EDITORIAL

Small-Animal PET: Advent of a New Era of PET Research

The article in this issue of *The Journal of Nuclear Medicine* by Chatzioannou et al. (*1*) about microPET, a PET scanner for small-animal functional imaging, demonstrates the successful development and implementation of a high-resolution PET device for animals. Thus, the article illustrates that dedicated animal PET systems are now a realistic research tool. The stunning results demonstrate that PET technology is now able to image the wealth of chemistry available for biomedical research. Through the incorporation of novel concepts along with the effective implementation of refined ones, the new system achieves substantial resolution improvements over existing clinical systems. There is an approximately twofold linear spatial resolution improvement or, as Chatziioannou et al. (*1*) opted to demonstrate, a nearly tenfold improvement for volumetric resolution. The new system's characteristics also surpass those of contemporary animal imaging systems. Although further improvements and advancements are expected in technology, chemistry and pharmacology, this current technological achievement is laudable and has several beneficial implications for future research on and clinical applications of PET. These improvements ultimately should result in more favorable clinical outcomes. This high-performance, application-specific research PET, designed for use with small animals, should facilitate more rapid and quantitatively accurate research results that can be translated more effectively to clinical medicine. Specifically, PET scanning of small animals with the achieved high resolution (1.5- to 2-mm full width at half maximum [FWHM]) (a) permits the entire time course of tracers to be measured effectively within a single animal, (b) provides the means for repeated studies with the same subject over arbitrary time periods and (c) facilitates monitoring the effects of therapeutic interventions over time.

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LIMITATIONS OF CURRENT TECHNIQUES

To answer a particular biologic question or paradigm under investigation, efforts are under way to rapidly search for more specific and novel radiotracers to facilitate quantitative in vivo measurements of biochemistry (*2–5*). There are two essential limitations with current in vivo evaluation and efficacy of radiotracers: (a) Determination of in vivo specificity with terminal biodistribution studies provides limited information, and (b) contemporary in vivo imaging techniques have limited capabilities. The use of high-resolution PET systems should help overcome these limitations.

The first limitation, namely detection of radiopharmaceutical biodistribution through the use of organ counting or imaging with autoradiographic techniques, involves the use of terminal studies with small animals. These techniques can yield highly quantitative results (*2*). Regional distribution, in homogeneous tissues, for example, cannot be measured easily with organ-counting biodistribution studies. Although autoradiography more easily can provide this regional distribution with ultra-high-resolution (10–100 μm) quantitative images, it can be considerably time intensive and cannot provide in vivo kinetic information. Devices have been developed that may provide limited kinetic information with nearly autoradiographic resolution (*6*). However, both organ-counting and autoradiograph techniques have fundamental limitations: Multiple time-course studies cannot occur in the same animal, studies may be susceptible to the times when animals are killed and data must be pooled and tested for significance across or between studies.

The second limitation with tracer evaluation in small animals is related to the imaging devices themselves. Some SPECT (*7–10*) and PET (*11–13*) devices for use with small animals largely have been adapted from human whole-body devices. Devices are available at clinical facilities with which in vivo animal biodistribution studies can be performed in the same animal and over many time points. However, use of these relatively expensive scanners for animal research limits their use in clinics, and thus, animal imaging generally has been limited to larger facilities housing multiple scanners. Although animal imaging with pinhole SPECT has achieved <2-mm resolution (*7,9*), the useful field of view with excellent resolution is limited (*7*), and except in multihead systems (*9,10*), poor sensitivity renders rapid and dynamic scanning unfeasible. Because of resolution limitations with contemporary animal PET systems, animal studies largely have concentrated on larger animals and not, for example, on smaller, more easily manageable rats and genetically engineered mice. Although small-animal PET studies have been undertaken with these types of scanners (*14–17*), results often are limited by poor regional differentiation. By providing more accurate quantitative information about the repeatable in vivo biodistribution and function of the systems under investigation, the use of higher resolution and more sensitive devices for small animals can hasten the endeavor to bring imaging techniques to clinics (*5*).

APPROACHES TO SMALL-ANIMAL PET

As Chatziioannou et al. (*1*) demonstrated with a variety of impressive imaging paradigms, dedicated, high-resolution, small-animal PET devices have the capability to overcome the limitations of their larger predecessors. Although microPET is not the first scanner specifically designed for small-animal functional imaging, to date it combines the attributes of several technologies and methodologies that enable its successful implementation (*18*). For example, in contrast with the clinical industry's standard use of bismuth germanate scintillation detectors, microPET is the first PET scanner (animal or otherwise) to incorporate the newly discovered, dense and bright lutetium oxyorthosilicate (LSO) scintillator (*19*). Small pillars of discrete crystals are coupled with large-diameter optical fibers that have excellent light-conducting characteristics (*20*). A single crystal-to-fiber combination, while sacrificing detection efficiency, facilitates the use of extremely small detection elements. Small detectors are relevant to achieving the high spatial resolution required to image fine structures in laboratory animals. Arrays of fiber-coupled crystals, in turn, are coupled with dense packages of multielement photomultiplier photodetectors (*21*), which, combined with novel electronic readout (22), enable one-to-one coupling of resolution element with photodetector. This feature has been observed empirically to achieve the theoretical limits in spatial resolution for PET (*23*). Due in part to the small size of the crystal elements, interplane septa are not used; thus, the scanner operates exclusively in three-dimensional mode. The newly developed front-end detector module is coupled with coincidence-processing electronics residing in and necessary for contemporary clinical PET systems. Moreover, efficient implementation of contemporary, fully three-dimensional reconstruction algorithms (*24,25*) and use of multiple bed position, whole-body imaging techniques (*26*) also contribute significantly to the success of the project. Although there was an approximately tenfold sensitivity loss with microPET compared with clinical PET systems, and a loss compared with other animal systems, the combination of these discussed technologies and approaches resulted in nearly tenfold volumetric resolution improvements.

While attempting to improve system sensitivity, energy and timing requirements necessary for effective PET imaging, other approaches to small-animal PET scanners also have concentrated on improving and developing the front-end detectors by minifying the detection elements. The motivation for all these techniques is the need for improved signal without boosting noise (*27*). Some previous animal PET research (*11,12,28,29*) was based on the widely successful pseudo-discrete element design that multiplexed crystals to fewer photodetectors (*30,31*). Because of the larger crystal sizes used in those detectors, the resultant spatial resolution was similar to that in clinical scanners. With the advent of large-area, position-sensitive photomultipliers, small, discrete and varied types of scintillation crystals were attached to these photodetectors (*32–34*). Successful PET imaging was limited by the capabilities of the photodetectors. Although the first solid-state photodetectors for PET were coupled with somewhat large crystals (*35*), solid-state photodetectors coupled with small crystals promise miniaturization of the detector elements and associated electronics. As some examples, crystal detectors have been coupled with discrete or pixellated silicon avalanche photodetectors (*36,37*) and alternatively coupled with combinations of pixellated silicon photodiode detectors and photomultiplier detectors (*38,39*). Originally developed for clinical scanners, continuous crystal detectors (*13*) and detectors based on layers of scintillators (*40*) are being adapted for small-animal systems. With microPET, the signal propagation uses clear optical fibers to transmit scintillation light from discrete scintillators, whereas other groups use multiple layers of continuous crystals and scintillating fibers (*41,42*) or simply the scintillating fibers themselves (*43*) as the PET detectors. In an effort to obtain fast timing and fine resolution, other approaches use crystals coupled with gas-filled wire chamber detectors (*44*) or simply a lead γ-ray converter plate coupled with a gas chamber (*45*). This cursory summary of animal PET devices describes some, but by no means all, detector systems that embody varied levels of sophistication and approaches to high-resolution PET imaging.

Each system attempts to optimize one or several aspects in its design to achieve high-quality animal PET images. Moreover, in an effort to obtain quantifiable and high-quality results useful to biomedical researchers, further research and development are necessary with these systems to truly challenge the limits imposed by positron physics.

EVALUATION OF SMALL-ANIMAL SYSTEMS

To demonstrate that a system can indeed furnish reliable and quantitative results, it should be thoroughly evaluated in its performance characteristics to determine its capability and limitations. Chatziioannou et al. (*1*) did just that. They followed accepted evaluation criteria (*46,47*). Close attention is paid to the evolving literature that describes figures of merit useful to describe PET scanner performance characteristics (*48–51*). Although not all classes of discrete element (*52*) or continuous crystal (*53*) scanners were compared by Chatziioannou et al. (*1*), various comparisons were made with other clinical scanners (*54–56*), demonstrating the capabilities of microPET. Comparisons also were made of similar image quality between rat imaging with microPET and human imaging with clinical scanners. Do the favorable comparisons imply that because mice are about 10 times smaller (in volume) than rats that additional order-of-magnitude improvements are necessary for small-animal PET devices to image mice effectively? This may not be the case. Nevertheless, research groups will endeavor to push the bound-

ary closer to the limits imposed by positron physics (e.g., the mean range of ^{18}F positrons in tissue is ~0.5 mm FWHM).

PERFORMANCE STANDARDS

Need for Objective Comparisons

It is important to recognize that the success of the microPET project encourages new standards to be established for small-animal systems. Standards are important for two basic reasons: (a) Because the geometries of camera systems can have great variations, objective evaluation of similar types of systems will provide easier intercomparisons, and (b) perhaps more importantly, the technological developments of PET devices for small-animal imaging have implications for the development of human imaging devices. Although the first point is necessary because there are many types of animal PET devices, the second point should be anticipated.

Some small-animal systems are designed to exploit certain aspects of annihilation detection at the expense of others. Chatziioannou et al. (*1*) recognized this fact and performed measurements with phantoms that mimicked their anticipated animal subject pool. Care must be taken, however, in devising new phantoms. For example, measurements of hot- and cold-rod resolution phantoms by these high-resolution systems should be more challenging than that demonstrated (*1*). One example is a cold-rod phantom in which the rod spacing is only twice the rod diameter (*7*), rather than the larger spacing used by Chatziioannou et al. To determine how partial volume effects (*57*) with these especially small volumes affect quantitation, quantitative evaluation using hollow microspheres in an appropriate phantom also should be evaluated. Thus, an objective evaluation of any such high-performance system should more likely follow a set of acceptable, yet challenging, standards. With the commercial availability of microPET (Concorde Microsystems, Inc., Knoxville, TN) and the continued development of similar systems, such small-animal, device-specific criteria are warranted.

Implications for Clinical Scanners

The second criterion for establishing performance standards addresses the question of how integration and development of new technologies for small-animal applications will affect clinical devices. With a 17-cm-diameter system demonstrating <2-mm spatial resolution (*1*), is there a possibility to translate that technology for human brain imaging? For example, a commercial version of microPET for pediatric patients is possible according to R. Goble (personal communication, February 1999). Thus, would it be possible to extend the gantry performance for adult brain cases to achieve better performance than is currently available (*13,50*)? Although the axial extent of the first microPET version is short, longer systems should improve performance further. Of course, parallax errors at the edge of the field of view and other effects may degrade the overall performance for small-diameter, long-cylindrical geometries. Thus, spheroid-type geometries (*58*) may be incorporated into the design. In addition, the use of the new, fast, dense and bright LSO scintillator with improved acquisition electronics (*59,60*) in more geometrically efficient systems should boost the total signal but also may be accompanied by additional problems. The move from two-dimensional PET to fully three-dimensional PET has seen a roughly threefold additional scatter contribution in clinical systems (*54,55*). Therefore, not only can scatter from the small animals potentially pose problems, but increasing the camera field of view (hence, geometric efficiency) may further degrade the true signal. Clearly, development of improved clinical systems should be anticipated from the progress on small-animal systems.

OTHER TECHNOLOGICAL ISSUES

Several technological issues need to be considered for small-animal imaging in addition to those mentioned by Chatziioannou et al. (*1*), including (a) necessity of obtaining input function parameters (*61*); (b) possibility of acquiring gated imaging studies (*62*), which is routine for magnetic resonance microscopy (*63*); (c) advantages and limitations of combined or registered MR/PET imaging (*64*); (d) determination of optimum tracer dosages for the small in vivo systems of interest (*65*); (e) the impact of relocating the animals of interest from their sterile facilities for repeat imaging studies or having the animal PET scanner within the sterile facility itself; and (f) assessment of how the improvements realized with these application-specific PET technologies may translate to the clinical domain.

CONCLUSION

The microPET project described by Chatziioannou et al. (*1*) clearly has demonstrated that high-resolution PET images of small, distinct structures are possible in small animals. The effectiveness and usefulness of the information from these images for biomedical researchers need further evaluation. It may be expected that the results of high-resolution small-animal PET imaging not only will help biomedical researchers answer questions about their animal models, as related to diseased or normal human function, but will pose new tasks for PET development and research.

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