Does time-of-flight improve image quality in the heart?

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With the advent of fast Lutetium-based scintillation crystals, time-of-flight (TOF) positron emission tomography (PET) became a clinical reality. Although the crystals are still not fast enough to let us simply put photons back where they came from, incorporation of TOF information into the reconstruction of PET images has led to a substantial gain in signal-to-noise ratio (SNR), particularly for larger patients. The benefits of TOF have been shown with numerous oncology studies but there has been, to date, little evidence regarding TOF in cardiac studies. In this issue of the *Journal of Nuclear Cardiology*, Armstrong et al. investigate the SNR gain from TOF in cardiac viability imaging with FDG PET.[1]

TOF works by evaluating the difference in the arrival time of the two coincidence gamma rays. Because the speed of light (c) is constant and finite, the difference in arrival times can be translated into a distance (x) from the center of the line-of-response (LOR) (Figure 1A). With this information, the location of the annihilation event can be determined by the difference in arrival times of the two annihilation photons (t_i). The distance a photon travels (d_i) in time t_i is given by $d_i = t_i \times c$. Therefore,

$$x = (d_2 - d_1)/2 = (t_2 - t_1)\, c/2 = \Delta t\, c/2 \qquad (1)$$

and the uncertainty in the position x (σ_x) are given by

$$\sigma_x = \sigma_{\Delta t} c/2 \qquad (2)$$

where $\sigma_{\Delta t}$ is the timing resolution of the scanner.

If the timing resolution was perfect, we would not even need to do a reconstruction because we could just put each detected count back at its point of origin. However, the timing resolution is not perfect. With BGO crystals, the typical timing resolution is on the order of 5 ns, which translates into a spatial resolution of about 75 cm. In this case, TOF does not add much information because the position uncertainty is larger than the bore size of the scanner. However, with the Lutetium-based scintillators, timing resolution is on the order of 500 ps and so the corresponding uncertainty in the position of the annihilation event is only 7.5 cm. Now, when we go to reconstruct the image, the probability of an event's location is not spread evenly over the entire LOR, but it is instead confined to a small portion of the line—a Gaussian probability with a full-width at half-maximum equal to the spatial positioning uncertainty (Figure 1B). One of the benefits of TOF is that reducing the uncertainty in where each event is located results in a reduction in the propagation of noise along each LOR. The influence of each count is restricted spatially and so the noise from distant objects in the field of view (FOV) is no longer present. Lower noise means a higher SNR.

The increase in SNR from TOF PET has been recognized for some time. In 1983, Budinger[2] described the relationship and showed that the gain in SNR should be approximately equal to

$$\mathrm{SNR_{TOF}} \propto \sqrt{D/\sigma_x}\,\mathrm{SNR_{non-TOF}} \qquad (3)$$

where $\propto$D is the diameter of a uniform cylinder. The use of a non-linear iterative reconstruction algorithm instead of filtered backprojection, as well as other factors, can alter the SNR[3] and so the gain in SNR from TOF is not quite as high as suggested by Eq. 3. Nevertheless, studies with FDG PET in oncology have still shown substantial gains, up to approximately a factor of 2 in larger patients.[4,5] The gain in SNR generally increases with increased patient size and with improved timing resolution. In addition to simple measurements of SNR, the improved image quality from TOF has also been

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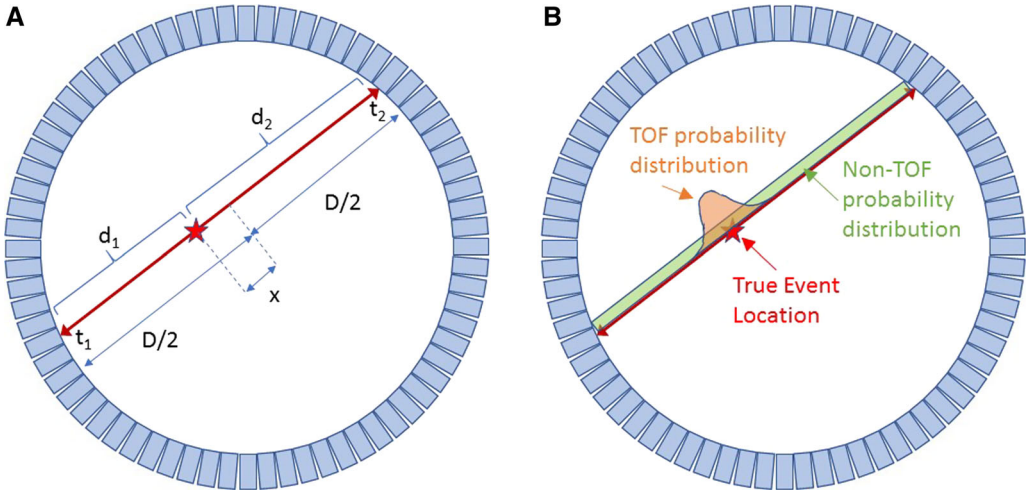

Figure 1. A The position of the event (x) is given by the difference in distances traveled (d_i; $d_1 + d_2 = D$) by the two photons which is, in turn, determined by the difference in arrival times (t_i). **B** During image reconstruction, the counts are not distributed evenly along the line-of-response (LOR) as they would be for non-TOF PET data. Instead, counts are placed with a Gaussian distribution, centered on the point determined by the difference in arrival times and with a spread proportional to the timing resolution.

demonstrated using more clinically realistic tasks and numerical or human observers.[6–8] These benefits from TOF have been demonstrated in oncology studies with phantoms, hybrid images—where artificial lesions are inserted into clinical normal datasets, and in studies of patient images.[3,4]

There are very little data, however, evaluating the advantages in cardiac applications. As indicated in Budinger's early work, Eq. 3 is for a uniform activity distribution. With cardiac imaging, the activity distribution in the FOV is generally concentrated in the heart producing a very non-homogeneous distribution. This reduces the uncertainty in the location of the activity and reduces the gains from TOF imaging. Nevertheless, particularly with 3D PET, there can be substantial activity in the sub-diaphragmatic organs, like the intestines, liver, and stomach, depending on the tracer used for cardiac imaging. The presence of high-activity background structures close to the myocardium would increase the potential gain from TOF. How much benefit might be derived from TOF for cardiac studies is thus unclear.

Armstrong et al.[1] looked specifically at the SNR gain in cardiac viability imaging with FDG PET. They estimated the noise in each voxel of the myocardium using multiple replicate images generated by dividing the list-mode dataset into several short-time frames. They used a phantom study and clinical images to demonstrate that the gain in SNR in the myocardium of FDG PET images was similar to that seen in FDG PET oncology studies, where the SNR was measured from a volume-of-interest placed in the liver. They measured a 21% SNR gain which could be translated into a reduction in counts (activity injected into the patient) of 25%.

The SNR is a useful metric that has been related to detectability of lesions in situations where the signal is ''known exactly'',[3] that is, the size, intensity, and location of the signal are known to the observer. However, SNR is only a component of image quality which depends greatly on the task for which the image is to be used. Several studies have been performed with PET oncology images using human observers to determine how changes in SNR translate into changes in lesion detectability.[5,6] However, the task in cardiac imaging is different from that of lesion detection in oncology. For lesion detection, it is a search for hot spots in a warm background, but for viability imaging, it is an evaluation of hot uptake in the myocardial wall in a cool background, and in perfusion imaging it is a search for cold spots in a hot background. This is also reflected in the apparent discrepancy between the results presented by Armstrong et al. and the study by Oldan et al.,[9] which showed no significant change between TOF and non-TOF reconstructions. However, Oldan et al. measured not the SNR, but instead compared the change in segmental relative uptake. To accurately assess the impact of TOF on image quality will require clinical evaluation of performance.

An additional consideration is the optimization of both TOF and non-TOF reconstructions. TOF is also known to increase the rate of convergence of the reconstruction algorithm. Differences can arise simply

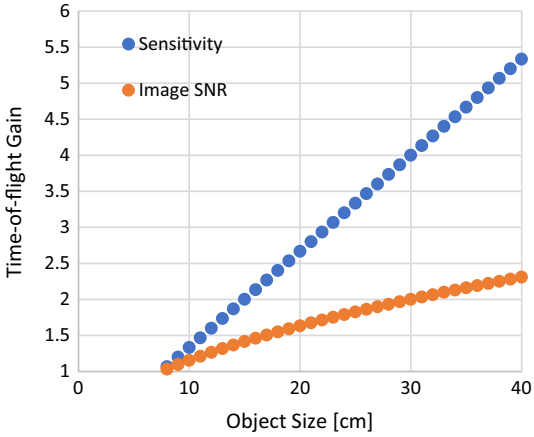

Figure 2. Sensitivity and image SNR gains due to TOF for a timing resolution of 500 ps. The expected gain increases as object size increases.

from the algorithms being halted at different points along their paths to convergence. As shown by DiFilippo et al.,[10] convergence of both TOF and non-TOF algorithms in obese patients may require more iterations than used in the studies by both Armstrong and Oldan. However, in clinical practice, algorithms are rarely run to convergence and the choice of stopping point may vary from lab to lab. This highlights, though, the importance of the particular choice of both reconstruction parameters and the post-reconstruction filtering applied. Before implementing any changes to clinical protocols, such as reduction in injected activity or reductions in acquisition times, the changes in image quality due to TOF should be confirmed using local image processing procedures. In this respect, the methodology proposed by Armstrong et al. may provide a very useful tool in assessing how changes in protocols influence image SNR.

It is widely accepted that the expected TOF improvements in image quality should be higher in larger objects. Using the formula shown in Eq. (3), the expected gains in SNR or equivalent count-rate sensitivity from a TOF system with 500 ps timing resolution is shown in Figure 2 for a uniform cylinder image. Therefore, it might be anticipated that larger patients should have more benefit in image quality; however, Armstrong et al. showed that the increase in myocardial image SNR was a very consistent value of 21% (Figure 3A). This corresponds to the TOF gain predicted for an object size of approximately 11 cm, which is somewhat larger than the size of the typical human heart, but much smaller than the dimensions of the thorax. This is consistent with the work by Budinger which suggests that the effective diameter of the object in cardiac imaging is greatly reduced due to the high contrast of tracer activity in the heart compared to background.

Looking at the changes in SNR as a function of patient BMI helps to put these data into clinical context as shown in Figure 3B. The highest increases in SNR were observed in the smallest patients who had the highest SNR to begin with, whereas the largest patient showed the smallest benefit from TOF reconstruction. This suggests that TOF is not particularly helpful to standardize image quality across different patient sizes in cardiac imaging, contrary to what has been observed for oncology studies[4] and as might be expected from the predictions of Figure 2. A uniform reduction in the injected activity as proposed by Armstrong and colleagues would be possible with the use of TOF, but a constant activity, as used in this study, would still produce lower image quality in the largest patients. An additional clinical strategy of weight-based dosing is needed to preferentially increase the image quality in the largest patients, where the SNR benefit is needed most.

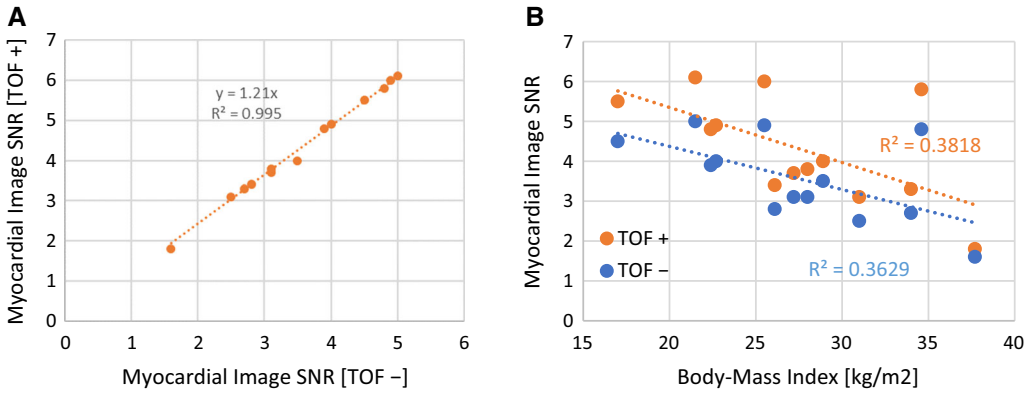

Figure 3. Myocardial SNR with and without TOF, correlation (**A**), and comparison to body-mass index (**B**). Data from Armstrong et al.[1], Table 2.

TOF is an exciting capability of modern PET scanners that can potentially lead to improved image quality which can in turn be traded off for reductions in the amount of tracer activity injected or reductions in scan times. The growth of cardiac PET makes it important to determine if the benefits of TOF seen for oncology studies will translate into the tasks particular to cardiac imaging. Studies like that of Armstrong et al. begin to address this question and provide data on the magnitude of the potential benefit that TOF might provide. Further studies on the improvement in clinical performance are needed but gains shown by Armstrong et al. suggest that the benefits of TOF may extend beyond whole body studies and apply as well to organ-specific studies on the heart.

Disclosure

The authors have no disclosures relevant to this article.

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