Time-of-Flight Positron Emission Tomography: Status Relative to Conventional PET

A practical contemporary viewpoint of the advantages and disadvantages of time-of-flight positron emission tomography (TOFPET) compared with conventional positron emission tomography (non-TOF) is given in Fig. 1. The advantages of non-TOFPET using a conventional detector such as bismuth germanate (BGO) are high efficiency, high spatial resolution and high temporal resolution due to the use of small detectors. The advantages of TOFPET are increased signal-to-noise ratio over non-TOFPET, the ability to handle high count rates, and a much lower accidental coincident rate than that of non-TOFPET. The detectors presently available for TOFPET are large because small phototubes with adequate timing capability are not yet available. Indeed, the scintillators themselves are less efficient than the BGO used in conventional PET, thus much of the gain in signal-to-noise ratio of TOF systems when calculated for equal efficiency of detectors is offset when the decreased efficiency of presently available fast scintillators is taken into account. This situation might change radically in the next few years; thus, let us set aside these problems of resolution limitation and detector efficiency and examine the facts relating to the improvement in signal-to-noise ratio or relative sensitivity to be expected from TOF as addressed in the comprehensive treatment, "Image Improvement and Design Optimization of the Time-of-Flight PET," in this issue of the Journal of Nuclear Medicine (*1*).

BASIS FOR SIGNAL-TO-NOISE IMPROVEMENT OF TOF

Recall the problem of the propagation of errors in emission computed tomography (*2*). The reconstruction of projection data increases the noise of the data by a factor about equal to the square root of the number of the resolution elements across the image space (Fig. 2). Normally we would expect the statistical uncertainty of 3.2% for 300,000 events in 300 resolution elements (Fig. 2); however, due to the reconstruction process, the expected errors are 13.2%.

Now this uncertainty would be eliminated if at the time of detection of the photons, one knew exactly the location of the annihilation event (Fig. 3). A perfect TOFPET will remove the increase in errors due to the reconstruction process. In that case, the expected error (Fig. 2) is merely one over the square root of the number of detected events for each resolution element.

In practice, the time-of-flight resolution is far from perfect, and the difference in the detected arrival of the two annihilation gammas provides only an approximate value for the position of the source. The timing accuracy of a TOFPET system is measured by the full-width at half-maximum of spread around a mean time difference of the detected events for two crystals in coincidence (Fig. 3). This time accuracy depends on the properties of the scintillation detector including its size and the electronic timing circuits. The relationship between the position of the positron source and difference in time-of-arrival at the detector is

$$\Delta t = \frac{2\Delta x}{c} \qquad (1)$$

where Δx is the distance from the source to the midpoint between the detectors. A timing of 300 picosec full-width at half-maximum (FWHM) is achievable with state-of-the-art electronics; thus, one can expect position information with an error of 4.5 cm FWHM. Clearly, this falls short of the resolution being sought by the positron emission tomographic instrument; but, improved resolution is not the important attribute of TOFPET. The object of TOFPET is to improve the statistical properties of the PET image and kinetic data by decreasing errors due to the reconstruction procedures.

The reason the TOFPET system gives an improvement in signal-to-noise, which is in effect an improvement in sensitivity, is based on the fact that the propagation of errors in reconstruction tomography depends on the number of resolution elements, and TOFPET reduces the effective number of resolution elements. Previous studies have shown the relation between signal-to-noise and the number of resolution cells is (*2*):

$$S/N = k(n_c)^{-1/4}(n_t)^{1/2} \tag{2}$$

where: S/N is the signal-to-noise; k is a factor for the reconstruction filter (or kernel) with a value about 1.0; n_c is the number of resolution cells and n_t is the average number of detected events per resolution and cell. Note for the case of one resolution element, the S/N per resolution element is nearly that which we would calculate for no reconstruction; i.e., $S/N = (n_t)^{1/2}$.

A TOFPET system reduces the number of resolution cells in accord with the distance of uncertainty corresponding to the timing precision, Eq. (1). This distance can be thought of as the diameter of an area of TOF positioning uncertainty. Thus, the effective number of resolution elements is

$$n_{TOF} = \pi \left(\frac{\Delta x}{2}\right)^2 \div d^2 \tag{3}$$

where d is the resolution (e.g., 1 cm FWHM). If we substitute eq. (2) into eq. (1)

$$S/N_{TOF} = k\left(\pi\left(\frac{\Delta x}{2d}\right)^2\right)^{-1/4} n_t^{1/2} \tag{4}$$

For a conventional system the S/N is given by

$$S/N_{PET} = k\left(\pi\left(\frac{D}{2d}\right)^2\right)^{-1/4} (n_t)^{1/2}. \tag{5}$$

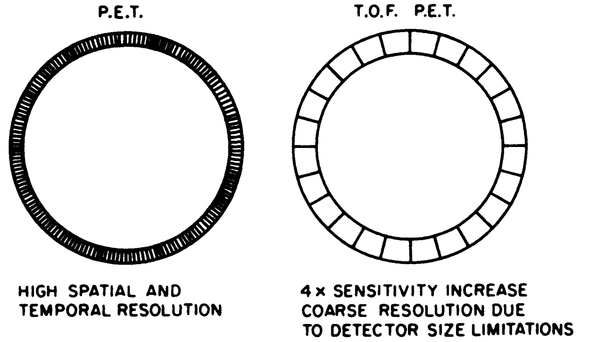

FIG. 1. Present basic differences in performance between time-of-flight positron emission tomography instrumentation abilities and non-time-of-flight conventional positron tomography. Temporal resolution is degraded if gantry motion used to improve spatial resolution.

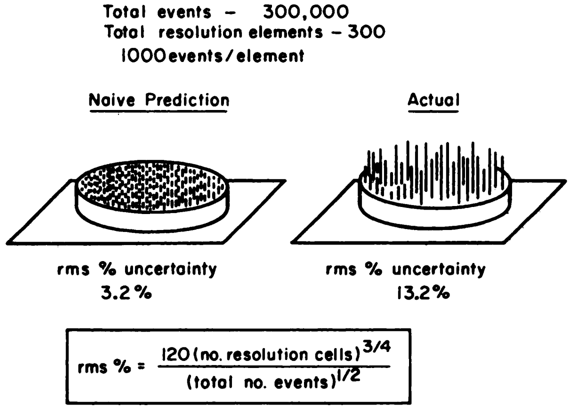

FIG. 2. Signal-to-noise is usually calculated as square root of number of events per resolution element for projection image. Propagation of errors due to reconstruction causes this signal-to-noise to diminish. Signal-to-noise is inverse of RMS uncertainty calculated here.

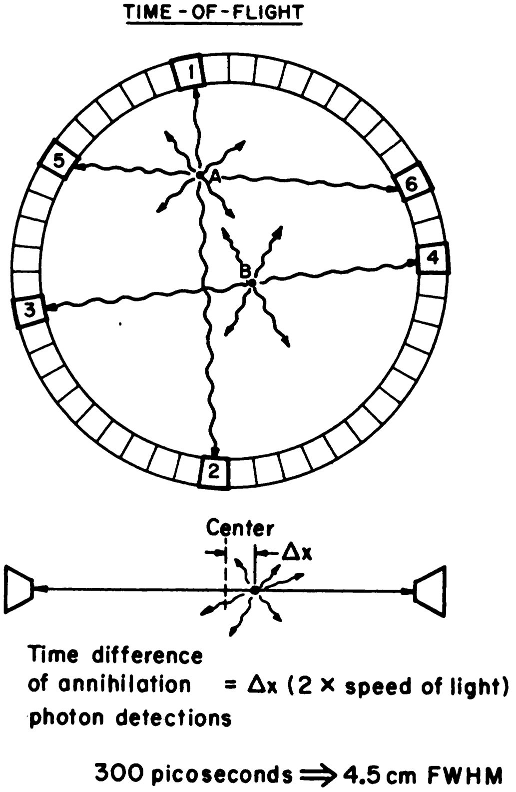

FIG. 3. Differential time of arrival of photons is related to position along coincidence line of source of annihilation photons. Errors in timing differential are usually greater than 300 picoseconds, which is related to errors in spatial position as shown.

TABLE 1

Material*	Width (mm)	Height (mm)	Depth (mm)	Sensitivity†
BGO	15	30	30	0.62
BGO	4	10	30	0.43
BaF_2	15	30	30	0.30

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* Pulse height threshold was 400 keV for BGO and 100 keV for BaF_2.

† Sensitivity is crystal efficiency squared.

where D is the diameter of the object being imaged. The S/N improvement for TOF compared with conventional PET is

$$\frac{S/N_{TOF}}{S/N_{PET}} = \left(\frac{\Delta x^2}{D^2}\right)^{-1/4} = \sqrt{\frac{D}{\Delta x}} \tag{6}$$

This equation tells us that if the timing error of a TOFPET is 300 picosec, then the improvement in S/N for a 20 cm diam object, such as the head, is

$$S/N_{increase} = \sqrt{\frac{20\ \text{cm}}{4.5\ \text{cm}}} = 2.1$$

It follows from Eq. 1 that a system with >1333 picosec resolution will have no S/N gain over a conventional PET except for rejection of some fraction of the scatter outside the object region and fewer false coincidences as discussed below.

EXPECTED GAIN IN RELATIVE SENSITIVITY

The arguments of eqs. (4), (5), and (6) give the reasons why TOFPET has a signal-to-noise advantage over conventional PET. This advantage can be translated into an effective or relative sensitivity advantage by noting that S/N is proportional to the square root of the number of events. Thus, for a gain in S/N by a factor of 2.1 we need 4.4 more events for a system with similar resolution.

These considerations can be summarized by the following relation for the gain in sensitivity of TOFPET.

$$G = \frac{2D}{c\Delta t} \tag{7}$$

Where: G is the relative sensitivity gain; c is the speed of light ($3 \times 10^{10}\ \text{cm} \cdot \text{s}^{-1}$); D is the diameter of the object; and Δt is the timing error in seconds (e.g., 300 picosec = 3×10^{-10} s). Note that as we move from a head PET to a body PET with D = 40 cm, the relative sensitivity improves by a factor of 2.

These considerations are consistent with two other somewhat more complicated, yet perhaps more rigorous, treatments by Snyder et al. (*3*) and Wong et al. (*1*) in this issue.

Having considered the benefits of TOFPET, let us turn to some practical and vital modifications that will diminish somewhat the good news of TOFPET.

First, suppose the actual distribution in the subject is confined to a few resolution elements then, what is the TOFPET relative sensitivity gain? For a distribution smaller than a region of 4.5 cm diam the gain will be negligible. For a TOFPET system, a gain less than a factor of two will be realized for positron-emitting radionuclide distribution exclusively in the heart; however, usually these distributions have a heart-to-background ratio of about 4:1, in which case the number of effective resolution elements is calculated from

$$n_t + \frac{n_b}{C}$$

where: n_t is the number of picture elements in the heart (blood pool or myocardium depending on the radiopharmaceutical); n_b is the number of background resolution elements; and C is the contrast. Typically, we can expect about 275 effective 1-cm resolution elements in the thorax; thus, for a TOFPET with 300 picosec timing we have

$$S/N_{\text{increase}} = \left(\frac{275}{\left(\frac{4.5}{2}\right)^2 \pi} \right)^{1/4} \cong 2.5$$

This is a substantial increase in relative sensitivity of 6.2, but not the factor of 8.9 (e.g., G = 40 cm/4.5 cm = 8.9) predicted by eq. (7), which does not take into account the usual situation of a nonuniform activity distribution.

A second disadvantage of the TOFPET approach is the fact that available crystals have limited sensitivity relative to the very efficient BGO presently used by conventional PET systems.

The efficiency of various crystal configurations representative of contemporary approaches is given in Table 1 from data supplied by S. E. Derenzo (*4*) using his Monte Carlo code. This is one of the most important problems of TOFPET; i.e., the poor efficiency of the scintillation detector detracts from the relative sensitivity gain of TOFPET over conventional PET.

In addition there is a timing error due to the size of the scintillator. This error arises because the speed of scintillation light in the crystal is different from that of 511 keV photons. If a scintillation event occurs at the back of one detector and the front of the opposing (coincidence) detector, a timing error occurs due to the effect of the index of refraction on the speed of low-energy photons such as light. The maximum error is

$$c\left(\frac{z}{c} - \frac{z}{c\eta}\right) = z - \frac{z}{\eta}$$

where: z is the crystal depth or path length, and η is the index of refraction. For example, CsF has an index of refraction of 1.48. Suppose our scintillation crystals are 3.0 cm deep, then the maximum error in position will be 1 cm. In practice the average error will be ½ of this. To decrease this error we can use thinner crystals (less deep); however, the efficiency (the square root of the relative sensitivity squared) decreases with thickness.

As mentioned in Fig. 1, another problem of TOFPET systems at present is the lack of small phototubes required for achieving a spatial resolution competitive with conventional PET. Wong and his co-workers analyze the trade-offs between increased resolution (number of resolution elements), TOF accuracy and object size for uniform distributions (*1*). For example, for a field size of 20 cm, a 4 mm intrinsic resolution non-TOF system has a higher S/N than an 8 mm TOFPET with 550 picosec timing accuracy.

Those applications of PET that involve rapid changes in concentration of tracer due to metabolism or decay and organ motion (e.g., heart) will not be served optimally by a coarse intrinsic resolution TOFPET that must wobble to acquire adequate spatial sampling (*5*).

OTHER ADVANTAGES OF TOFPET

As a consequence of the brief duration of scintillation light in crystals appropriate for TOF, a TOFPET can handle very high event rates without saturation due to pile-up of light in the crystal. This leads to potentially less deadtime for these crystals. Of course, this will not be an advantage if efficient crystals with similar light decay characteristics are used in conventional PET.

A major advantage of TOFPET is in the rejection of accidental coincidences, which account for 50% of the detected events in conventional PET systems operating at high count rates necessary for dynamic studies. The reduction in accidental coincidental events allows one to use more intense transmission sources for acquisition of attenuation data required for quantitative studies. This can be decreased by a factor of five in TOFPET systems (*6*). Conventional PET can also reject accidentals in transmission measurements by using a moving transmission source because detected coincidence lines (chords) which do not pass through the known source position can be rejected.

SUMMARY

An advantage of using the TOF information in PET is the sensitivity gain that can be calculated as the ratio of the total counts required to obtain the same random noise in the image, with and without the TOF information. This gain ranges from one to about eight and depends on the TOF performance, activity distribution, and the relative efficiency of the available detectors. This sensitivity gain is a driving force for time-of-flight technology; however, the gains are not quite as good as one would expect in the practical imaging situation wherein a priori distribution occupies only a limited number of resolution elements, and the efficiency of the available crystals for TOF might lead to a reduction in the sensitivity relative to conventional PET.

Inherent in TOFPET is the ability to perform very high count rate experiments for fast dynamic studies (e.g., ^{15}O, ^{82}Rb, ^{122}I). In addition, random coincidences are lower than in non-TOFPET. Finally, an important attribute of TOFPET is the fact that the low random coincidences at high count rates allow transmission data to be obtained more efficiently than in conventional PET.

At present, due to lack of availability of small and highly efficient, crystal-phototube detectors, TOFPET does not have the high spatial resolution capabilities of non-TOFPET.

HISTORICAL NOTES

During the 1969 IAEA symposium, Brownell, Burnham, and Wilenski discussed time-of-flight possibilities (*8*) and Anger in 1966 mentioned the concept for his planar detector system (*9*). Measurements of localization possibilities appeared in a thesis by Dunn in 1975 (*10*). Predictions for the use of time-of-flight for a ring detector geometry were made in 1977 (*11*), and a three-dimensional camera concept was presented in 1978 (*12*). The advantages of time-of-flight PET were discussed by Allemand et al. (*13*) and also by Mullani et al. in 1980 (*14*).

An analysis of TOFPET by Ter Pogossian et al. appeared in 1981 (*15*) with statistical treatments published in 1981 and 1982 (*3,15,16,17,18*).

The first TOFPET operating systems were completed by groups at Washington University, St. Louis and LETI-Centre d'Etudes Nucleaires de Grenoble, France. These and other developments in TOFPET were presented in a symposium this year (*19*).

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ACKNOWLEDGMENTS

This perspective and tutorial was stimulated by discussions with Drs. D. Snyder, M. Ter-Pogossian, R. Nickles, R. Allemand, M. Laval, F. Soussaline, N. Mullani, G. Brownell, R. Beck, E. Hoffman, and G. Muehllehner. I am indebted to Drs. S. Derenzo and R. Huesman for their critical discussions. Dr. Derenzo made the calculations of Table 1. This work was supported by the Office of Health and Environmental Research, Office of Energy Research, U.S. Department of Energy under Contract No. DE-AC03-76SF00098; and also by the National Heart, Lung, and Blood Institute of the National Institutes of Health Grant No. P01 HL 25840-03.

REFERENCES

1. WONG W-H, MULLANI NA, PHILLIPE EA, et al: Image improvement and design optimization of the time-of-flight PET. *J Nucl Med* 24:52-60, 1982
2. BUDINGER TF, DERENZO SE, GREENBERG WL, et al: Quantitative potentials of dynamic emission computed tomography. *J Nucl Med* 19:309-315, 1978
3. SNYDER DL, THOMAS LJ, TER-POGOSSIAN MM: A mathematical model for positron-emission tomography systems having time-of-flight measurements. *IEEE Trans Nucl Sci* NS-28(3):3575-3583, 1981
4. DERENZO SE: Monte Carlo calculations of the detection efficiency of arrays of NaI(Tl), BGO, CsF, Ge, and plastic detectors for 511 keV photons. *IEEE Trans Nucl Sci* NS-28 (1): 131-136, 1981
5. BUDINGER TF, DERENZO SE, HUESMAN RH, et al: Medical criteria for the design of a dynamic positron tomograph for heart studies. *IEEE Trans Nucl Sci* NS-29(1):488-492, 1982

6. **Derenzo SE**: Method for optimizing side shielding in positron-emission tomographs and for comparing detector materials. *J Nucl Med* 21:971-977, 1980
7. **Derenzo SE**: Comparison of detector materials for time-of-flight positron tomography. IEEE Computer Society *Proceedings of the International Workshop on Time-of-Flight Positron Tomography*, St. Louis MO, May 1981 (in press)
8. **Brownell GL, Burnham CA, Wilenski S**, et al: New developments in positron scintigraphy and the application of cyclotron-produced positron emitters. In *Medical Radioisotope Scintigraphy*. Vol. 1, Proceedings of a Symposium, Salzburg, August 6-15, 1968, Vienna, I.A.E.A., 163, 1969
9. **Anger HO**: Survey of radiosotope cameras. *Trans ISA* 5:311-334, 1966
10. **Dunn WL**: Time-of-flight localization of positron emitting isotopes. Thesis in Physics, Vanderbilt University, Nashville, TN, 1975
11. **Budinger TF**: Instrumentation trends in nuclear medicine. *Semin Nucl Med* 7:285-297, 1977
12. **Nickles RF, Meyer HO**: Design of a three-dimensional positron camera for nuclear medicine. *Phys Med Biol* 23:686-695, 1978
13. **Allemand R, Gresset C, Vacher J**: Potential advantages of a cesium fluoride scintillator for a time-of-flight positron camera. *J Nucl Med* 21:153-155, 1980
14. **Mullani NA, Ficke DC, Ter-Pogossian MM**: Cesium fluoride: A new detector for positron emission tomography. *IEEE Trans Nucl Sci* NS-27(1):572-575, 1980
15. **Ter-Pogossian MM, Mullani NA, Ficke DC**: Photon time-of-flight assisted positron emission tomography. *J Comput Assist Tomogr* 5:227-239, 1981
16. **Snyder DL**: Some noise comparisons of data-collection arrays for emission tomography-systems having time-of-flight measurements. *IEEE Trans Nucl Sci* NS-29(1): 1029-1033, 1982
17. **Mullani N, Wong W, Hartz R**, et al: Sensitivity improvement of TOFPET by the utilization of the inter-slice coincidences. *IEEE Trans Nucl Sci* NS-29(1): 479-483, 1982
18. **Tomitani T**: Image reconstruction and noise evaluation in photon time-of-flight-assisted positron emission tomography. *IEEE Trans Nucl Sci* NS-28(6): 4582-4589, 1981
19. **Thomas LJ**, Ed. *IEEE Proc*, 1982 (in press)