect to a gold standard (e.g., coronary angiography) rather than those of the non-TOF iterative reconstruction.

In the case of a clinical trial of a promising new PET radiotracer of perfusion study, the use of the PET correction techniques, such as TOF and PSF, should be optimized for cardiac studies on each single PET scanner before starting the acquisition of the enrolled patients.

Disclosure

R. Matheoud and M. Lecchi have nothing to disclose in relation to this Editorial.

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