Small-Animal PET: A Technology That Changed Our Field

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As we continue to cope with the coronavirus disease 2019 pandemic, we can take the opportunity to reflect back and learn from history how unexpected events changed the way we live and work, sometimes in good ways.

On September 11, 2001, many of us were at Rockville, Maryland, attending the HiRes meeting (High Resolution Imaging in Small Animals with PET, MR and Other Modalities: Instrumentation, Applications, and Animal Handling). This conference brought together physicists, biomedical researchers, veterinarians, physicians, and engineers to develop new in vivo imaging tools and methods for biomedical research on small animals. Although the conference was cut short and overshadowed by the tragic event on 9/11, the field of molecular

imaging continued to grow and gain recognition for its potential impact on biomedical research (1,2). The driving force behind the growth was several technologic breakthroughs in small animal imaging, in particular the small-animal PET technology described in the article by Chatzioannou et al. in this anniversary issue of *JNM* (3).

Initially developed to probe physiologic functions in human and nonhuman primates, PET was not known for its spatial resolution. Several groups attempted to develop high-resolution PET scanners for laboratory animals in the 1990s, with limited success in rodents. Yet, the advances in molecular biology and the availability of transgenic mice called for imaging technologies that could quantify molecular changes in mice noninvasively. The technologic breakthrough came after the group at UCLA adapted a new scintillator: cerium-doped lutetium oxyorthosilicate, leveraging its high light yield to create detectors with high spatial resolution without compromising other performance characteristics (e.g., energy resolution, timing resolution, and scatter fraction). Optical fibers were used to couple scintillation light from lutetium oxyorthosilicate to a position-sensitivity photomultiplier tube to overcome the physical limitations of light

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BASIC SCIENCE INVESTIGATIONS

Performance Evaluation of microPET: A High-Resolution Lutetium Oxyorthosilicate PET Scanner for Animal Imaging

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A new dedicated PET scanner, microPET, was designed and developed at the University of California, Los Angeles, for imaging small laboratory animals. The goal was to provide a compact system with superior spatial resolution at a fraction of the cost of a clinical PET scanner. **Methods:** The system uses fiberoptic readout of individually cut lutetium oxyorthosilicate (LSO) crystals to achieve high spatial resolution. Each microPET detector consists of an 8 × 8 array of 2 × 2 × 10-mm LSO scintillation crystals that are coupled to a 64-channel photomultiplier tube by optical fibers. The tomograph consists of 30 detectors in a continuous ring with a 17.2-cm diameter and fields of view (FOVs) of 11.25 cm in the transaxial direction and 1.8 cm in the axial direction. The system has eight crystal rings and no interplane septa. It operates exclusively in the three-dimensional mode and has an electronically controlled bed that is capable of wobbling with a radius of 300 μm. We describe the performance of the tomograph in terms of its spatial, energy and timing resolution, as well as its sensitivity and counting-rate performance. We also illustrate its overall imaging performance with phantom and animal studies that demonstrate the potential applications of this device to biomedical research. **Results:** Images reconstructed with three-dimensional filtered backprojection show a spatial resolution of 1.8 mm at the center of the FOV (CFOV), which remains <2.5 mm for the central 5 cm of the transaxial FOV. The resulting volumetric resolution of the system is <8 μL. The absolute system sensitivity measured with a 0.74 MBq (20 μCi) ⁶⁸Ge point source at the CFOV is 5.62 Hz/kBq. The maximum noise equivalent counting rate obtained with a 6.4-cm

Key Words: PET; instrumentation; performance evaluation; animal imaging

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Research in the areas of gene expression and gene therapy, as well as the needs of the pharmaceutical industry, have added to the importance of developing methods for in vivo molecular imaging in small animals (1,2). The increasing number of animal models of human disease and the demand for longitudinal studies in many experimental designs introduce a new area in which nuclear medicine tracer techniques inherently have numerous advantages. The technological barriers for the implementation of nuclear medicine imaging technology in this research are formidable but can and should be addressed.

By allowing radiotracer concentrations to be determined in vivo, a dedicated animal scanner permits the entire time course of a tracer to be measured in a single animal and provides the means for repeated studies of that same subject over an arbitrary period of time, instead of pooling and averaging the data from a larger animal population sample. Such a tomograph also can be used to monitor the effects of therapeutic interventions, again in each animal throughout

282

Number of Citations

sensors at that time. The scanner delivered for the first time an image resolution better than 2 mm in full width at half maximum in all 3 dimensions, a peak system sensitivity of 5.62%, an average energy resolution of 19% in full width at half maximum at 511 keV, and a timing resolution of 2.4 ns in full width at half maximum. Importantly, the system had an excellent linearity and quantitative accuracy between the image value (cps/cm³) and the activity concentration measured by a well counter (MBq/cm³). Representative animal studies demonstrated whole-body PET imaging using FDG and ¹⁸F in rodents, cardiac imaging in a rat, and dynamic imaging of neuroreceptor ligands in a rat. This work marked the beginning of an era during which in vivo quantitative PET imaging of rodents for longitudinal studies become a reality.

After the development of the small-animal PET at UCLA, several seminal works were published demonstrating the potential of molecular imaging for studying biologic processes (2), measuring gene expression in vivo (4), and accelerating drug development (5), among others. The interest in and demand for preclinical PET imaging grew rapidly, leading to the commercialization of small-animal PET technology. The procedures described in the work of Chatziioannou et al. (3) were adapted and became part of the National Electrical Manufacturers Association standard for evaluating the performance of preclinical PET systems. Embraced by many research groups and pharmaceutical companies, in vivo PET imaging became an essential tool to study disease models, to assess novel molecular probes, and to accelerate the screening and validation of targets and drugs using small animals. With additional anatomic or functional images from CT or MRI, preclinical PET/CT and PET/MRI systems are now an integral part of a research pipeline that supports innovation, validation, and translation of novel molecular probes from bench to human for clinical imaging and therapeutic applications. In 2012, our society changed its name to the Society of Nuclear Medicine and Molecular Imaging, embracing the development of novel molecular probes for preclinical and

clinical imaging and therapeutics as our core mission. Although imaging and therapies

at the molecular level have always been the backbone of our discipline since its inception 60 years ago, small-animal PET technology likely played a role in accelerating the transformation and reshaping the landscape of our field over the past 2 decades. A recent technologic breakthrough—the total-body PET system (6)—brings immense excitement as we look forward to the new discoveries and clinical applications that will be enabled in the next decade.

As for what happened to the conference after 9/11—with all the airports shut down in North America, many of us took a road trip and drove across the country together to go home. Even in the worst of times, one can find comfort in friends—except that you will need to wear a mask and practice social distancing this time, please!

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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A new dedicated PET scanner, microPET, was designed and developed at the University of California, Los Angeles, for imaging small laboratory animals. The goal was to provide a compact system with superior spatial resolution at a fraction of the cost of a clinical PET scanner. **Methods:** The system uses fiberoptic readout of individually cut lutetium oxyorthosilicate (LSO) crystals to achieve high spatial resolution. Each microPET detector consists of an 8×8 array of $2 \times 2 \times 10$ -mm LSO scintillation crystals that are coupled to a 64-channel photomultiplier tube by optical fibers. The tomograph consists of 30 detectors in a continuous ring with a 17.2-cm diameter and fields of view (FOVs) of 11.25 cm in the transaxial direction and 1.8 cm in the axial direction. The system has eight crystal rings and no interplane septa. It operates exclusively in the three-dimensional mode and has an electronically controlled bed that is capable of wobbling with a radius of 300 pm. We describe the performance of the tomograph in terms of its spatial, energy and timing resolution, as well as its sensitivity and counting-rate performance. We also illustrate its overall imaging performance with phantom and animal studies that demonstrate the potential applications of this device to biomedical research. **Results:** Images reconstructed with three-dimensional filtered backprojection show a spatial resolution of 1.8 mm at the center of the FOV (CFOV), which remains <2.5 mm for the central 5 cm of the transaxial FOV. The resulting volumetric resolution of the system is <8 μ L. The absolute system sensitivity measured with a 0.74 MBq (20 μ Ci) ^{68}Ge point source at the CFOV is 5.62 Hz/kBq. The maximum noise equivalent counting rate obtained with a 6.4-cm diameter cylinder spanning the central 56% of the FOV is 10 kcps, whereas the scatter fraction is 37% at the CFOV for an energy window of 250–650 keV and the same diameter cylinder. **Conclusion:** This is the first PET scanner to use the new scintillator LSO and uses a novel detector design to achieve high volumetric spatial resolution. The combination of imaging characteristics of this prototype system (resolution, sensitivity, counting-rate performance and scatter fraction) opens up new possibilities in the study of animal models with PET.

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Research in the areas of gene expression and gene therapy, as well as the needs of the pharmaceutical industry, have added to the importance of developing methods for in vivo molecular imaging in small animals (1,2). The increasing number of animal models of human disease and the demand for longitudinal studies in many experimental designs introduce a new area in which nuclear medicine tracer techniques inherently have numerous advantages. The technological barriers for the implementation of nuclear medicine imaging technology in this research are formidable but can and should be addressed.

By allowing radiotracer concentrations to be determined in vivo, a dedicated animal scanner permits the entire time course of a tracer to be measured in a single animal and provides the means for repeated studies of that same subject over an arbitrary period of time, instead of pooling and averaging the data from a larger animal population sample. Such a tomograph also can be used to monitor the effects of therapeutic interventions, again in each animal throughout the time course of therapeutic responses. Recognizing these possibilities, dedicated animal scanners previously have been developed using modifications of existing detector technology (3,4). The need for higher resolution imaging, particularly for studying smaller laboratory animals such as mice and rats, has stimulated the development of high-resolution animal PET detectors by several groups world-wide (5–13).

The fundamental spatial resolution of PET imaging is limited physically because of two effects: first, by the average distance that the emitted positron travels before it annihilates and, second, by the residual momentum of the electron-positron pair at annihilation, which results in gammarays being emitted with a small deviation from the assumed 180° . The first factor, which is affected by the energy of the emitted positron, contributes a full width at half maximum (FWHM) of approximately 0.23 mm in water (14), for compounds labeled with ^{18}F . The second factor produces a blurring of the distribution of annihilation photons proportional to the diameter of the tomograph, with an FWHM of 0.028 mm/cm diameter (15). For the 17.2-cm diameter microPET system, this results in a blurring of 0.48 mm. As a result, the spatial resolution of current small-diameter PET systems is still mainly determined by the accuracy with which the detector can localize the position of interaction.

With the introduction of fiberoptic readout of individually cut crystals (16) and the arrival of the new scintillator material lutetium oxyorthosilicate (LSO) (17), which is suitable for high-energy coincidence imaging, it is possible to overcome many of the

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technological barriers that have prevented widespread use of PET with small animals. With the fiberoptic readout, the size of the bulky photomultiplier tubes is no longer the key factor in deciding the smallest detector block size and the highest resolution that can be achieved. The individual readout of the signals from each crystal allows the miniaturization of the fundamental resolution element: the physical dimensions of the scintillator crystals. The introduction of the LSO scintillator permits this to happen without loss of timing accuracy or energy resolution compared with the conventional bismuth germanate (BGO)-based PET block detector. The microPET tomograph incorporates both of these technological developments and improves the volumetric resolution of the images by almost one order of magnitude compared with state-of-the-art clinical PET systems (18,19), while at the same time reducing the overall material costs because of the small size of the scanner.

MATERIALS AND METHODS

System Description

The microPET system is based on the microPET detector block (Fig. 1) (7). At the front end of each of the microPET detectors is an 8×8 array of individually cut LSO crystals, each measuring $2 \times 2 \times 10$ mm, arranged with a pitch of 2.25 mm to allow space for the white Teflon reflective material between each element. The scintillation light from each of the 64 crystals of the front-end array is guided to 1 of 64 individual channels of a Philips XP1722 multichannel photomultiplier tube (MC-PMT) (Philips Components, Slatersville, RI) by 24-cm long double-clad optical fibers (Kuraray Corp., Japan). The 1-to-1 coupling between LSO crystals and the MC-PMT channels, in combination with the low crosstalk among the channels of the MC-PMT, allows for excellent identification of the small crystals (20). This is illustrated in Figure 1B, which shows a typical position profile from flood field irradiation of one of the microPET detectors. The clearly resolved individual crystals illustrate the high intrinsic resolution of the microPET detector and suggest that the limits of using small, individually cut crystals with fiberoptic readout technology are yet to be completely exploited. The 64 MC-PMT outputs are

multiplexed with a custom-designed readout board (21) that emulates the output from the 4 PMTs of conventional block detectors (22). Thereby, the microPET detector can be used directly in conjunction with commercially available electronics from a manufacturer of clinical PET systems. After the readout board, the signals are fed through analog electronics (CTI PET Systems, Inc., Knoxville, TN) that identify the crystal of interaction and determine whether the event falls in the appropriate energy range. To account for the fast decay of LSO, the pulse integration time is set to 256 ns (in contrast with the 768 ns used for BGO detectors), which is the minimum allowed by the electronics. The rest of the data acquisition system consists of a standard coincidence processor, the same version as supplied with the ECAT ART scanner (CTI PET Systems, Inc.) (23), with a modified advanced computational system (ACS) containing a translator, real-time sorter, counter and histogram memory on a VME bus controlled by a SUN SPARC-2 CPU (Sun Microsystems, Palo Alto, CA). The system has a coincidence timing window of 12 ns and allows on-line subtraction of the accidentals (randoms) with a delayed coincidence window.

The complete tomograph has 30 microPET block detectors arranged in a continuous ring. Because each block consists of an 8×8 array of individual detectors, the tomograph has 8 crystal rings with 240 crystals in each ring. The inner diameter of the tomograph is 17.2 cm from crystal face to crystal face, and the axial field of view (FOV) is 1.8 cm. In the transverse direction, the FOV is electronically trimmed to accept coincidences from 50 opposing crystal elements, resulting in a transverse FOV of 11.25 cm. Following a widely accepted convention that improves the transverse at the expense of the angular spatial sampling frequency, the data from every other angle of the 240 crystals on each ring are interleaved to produce sinograms with 100 samples per projection (linearly spaced at 1.125 mm) and 120 projection angles. In a similar manner, axial interleaving results in a sampling distance of 1.125 mm in the axial direction. The 8 crystal rings in the axial direction, in combination with the three-dimensional geometry of the system, produce 64 sinograms for every bed position, resulting in fully three-dimensional datasets with a very manageable size of 1.54 Mbytes. Sinogram data are stored on a local disk and reconstructed with a SUN ULTRA-1 147 computer (Sun Microsystems) that handles both the user interface and the acquisition through remote procedure calls to the ACS. The data are stored in a format that can be analyzed with a

commercially available clinical applications programming package (CTI PET Systems, Inc.).

The bed is electronically controlled in the axial direction for acquisitions spanning multiaxial FOVs at an accuracy better than 100 μ m. It is also capable of in-plane wobbling with a radius of 300 μ m and $<1^\circ$ accuracy to improve spatial sampling, although this capability has yet to be fully investigated. The gantry also is equipped with a laser positioning system that allows the accurate localization of the area of interest with respect to the axial FOV of the tomograph. The overall gantry measures 120 (height) $\times$ 100 (width) $\times$ 60 cm (depth) and has an imaging aperture of 16 cm in diameter, which is large enough to accommodate whole-body studies in mice, rats, cats and rabbits, as well as brain studies in small non-human primates. A summary of the design parameters of microPET is shown in Table 1.

Spatial Resolution

Intrinsic Spatial Resolution. The high spatial resolution of the system and its fully three-dimensional geometry necessitated

FIGURE 1. (A) Photograph of microPET tomograph gantry with bed and laser positioning system. (B) Position histogram from typical microPET block detector, illustrating clear separation of 64 crystals. (C) MicroPET block detector with crystal array on left, coupled through optical fibers to MC-PMT on right.

the use of a specially manufactured positron-emitting point source. Thus, the intrinsic spatial resolution was measured with an 18.5 MBq (0.5 mCi) ^{22}Na point source ($t^{1/2} = 2.61\text{y}$, $E_{\text{avg}}\beta^+ = 216\text{ keV}$), measuring just 0.5 mm and embedded in a lucite disk measuring 25 mm in diameter and 5 mm in height (Isotope Product Laboratories, Burbank, CA). The average range of the ^{22}Na positrons in this lucite disk is similar to the average range of the ^{18}F positrons in water (0.23 mm), because both isotopes have similar average emission energies ($E_{\text{avg}}\beta^+ = 250\text{ keV}$). As a result, one can safely assume that the ^{22}Na source size was dominated by its physical dimensions. The ^{22}Na source was suspended in air and stepped at 250- μm increments in the radial direction across the face of the detectors at the center of the FOV (CFOV). The sinogram elements from the projections perpendicular to the direction of the source motion were extracted and plotted against the known source location. The plotted profiles were fitted with a Gaussian function, and the FWHM of the fitted curves was calculated as a measure of the intrinsic spatial resolution.

Image Spatial Resolution. The reconstructed-image spatial resolution was measured with the same point source, suspended in air and positioned centrally in the axial direction and at radial offsets ranging from 0 to 5 cm. The same measurements also were made with the source positioned at an axial offset of 5.7 mm from the axial CFOV, an offset representing $\sim 64\%$ of the 9-mm distance from the axial center to the axial edge of the CFOV. The data were acquired with no wobbling motion, generating 64 sinograms that included all ring differences (0–7). The sinograms subsequently were reconstructed with a ramp filter to the Nyquist frequency (0.444 mm^{-1}), using a three-

dimensional filtered backprojection algorithm with reprojection of the missing data (PROMIS) (24). All ring differences were used, and no approximations such as angular averaging in the transverse or axial direction were made. All reconstructions were performed on the SUN ULTRA-1 147 computer and required 10 min for each dataset. The radial (R_{FWHM}), tangential (T_{FWHM}) and axial (A_{FWHM}) resolution components of the reconstructed images were measured by fitting Gaussian functions to the respective profiles along the center of mass of the reconstructed images of the point source and calculating their respective FWHM.

Volumetric Resolution. The ultimate figure of merit for a three-dimensional tomograph is not only the linear measure of each of the three components of the resolution but the measure of the smallest volume element that can be resolved accurately with the device. A reasonable estimate of this measure is the product of the three components of the resolution, R_{FWHM} , T_{FWHM} and A_{FWHM} :

$$V_{\text{FWHM}} = R_{\text{FWHM}} \times T_{\text{FWHM}} \times A_{\text{FWHM}} \quad \text{Eq. 1}$$

We call this product the volumetric resolution, V_{FWHM} , and it forms a useful basis for resolution comparisons between three-dimensional tomographs.

Sensitivity

A conventional sensitivity measurement, performed with a uniform ^{68}Ge cylinder that spans 50% of the FOV, would not be a useful measure, because the much smaller radius of the gantry port of microPET (or other dedicated small-animal tomographs) would necessitate the use of a nonstandard, small-diameter cylinder (25). The differences in the amount of isotope activity, scatter fraction and attenuation factors in a small cylinder, compared with the 20-cm diameter performance cylinder used in clinical PET scanners, make a conventional sensitivity comparison with the cylinder measurement difficult to interpret. This type of measurement is further complicated by the large differences in the physical size of the FOV in both the transverse and axial directions between animal PET tomographs. For this reason, we performed absolute sensitivity measurements along the lines proposed by Bailey et al. (26), but we used a point instead of a line source and measured the sensitivity at all positions in the FOV as follows. A 0.74 MBq (20 μCi) ^{68}Ge point source measuring 1 mm was suspended in air and stepped at 1-mm increments in the axial direction and at 5-mm increments in the radial direction across the entire FOV. The true coincidence counts (prompt – delayed) were recorded at each position. These measurements were repeated for lower energy thresholds of 250, 350 and 450 keV, whereas the upper energy threshold was fixed at 650 keV. For comparison, the same measurements at 1-cm increments in the axial direction and at 2-cm increments in the radial direction were performed on an EXACT HR+ tomograph (CTI PET Systems, Inc.), operating with the standard 350- to 650-keV energy window, for the case of septa-in (two-dimensional) and septa-out (three-dimensional) acquisitions. The result of these measurements is a map of the absolute sensitivity of the two systems in hertz per kilobecquerel for a plane that crosses the center of the imaging volume and extends along the axis of the tomograph. This measurement easily can be extended to the entire FOV on the basis of circular symmetry arguments that are valid for ring PET systems such as microPET and EXACT HR+.

Energy Resolution and Scatter Fraction

Energy Resolution. The energy resolution was measured with the 18.5 MBq (0.5 mCi) ^{22}Na point source, which was suspended in air and positioned at the center of the axial FOV. Boundaries were drawn on the two-dimensional position histogram of a microPET detector to

TABLE 1
microPET System Parameters

Detector	Crystal material	LSO
	Crystal size	$2 \times 2 \times 10\text{ mm}$
	Crystal pitch	2.25 mm (in-plane and axially)
	Crystal array	64 (8×8 crystals/PMT)
System	PMTs	Philips XP1722, 64 channels
	Number of detectors	30
	Number of crystals	1920 (240 per ring $\times$ 8 rings)
	Ring diameter	17.2 cm
	Gantry aperture	16 cm
	Axial FOV	1.8 cm
	Transaxial FOV	11.25 cm
	Overall dimensions	120 (width) $\times$ 100 (height) $\times$ 60 cm (depth)
	Total sinograms	64 (three-dimensional only)
	Sinogram size	100 samples $\times$ 120 angles
Dataset	Dataset size	1.54 Mbytes
	Sampling distance	1.125 mm for nonwobbled acquisitions
Bed	In-plane bed wobble	0.3-mm radius
	Axial bed motion	0.1-mm accuracy

LSO = lutetium oxyorthosilicate; PMT = photomultiplier tube; FOV = field of view.

define the lookup table that relates the position in the two-dimensional histogram to the appropriate element in the LSO array. To obtain energy spectra, the raw data were re-sorted on the basis of the lookup table, and a histogram of pulse amplitudes was generated for each crystal. The energy resolution was defined as the FWHM of the photopeak response divided by the amplitude of the photopeak, expressed as a percentage (7).

Scatter Fraction. The fraction of scattered events was measured with a solid lucite phantom measuring 6 cm in diameter and 6 cm in length, with two 2-mm holes drilled along its axial direction, creating two line sources: one at the center and one at a 2-cm radial offset. The two holes were filled with ^{18}F for separate acquisitions, and sinograms with a total of 30 million coincidence events were acquired for each scan. The two measurements were repeated for lower energy threshold settings of 250, 350 and 450 keV, whereas the upper energy threshold for each acquisition was fixed at 650 keV. To calculate the scatter fraction, the tails of the measured sinogram projections starting at 1.0 cm outside of each source were fitted with a Gaussian function to estimate the scatter events under the source. The integral of the measured counts in this smooth scatter function over all angles was compared with the integral of the total events in the sinograms to produce the scatter fraction for each source, according to the following equation:

$$\text{Scatter Fraction} = \frac{\sum_{\text{projection, angle}} \text{Scatter}}{\sum_{\text{projection, angle}} (\text{Trues} + \text{Scatter})} \quad \text{Eq. 2}$$

The overall scatter fraction was calculated by weighting the measurements from the two source radial offsets according to the area of the annulus they covered as a fraction of the total phantom cross-section (25).

Timing Resolution

The timing resolution was measured with the 18.5 MBq (0.5 mCi) ^{22}Na point source, positioned at the CFOV. For each coincidence event, the sum of the position signals from the readout boards of two microPET detectors was sent to constant fraction discriminators that generated timing pulses. These timing pulses, in turn, were fed to a calibrated time-to-amplitude converter with output digitized to produce a timing spectrum. The timing resolution is reported as the FWHM and full width at tenth maximum (FWTM) of the timing spectrum, expressed in nanoseconds.

Counting-Rate Performance and Noise-Equivalent Counting Rates

The counting-rate performance was measured with three cylindrical phantoms with sizes simulating the head of a vervet monkey, the head

TABLE 2
Noise-Equivalent Counting-Rate Phantom Parameters

Parameter	Small (rat body)	Medium (cat head)	Large (monkey head)
Diameter (cm)	5.08	6.35	8.89
Height (cm)	10.85	3.63	6.12
Volume (mL)	220	115	380
k	0.45	0.56	0.79

k = fraction of transverse field of view covered by each phantom.

FIGURE 2. Intrinsic spatial resolution for typical microPET block detectors in coincidence, measured by stepping ^{22}Na point source across FOV.

of a cat and the whole body of a laboratory rat. These cylinders, therefore, are representative of the types of animals that are expected to be scanned with microPET. The exact physical dimensions and volumes of the phantoms, as well as the fraction k of the transverse FOV occupied by each phantom, are summarized in Table 2. These phantoms were filled with ^{13}N and scanned over 12 isotope half-lives ($t_{1/2} = 9.97$ m) at three different lower energy threshold settings: 250, 350 and 450 keV. For all these measurements, the upper energy threshold was fixed at 650 keV. The noise-equivalent counting rate (NEC) (27) was calculated from the measured trues (T), randoms (R) and estimated scattered (S) counting rates according to the following equation:

$$\text{NEC} = \frac{T^2}{T + S + 2 \times k \times R} \quad \text{Eq. 3}$$

The amount of scattered radiation for the NEC measurements was estimated with a method similar to the scatter fraction for the aforementioned scatter phantom. The profiles of the measured sinograms up to 1 cm outside of each cylindrical phantom were fitted with

FIGURE 3. Linear spatial resolution components (radial, tangential and axial) of reconstructed image as function of radial offset from CFOV.

FIGURE 4. Volumetric spatial resolution of reconstructed image, expressed in microliters, as function of radial offset from CFOV.

a Gaussian function and extrapolated to the center of each of the cylinders.

Data Corrections

Random Coincidences. The accidental coincidences in the 12-ns prompt time window were estimated with a delayed coincidence line and subtracted on-line from the appropriate sinogram memory location.

Detector Efficiency Normalization. Normalization scans were performed with a 6.5-cm diameter cylindrical source containing 37 MBq (1 mCi) ^{68}Ge , positioned at the CFOV. Using the circular symmetry in the ring tomograph and assuming the coincidence detector efficiencies to be proportional to the single efficiencies of individual detectors, sinogram files with detector efficiency correction factors accounting for both the detection efficiency and the systematic interference geometric factors were generated (28). With this assumption, the 64 sinogram measurements contained a great redundancy of data and permitted high-quality detector efficiency normalizations to be obtained from 1-h acquisitions containing a total of approximately 50-million coincidence events (29).

FIGURE 5. Map of absolute system sensitivity in transverse and axial directions across FOV of microPET for 250- to 650-keV energy window.

Attenuation Correction. For uniformly attenuating objects with convex geometry, attenuation correction is performed with an automated implementation of the calculated method described by Bergstrom et al. (30). For objects with nonuniform density distributions, e.g., the chest area of a rodent, attenuation is measured with a 37 MBq (1 mCi) ^{68}Ge ring transmission source that spans the axial FOV of the system. The transmission data are processed with a modification of the methods presented in the literature (31).

Scatter Correction. Scattered radiation inside an object is estimated by fitting the tails of the measured projections of the sinograms outside the object and extrapolating these profiles toward the CFOV with a Gaussian function. These fitted profiles subsequently are subtracted from the sinograms to produce the estimate of the sinograms corrected for scatter (32,33).

Dead Time Correction. To perform a dead time correction, the system is divided electronically into five segments (buckets), each containing six microPET detectors. The total singles rate and live time for each bucket are measured from the analog electronics, and the resulting dead time correction factor for the whole system is a calculated estimate from the corrected and uncorrected singles measurements from each bucket (34,35).

Quantification

The capability of microPET to accurately quantify activity concentrations was studied with a cylindrical phantom that contained compartments filled with different amounts of activity. The diameter of the phantom was 70 mm, and it contained two cylindrical compartments, each with a diameter of 10 mm, which were sufficiently large to avoid partial volume effects (36). These compartments and the background chamber were filled with different amounts of activity and imaged in a series of 60-min acquisitions. The total activity in the phantom ranged from 27.75 to 55.5 MBq (0.75–1.5 mCi), whereas the activity concentration in the compartments was measured with a well counter and ranged between 0.37 and 3.7 MBq/mL (10–100 $\mu\text{Ci/mL}$). The activity concentration in the background chamber ranged between 0.37 and 0.925 MBq/mL (10–25 $\mu\text{Ci/mL}$). The sinograms were reconstructed with the three-dimensional filtered backprojection algorithm, and all data corrections were applied, except the correction for scattered radiation. Regions of interest (ROIs) in the reconstructed images were drawn over the two 10-mm compartments of the phantom and the background chamber, and the measured count density was plotted against the known activity concentration from the well-counter measurements.

Imaging Studies

Phantom Studies. Two miniature versions of a Derenzo phantom (37), one version with hot rods and the other version with cold rods, were each filled with 37 MBq (1 mCi) of ^{18}F and imaged for 60 min, acquiring a total of 300-million counts. The diameters of the rods in the five segments of each phantom were 2.5, 2.0, 1.5, 1.25 and 1.0 mm, respectively, and the center-to-center spacing was four times the rod diameter. The outer diameter of the phantoms was 4 cm, and the data were reconstructed with the three-dimensional filtered backprojection algorithm and a ramp filter cutoff at the Nyquist frequency (0.444 mm^{-1}). The same phantoms containing the same amount of activity also were scanned for 30 min in two-dimensional on the EXACT HR+ and reconstructed with two-dimensional filtered backprojection and a ramp filter cutoff at the Nyquist frequency (0.222 mm^{-1}).

TABLE 3
Absolute System Sensitivity*

System	250- to 650-keV energy window		350- to 650-keV energy window		450- to 650-keV energy window	
	CFOV	Average	CFOV	Average	CFOV	Average
microPET	5.62	3.92	4.00	2.54	1.77	1.14
(3-D)	0.56%	0.39%	0.40%	0.25%	0.18%	0.11%
HR+ (2-D)	NM	NM	5.24	4.46	NM	NM
	NM	NM	0.52%	0.45%	NM	NM
HR+ (3-D)	NM	NM	36.57	22.68	NM	NM
	NM	NM	3.66%	2.27%	NM	NM

*Sensitivity is reported in cps/kBq and as detected percentage of total annihilations. Reported values are for CFOV and average across field of view.

CFOV = center of field of view; 3-D = three-dimensional; 2-D = two-dimensional; NM = no measurements made for these points.

Animal Studies. More than 700 dynamic and whole-body imaging studies have been performed on a wide variety of animal models, ranging from 30-g mice to 8-kg adult vervet monkeys. Various isotopes and tracers have been used, including [^{18}F]fluorodeoxyglucose (FDG), [^{18}F]fluoroethylspiperone (binds to dopamine receptors) and [^{11}C]WIN 35,428 (binds to dopamine transporter). The amount of activity injected was determined by taking into consideration the NEC measurements with the three countingrate performance phantoms and the specific activity of the tracer and its impact on tracer mass (ensuring study is in tracer range) and volume of the injectate (limited to 0.2 mL in mice and 2 mL in rats to prevent hemodynamic effects). Typical doses ranged from 37 to 74 MBq (1–2 mCi) in the rat, down to 3.7–7.4 MBq (0.1–0.2 mCi) in the mouse, with the exception of ^{18}F ion studies (incorporated into bone), in which higher doses can be injected. The individual frame durations in dynamic acquisitions ranged

FIGURE 6. NEC rates for three phantoms, representing rat body (small), cat head (medium) and monkey head (large), for 250- to 650-keV energy window.

FIGURE 7. Plot of quantitative evaluation of microPET shows true activity measured with well counter versus activity measured with ROIs in reconstructed images of compartment phantom.

from 1 to 20 min, whereas for whole-body measurements, 8-min acquisitions generally were used for each bed position. The total number of bed positions for whole-body studies depended on the axial length of the animal and ranged from 5 to 8 for mice to 16 for rats. All the studies acquired with microPET were reconstructed with the three-dimensional filtered backprojection algorithm, and the system sensitivity provided adequate counts for a ramp filter cutoff at the Nyquist frequency with no additional spatial smoothing.

FIGURE 8. Reconstructed images of two miniature versions of Derenzo phantom imaged with microPET (A and B) and EXACT HR+ (C and D). Images show hot-rod versions (A and C) and cold-rod versions (B and D). Diameters of rods in each of five segments were 2.5, 2.0, 1.5, 1.25 and 1.0 mm, respectively, and center-to-center spacing was four times rod diameter.

RESULTS

Spatial Resolution

Intrinsic Spatial Resolution. The intrinsic spatial resolution of the microPET detector, measured across seven crystal pairs inside the gantry along the transverse direction in the FOV, is illustrated in Figure 2. The curves in this figure are not normalized for detector efficiency and illustrate an intrinsic FWHM ranging from 1.48 to 1.94 mm. The average FWHM of these peaks is 1.58 mm.

Image Spatial Resolution. The three components of the measured-image spatial resolution, R_{FWHM} , T_{FWHM} and A_{FWHM} , are illustrated in Figure 3 for different radial offsets across the FOV. The tangential and axial components of the resolution show a slow increase toward the edge of the FOV, whereas the radial component has a more rapid deterioration because of the penetration of the small 2-mm crystals at larger radial offsets. The strong fluctuations of all the components of the resolution close to the CFOV are typical of a high-resolution ring PET system and are attributed to insufficient linear sampling with a stationary ring system that has an intrinsic resolution of 1.58 mm and a linear sampling distance of 1.125 mm. These effects are expected to disappear with the introduction of the wobbling motion that will improve the system's spatial sampling distance.

Volumetric Resolution. The volumetric resolution, V_{FWHM} , of microPET is expressed as the product of the three linear components (Fig. 4). At the CFOV, the volumetric resolution is $\sim 6 \mu\text{L}$, and for all the radial offsets up to 2.5 cm, it remains $< 8 \mu\text{L}$. This central region encloses approximately half the imaging FOV of microPET.

Sensitivity

The values of the absolute system sensitivity, measured with the 0.74 MBq (20 μCi) ^{68}Ge point source at the CFOV and the three different energy window settings, are listed in Table 3. The average sensitivity across the whole FOV for both microPET and the EXACT HR+ also is shown. The average sensitivity of microPET

(3.92 Hz/kBq) at the default operating window of 250–650 keV is similar to the average sensitivity of the EXACT HR-I+ in two-dimensional acquisition mode (4.46 Hz/kBq), operating at its default energy window of 350–650 keV. A map of the sensitivity across the FOV of microPET is illustrated in Figure 5 for the 250- to 650-keV energy window. The shape of the sensitivity across the FOV for both the 350- to 650- and 450- to 650-keV energy windows is a scaled version of the sensitivity at the 250- to 650-keV window. The shape of the sensitivity map for the three-dimensional acquisitions in the EXACT HR+ is similar to the shape of the sensitivity map of microPET, with the exception that the former does not show such a strong increase as the radial offset from the CFOV increases. The increase in the sensitivity of microPET at larger radial offsets is attributed to the longer average path lengths of the 511-keV photons in the 1-cm deep crystals. The EXACT HR+ with its 3-cm deep crystals stops most of the incoming photons for any source location in the FOV.

Energy Resolution, Timing Resolution and Scatter Fraction

Energy Resolution. The measured energy resolution for the 64 crystals in a microPET detector ranged between 15% and 25%, with an average of 19%. This energy resolution is expected from an LSO system in which the scintillation light is collected through optical fibers (38) and is similar to the energy resolution of BGO-based clinical PET systems in which crystals are coupled directly to the PMTs.

Timing Resolution. The timing-resolution spectrum for two typical microPET block detectors in coincidence had an FWHM of 2.4 ns and an FWTM of 6.4 ns. The ideal coincidence timing window is in the 6- to 8-ns range. Because the coincidence board used is limited to choices of 4, 12 and 20 ns for the coincidence timing window, a value of 12 ns was chosen to provide maximum sensitivity. The additional accidental coincidences resulting from using the wider window are not significant in animal emission imaging applications, although they do affect the ability to perform

FIGURE 9. Images from 300-g rat injected with 74 MBq (2 mCi) ^{18}F FDG and scanned for 16 bed positions and 8-min acquisitions per bed position.

FIGURE 10. Coronal slices from brain of 300-g rat injected with 74 MBq (2 mCi) ^{18}F FDG and imaged for 40 min. Cortex is clearly resolved, and major subcortical structures such as thalamus and striatum also can be discerned.

FIGURE 11. Short- and long-axes slices through heart of 352-g rat injected with 70 MBq (1.9 mCi) ^{18}F FDG and imaged for 32 min.

transmission scans for attenuation correction by reducing the signal-to-noise ratio in the measured transmission data.

Scatter Fraction. The measured scatter fraction varied from 36% to 30% to 22% for the lower energy windows of 250, 350 and 450 keV, respectively. These scatter fractions are significant and indicate that scatter correction is important for quantitative animal imaging with microPET.

Counting-Rate Performance

The NEC rate curves for the 250- to 650-keV energy window, calculated from the measurements with the three cylindrical phantoms in Table 2, are illustrated in Figure 6. The differences in the transverse and axial sizes of the three phantoms, combined with the three-dimensional geometry of microPET, account for the fact that the medium cylinder (simulating a cat brain) has the lowest singles event rate. The small cylinder (simulating a rat body) has a significant singles rate because of out-of-FOV activity, whereas the large cylinder (simulating a monkey head), in addition to the out-of-FOV activity, has a higher singles fraction because of its higher photon attenuation and larger scatter fraction. The higher singles fractions for these two phantoms account for the higher measured accidental coincidence rates and ultimately for the lower calculated NEC rates. In addition, the NEC rates for these phantoms peak at lower

activity concentrations: 4.2 kcps at 196 kBq/mL (5.3 μ Ci/mL) for the monkey brain phantom and 4.1 kcps at 296 kBq/mL (8 μ Ci/mL) for the rat body phantom, compared with 9.9 kcps at 667 kBq/mL (18 μ Ci/mL) for the cat brain phantom. The NEC rate curves for the other energy windows (350–650 keV and 450–650 keV) are similar to the curves for the 250- to 650-keV energy window, with the NEC rate for the monkey brain phantom being most sensitive because of the changes in the amount of accepted scatter radiation. It should be noted that typical activity concentrations in animal studies fall in the range of 37–185 kBq/mL (1–5 μ Ci/mL). At these concentrations, the NEC rates are highest for a lower energy threshold of 250 keV, which therefore is used as the default energy threshold for all animal studies.

Quantification

The concentrations of activity in the different compartments of the phantom, as measured with the well counter, are plotted in Figure 7 against the measured count density from ROI analysis of the reconstructed images. There is excellent linear correlation between the ROI-measured count density and the well-counter-measured activity concentration, despite the lack of scatter correction in this study. This linear correlation is valid for the wide range of activity concentrations used, between 0.37 and 3.7 MBq/mL (10–100 μ Ci/mL). The lowest point in the curve is for the case in which the 10-mm chamber was filled with water and the counts measured in the ROI were due to the presence of scattered radiation.

FIGURE 12. Coronal slices showing bone scan of 30-g mouse injected with 37 MBq (1 mCi) $^{18}\text{F}^-$ and imaged for 8 bed positions and 8 min per bed position.

Imaging Studies

Phantom Studies. Reconstructed transverse slices of the two miniature versions of the Derenzo phantom, acquired with microPET, are shown in Figures 8A and 8B. In the case of the hot-rod phantom in Figure 8A, even the region with 3 cm the smallest 1.0-mm diameter rods clearly is resolved, although the perceived rod source contrast is reduced because of partial volume effects. The presence of scattered radiation and partial volume effects makes imaging the cold-rod Derenzo phantom more demanding. This is clear in Figure 8B, in which the smallest region that is resolved is the region with the 1.25-mm diameter rods. As is expected from the resolution measurements across the FOV with the point source, there is no degradation of the resolution in the part of the FOV encompassed by the 4.0-cm diameter of the two phantoms. In comparison with a state-of-the-art clinical PET tomograph, the images of the same phantoms acquired on the EXACT HR+ are presented in Figures 8C and 8D.

Animal Studies. Representative samples of animal studies performed with microPET are shown in Figures 9–14. Figure 9 shows whole-body images of a 300-g rat injected with 74 MBq (2 mCi) ^{18}F FDG and imaged for 16 bed positions (8-min acquisitions per bed position). Figure 10 shows images of the rat brain after an injection of 74 MBq (2 mCi) ^{18}F FDG, demonstrating separation of cortex, striatum and thalamus. Figure 11 shows ^{18}F FDG images of the rat heart, in which myocardium clearly can be distinguished from the blood pool, even though the diameter of the whole heart is only 1 cm. These studies establish the feasibility of studying rat models with microPET.

Figure 12 shows the biodistribution of 37 MBq (1 mCi) $^{18}\text{F}^-$ in the skeleton of a 30-g mouse, which was scanned for 8 bed positions and 8 min per bed position. Figure 13 shows the distribution from a 185-MBq (5-mCi) injection of the cocaine analog ^{11}C -WIN 35,428 in the brain of the vervet monkey. Figure 14 shows images and time-activity curves for WIN in the rat and mouse brains with injected doses of 37 MBq (1 mCi) and 6.7 MBq (180 pCi), respectively. Even in the mouse brain, left and right striata that are separated by only 3 mm can be resolved clearly, and time-activity curves show a clear difference between dopamine-rich and dopamine-poor regions in the mouse brain. This study demonstrates the possibility of studying the mouse brain with PET when highly specific tracers such as ^{11}C -WIN 35,428 are used. Additional examples of microPET imaging using ^{18}F -fluoroethylspiperone in vervet monkey brain and ^{68}Ga -ethylenediaminetetraacetic acid in rabbit brain have been published previously (39).

DISCUSSION

The evaluation of the performance of microPET indicates that the tomograph meets or exceeds its design specifications as a high-resolution, dedicated small-animal PET imaging system. Its volume resolution shows an improvement of one order of magnitude over the resolution of state-of-the-art, nondedicated, commercial clinical PET systems. This high resolution is realized for a diameter large enough to cover the bodies of mice and rats or the brains of small nonhuman primates. Although the absolute sensitivity of this prototype system is not very high, it has been tested successfully in some of the most difficult imaging protocols, such as whole-body ^{18}F FDG biodistribution studies and dynamic studies of receptor ligands in the rat brain. The results of these studies in rats are similar in quality to clinical whole-body imaging studies of humans, both in terms of signal-to-noise ratio and relative spatial resolution, even

FIGURE 13. Transverse (A) and coronal (B) slices of adult vervet monkey injected with 185 MBq (5 mCi) ^{11}C -WIN 35,428 and imaged at 2 bed positions for 50 min. Images show ^{11}C -WIN 35,428 binding to dopamine transporter in striatum.

though humans weigh two orders of magnitude more. The system sensitivity and counting-rate capability permit the use of a ramp reconstruction filter even for studies necessitating small doses, such as receptor studies in the mouse brain.

More than 700 studies on microPET have been completed successfully. The scanner has been extremely reliable, stable and easy to maintain. Its largest drawback has been the limited axial FOV of 18 mm. Obviously, both the axial FOV and the overall system sensitivity can be improved easily by extending the design to multiple rings of detector modules.

Additional improvements in system performance could be realized by developing electronics specifically designed to deal with the fast decay time of LSO. By further reducing the integration time on the front-end electronics and by reducing the coincidence timing window from 12 to 8 ns, significant improvements in NEC performance could be obtained. The use of body shields to help reduce the singles rate

from activity just outside the FOV in rat and mouse studies would further improve the NEC characteristics.

Future work will examine the implementation of the bed wobble motion to remove linear sampling limitations and fully realize the intrinsic resolution of the detectors. This approach will make the spatial resolution more uniform at the CFOV. We also are pursuing the use of fully three dimensional iterative reconstruction algorithms for application to microPET studies (40). The development of an even higher resolution detector module for incorporation into the next generation of microPET systems also is being investigated.

CONCLUSION

MicroPET is a fully functional, dedicated animal PET system with a volumetric resolution of $\sim 6\ \mu\text{L}$, which represents an order of magnitude improvement over state-of-the-art commercial clinical PET systems. Its high resolution, combined with its sufficient sensitivity and relatively low cost, allows PET to be applied successfully in a wide range of studies of smaller laboratory animals such as mice and rats. MicroPET represents a new noninvasive tool for researchers in the biomedical sciences and in the pharmaceutical industry and will be particularly valuable in animal studies with a longitudinal or interventional design.

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FIGURE 14. Transverse slices and time-activity curves for 300-g rat injected with 37 MBq (1 mCi) ^{11}C -WIN 35,428 (A) and 30-g mouse injected with 6.7 MBq (180 μCi) ^{11}C -WIN 35,428 (B). Images show ^{11}C -WIN 35,428 binding to dopamine transporter in striatum.

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