Arterial Input Function Measurement Without Blood Sampling Using a β-Microprobe in Rats

Frédéric Pain, PhD[1]; Philippe Lanièce, PhD[1]; Roland Mastrippolito, PhD[1]; Philippe Gervais, PhD[2]; Philippe Hantraye, PhD[3,4]; and Laurent Besret, PhD[3]

[1]Unité Mixte de Recherche 8608, Institut de Physique Nucléaire, Université Paris XI, Orsay, France; [2]Commissariat à l'Energie Atomique, Direction des Sciences du Vivant, Departement de Recherche Medicale, Service Hospitalier Frédéric Joliot, Orsay, France; [3]Unité de Recherche Associée 2210, Commissariat à l'Energie Atomique, Centre National de la Recherche Scientifique, Service Hospitalier Frédéric Joliot, Orsay, France; and [4]Isotopic Imaging Biochemical and Pharmacological Unit, Service Hospitalier Frédéric Joliot, Orsay, France

The evaluation of every new radiotracer involves pharmacokinetic studies on small animals to determine its biodistribution and local kinetics. To extract relevant biochemical information, time–activity curves for the regions of interest are mathematically modeled on the basis of compartmental models that require knowledge of the time course of the tracer concentration in plasma. Such a time–activity curve, usually termed *input function,* is determined in small animals by repeated blood sampling and subsequent counting in a well counter. The aim of the present work was to propose an alternative to blood sampling in small animals, since this procedure is labor intensive, exposes the staff to radiation, and leads to an important loss of blood, which affects hematologic parameters. **Methods:** Monte Carlo simulations were performed to evaluate the feasibility of measuring the arterial input function using a positron-sensitive microprobe placed in the femoral artery of a rat. The simulation results showed that a second probe inserted above the artery was necessary to allow proper subtraction of the background signal arising from tracer accumulation in surrounding tissues. This approach was then validated in vivo in 5 anesthetized rats. In a second set of experiments, on 3 rats, a third probe was used to simultaneously determine ^{18}F-FDG accumulation in the striatum. **Results:** The high temporal resolution of the technique allowed accurate determination of the input function peak after bolus injection of ^{18}F-FDG. Quantitative input functions were obtained after normalization of the arterial time–activity curve for a late blood sample. In the second set of experiments, compartmental modeling was achieved using either the blood samples or the microprobe data as the input function, and similar kinetic constants were found in both cases. **Conclusion:** Although direct quantification proved difficult, the microprobe allowed accurate measurement of arterial input function with a high temporal resolution and no blood loss. The technique, because offering adequate sensitivity and temporal resolution for kinetic measurements of radiotracers in the blood compartment, should facilitate quantitative modeling for radiotracer studies in small animals.

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For correspondence or reprints contact: Frédéric Pain, Groupe IPB, Institut de Physique Nucléaire d'Orsay Bat 104, 91406 Orsay Cedex France.

E-mail: pain@ipno.in2p3.fr

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Radiotracer studies on living animals require venous injection of a radioactive tracer. To extract relevant biochemical information, time–activity curves for the regions of interest are mathematically modeled on the basis of compartmental models describing the transfer steps of the tracer from blood to the target organ and its subsequent incorporation into specific biochemical pathways. For instance, the local metabolic rate of glucose can accurately be quantified after injection of ^{18}F-FDG, a radiolabeled analog of glucose. Using a classic modeling approach, each of the kinetic rate constants governing passage from one compartment to another can formally be identified (*1*). However, such a modeling approach requires accurate determination of the time–activity curve of the tracer in plasma—also termed *input function.* This value is used to describe the availability of the tracer to the regions of interest. Usually, the input function is obtained by repeated blood sampling and external counting of the radioactivity concentration. This involves labor-intensive manual withdrawals that present several drawbacks: repeated exposure of staff to radioactivity; a temporal resolution limited to 5–10 s between each sample, affecting the accuracy of the input function; and, finally, the need to collect relatively large amounts of blood, with a possible significant effect on the physiologic parameters of the animal. In that context, the purpose of this study was to evaluate the potential of an intraarterial β-sensitive microprobe to provide an alternative to blood sampling for measuring ^{18}F-FDG input functions with high temporal accuracy in rats. As a first step, Monte Carlo simulations were performed to evaluate the theoretic ability of the technique to measure quantitatively the tracer concentration in blood. In view of the fact that a probe would be inserted into the femoral artery, we inves-

tigated the relative amounts of detected signal arising from radioactivity within the artery and from radioactivity in the surrounding tissues. We also investigated the influence of probe position relative to the artery walls. The results of these simulations led us to propose an experimental approach using 2 β-sensitive probes. The first was inserted into a femoral artery, and the second was placed in the vicinity of the artery to allow subtraction of the positron background signal arising from accumulated tracer in the surrounding tissues. As a second step, this approach was validated in vivo in rats and compared with the gold-standard blood-sampling method, which was performed by simultaneously drawing blood samples from the other femoral artery. Finally, to illustrate the potential of the technique in the context of compartmental modeling, we tested the feasibility of using the input function derived from β-microprobe measurements to evaluate quantitatively the cerebral metabolism of glucose in the rat striatum.

MATERIALS AND METHODS

The β-Microprobe System

The β-microprobe is a local β-radioactivity counter that takes advantage of the limited range of β-particles within biologic tissues to define a detection volume in which the radioactivity is counted. For ^{18}F, the detection volume corresponding to 90% of the detected positrons is a cylinder of approximately 0.8-mm radius centered on the probe axis. A detailed description and discussion of the system can be found elsewhere (*2*,*3*). The device has previously been validated for pharmacokinetic studies, some involving coupling with microdialysis (*4*,*5*) and some involving quantitative measurements of cerebral metabolism using ^{18}F-FDG (*6*) or of blood flow using $H_2{}^{15}O$ (*7*). β Microprobe is now a commercial product from Biospace Measures SA.

Monte Carlo Simulation

To evaluate the ability of the technique to absolutely quantify the tracer concentration in blood, Monte Carlo simulations were performed to determine the influence of arterial dimension on the amount of signal detected within the artery for commonly used PET isotopes and the influence of intraarterial probe position on the detected counting rate.

These parameters were investigated using the Monte Carlo N-Particle code, which allows simulation of the interactions and trajectories of charged particles and photons in a user-defined geometry (*8*). The materials used (polystyrene core for the microprobe, blood, soft tissues) were defined using their mass percentage per atomic element, as obtained from the National Institute of Standards and Technology (*9*). We simulated a 6-cm-long 250-μm-diameter probe immersed in a cylinder of 2-mm radius, homogeneously filled with ^{18}F, ^{11}C, or ^{15}O solution to determine, for each isotope, the percentage of signal detected within the artery, as a function of arterial diameter.

To study the influence of probe position relative to the artery for ^{18}F, the probe was inserted into a cylinder simulating an artery (800-μm diameter, 6.5-cm length). Three probe positions relative to the artery were considered and are presented in Figure 1.

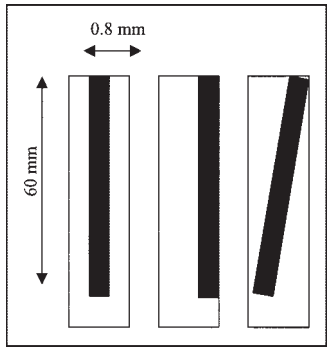

FIGURE 1. Probe positions used for the Monte Carlo simulation: probe axis aligned with artery axis (left), probe laid on artery wall (middle), and probe axis twisted at a 0.8° angle relative to artery axis (right).

β-Microprobe Experimental Setup for Input Function Measurements

The diameter of the probes (250 μm) was close to that of common microdialysis probes and allowed for easy insertion into the femoral artery of a rat. However, this smaller diameter led to a reduced sensitivity for the probe because of a smaller sensitive volume and a more fragile fusion point at the interface between the clear and scintillating fibers. In the particular case of input function measurement, it was possible to overcome these drawbacks simply by using probes made entirely of scintillating fiber directly coupled to a photomultiplier tube. Because the diameter of a rat femoral artery (between 0.2 and 1 mm) is smaller than the maximum range of ^{18}F β-particles in tissues (about 2.3 mm), the activity detected in the artery is the sum of 2 contributions: the β-radioactivity in blood and the accumulated radioactivity in surrounding tissues and artery walls. To subtract this background contribution, a second probe was inserted into tissues above the artery. Each detection channel (probe, photodetector, and associated electronics) was calibrated using a beaker filled with a homogeneous solution of ^{18}F-FDG of known radioactivity concentration. The detected counting rates were recorded while the 6-cm active length of the probes was entirely immersed in the solution. Sensitivities of 1.80 and 1.55 cps/kBq/mL were determined for the signal and background channels, respectively. For a second set of experiments, a 1-mm-diameter 7-mm-long probe with a 1-mm-long sensitive tip was implanted in the left striatum to simultaneously measure the ^{18}F-FDG time–activity curve in striatum and the input function. The striatum probe was calibrated similarly and presented a sensitivity of 0.78 cps/kBq/mL. High voltage was applied to the photomultipliers about 15 min before starting the experiments to allow for stabilization of the photodetectors and to evaluate dark counting rates. For the 2 photomultiplier tubes used in these experiments, the dark count ranged from 1 to 6 cps. For each channel, the counts were averaged and subtracted from the experimental counting rates measured after tracer injection.

Animal Preparation

All experiments were conducted on male Wistar rats (IFFA CREDO) weighing a mean (±SD) of 463 ± 55 g. With the rats anesthetized, catheters were placed into the right femoral vein and artery for radiotracer injection and blood sample collection, respectively.

Then, a first β-sensitive probe was inserted into the left artery. More precisely, the 6-cm-long probe was placed into the vessel.

The diameter of the probe was 250 μm, that is, far smaller than the catheter used for cannulation and small enough to avoid occlusion of the vessel. Moreover, the flexibility and the smooth tip prevented perforation of the artery. A second probe identical to the first was positioned to follow the trajectory of the artery; this probe was attached to the tissue surrounding the vessel far enough away (1 mm) to measure the background without detecting any signal coming from the blood.

For the set of experiments on the potential of the technique for compartmental modeling, the animal was mounted in a stereotactic frame and a craniotomy was performed for the insertion of a microprobe into the left striatum (anteriorly, 0.5 mm from bregma; laterally, ±3 mm from bregma; ventrally, −5 mm from dura matter). The time needed to get the animal ready for such an experiment was approximately 90 min, including 10–15 min for artery and background probe placement.

For all experiments, the injected activities ranged from 17.4 to 31.8 MBq of ^{18}F-FDG in a 1-mL saline solution. Timed arterial blood samples were collected continuously for the first 3 min after ^{18}F-FDG administration and then at increasing intervals up to 60 min. Radioactivity was then counted in 10 μL of whole blood using a Beckman counting system.

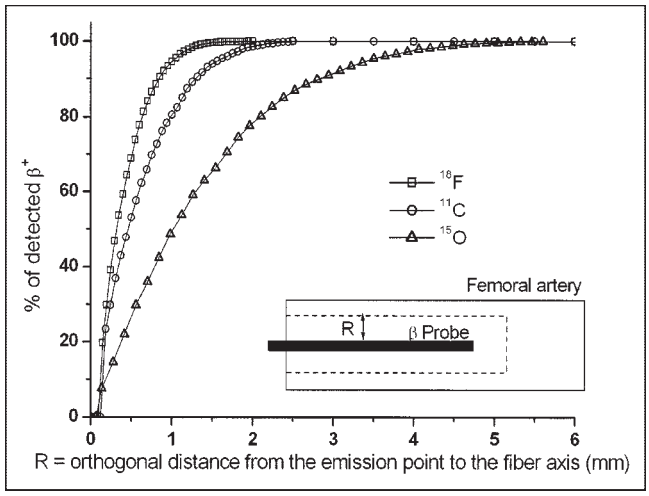

FIGURE 2. For ^{18}F-, ^{11}C-, and ^{15}O-labeled molecules, Monte Carlo evaluation of the fraction of detected signal corresponding to radioactivity in the femoral artery as a function of artery radius.

Mathematic Modeling

A classic ^{18}F-FDG compartmental model with 3 compartments was used to determine the ^{18}F-FDG kinetic rate constants in the striatum (*1*). These compartments, for which the kinetic rate constants were identified as K1, k2, and k3, corresponded to, respectively, the concentration of ^{18}F-FDG in plasma, the concentration of ^{18}F-FDG in tissues, and the concentration of ^{18}F-FDG-6P in tissues. Because these experiments were performed for 45 min after a single injection of ^{18}F-FDG, the activity of the glucose phosphatase enzyme (reverse of glucose phosphorylation by hexokinase) was considered negligible (k4 = 0). A 4% vascular fraction was considered. The parameters were fitted using Comkat (*10*), an open-source compartmental-modeling software program dedicated to nuclear medicine applications. This software uses minimization of a weighted least-squares function and a Levenberg–Marquardt algorithm.

RESULTS

Monte Carlo Simulations

According to the literature, the mean diameter of the femoral artery in rats with a mean weight of 312 ± 15 g is about 741 ± 22 μm (*11*,*12*). However, the diameter may vary under normal conditions from 0.50 to 1 mm. We evaluated the percentage of detected β-particles as a function of the distance from their origin to the axis of the fiber for 3 currently used β-isotopes. As can be seen in Figure 2, for ^{18}F-labeled molecules about 90% of the detected signal arises within a 800-μm-radius cylinder around the probe. However, the artery-to-background signal decreases as a function of the diameter of the artery. For a 400-μm-radius artery, 59% of the total signal arises from the artery, the rest being positron background signal arising from the artery walls and surrounding tissues. For a 200-μm-radius artery, only 30% of the total signal corresponds to effective blood activity. These observations led us to propose the use of 2 probes: one inserted into a femoral artery and the other placed in the vicinal tissues to allow positron background suppression.

For ^{18}F, the detection efficiencies corresponding to the 3 probe positions relative to the artery (Fig. 1) were 14.5%, 10.0%, and 11.8% of the β emitted within the artery, corresponding to calculated apparent sensibilities of 2.07, 1.4, and 1.6 cps/kBq/mL, respectively. These simulations demonstrated that the dimension of the artery and the position of the probe inside the artery can significantly influence the amount of detected signal. Thus, it may be difficult to directly measure quantitative input function from the recorded counting rates. To overcome this difficulty, we normalized the input functions determined by the microprobe to the activity of a late blood sample (obtained at 40 min), which was also required at the end of the experiment to monitor the physiologic parameters of the animal (partial pressure of oxygen in arterial blood, partial pressure of carbon dioxide in arterial blood, oxygen saturation, and pH).

Input Function Measurements in Anesthetized Rats

Both signals (artery and background probes) were first corrected for the dark counts and then normalized to the detection sensitivity of each channel. The background signal was then subtracted from the artery signal. Finally, the result was corrected for radioactive decay of ^{18}F (half-life = 1.829 h). Figure 3 shows the raw data from the 2 probes for a representative experiment. After the first 90 s, data were averaged every 10 s for the sake of clarity. The resulting input function normalized to a late blood sample compared well with the whole-blood input function simultaneously measured by blood sampling, as can be seen in Figure 4. The ratios of the areas under the curves obtained by the 2 techniques were 0.96 in animal 1, 0.85 in animal 2, 1.07 in animal 3, 0.87 in animal 4, and 1.54 in animal 5. Further-

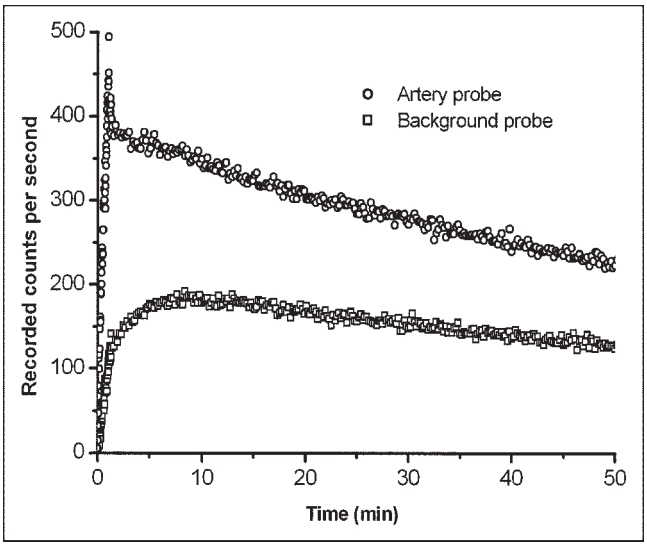

FIGURE 3. Raw time–activity curves recorded by the artery and background probes after bolus injection of ^{18}F-FDG.

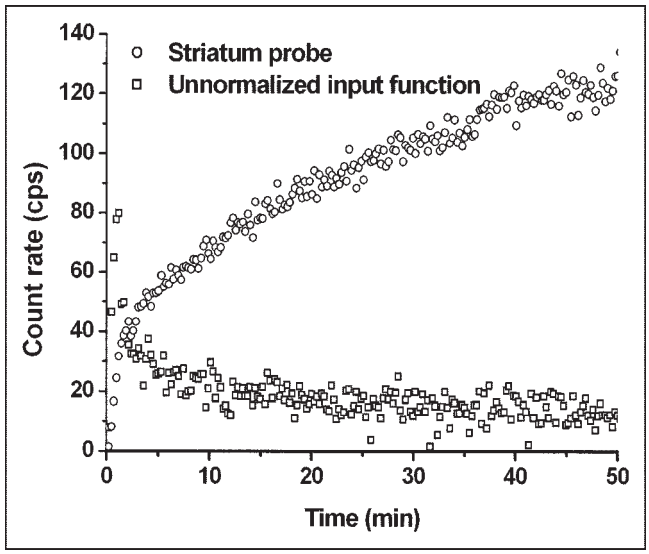

FIGURE 5. Simultaneous determination of arterial input function and striatum time–activity curves after bolus injection of ^{18}F-FDG.

more, the high temporal resolution (data points were acquired every second) allows much more accurate determination of the peak of activity concentration in blood than do manual samplings. At the end of the experiment, we checked for possible tracer contamination that might have accumulated on the fiber (*13*). The counting rate measured just after the probe was removed from the artery was equal to the dark counting rate of the photodetectors.

Compartmental Modeling Using Input Function Generated by β-Microprobe Measurements

For 3 animals, a third probe was stereotactically implanted in the rat striatum to record local ^{18}F-FDG accumulation. Figure 5 shows the time–activity curves simultaneously recorded for ^{18}F-FDG in the striatum and the blood input function determined either in situ or with blood withdrawals. As shown in Figure 6, we successively used both blood time–activity curves as input functions to the compartmental model of ^{18}F-FDG metabolism. Table 1 summarizes the kinetic rate constants K1, k2, and k3 determined using both methods.

DISCUSSION

In studies using radiolabeled molecules, knowledge of the tracer arterial input function is required when compartmental modeling is to be performed, unless a tissue model is used (*14*). The most common technique to measure this

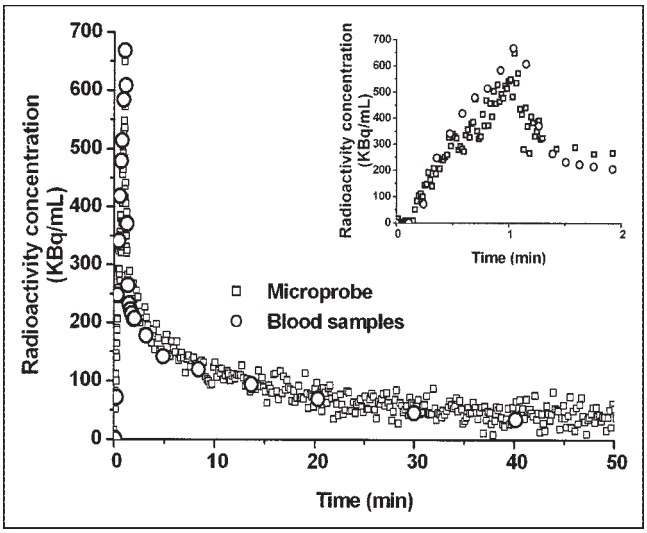

FIGURE 4. Arterial input functions determined with blood sampling or the β-microprobe. Graph shows 1 datum point every 10 s and then averaging of the data every 10 s. Inset zooms in on the first 2 min after bolus injection.

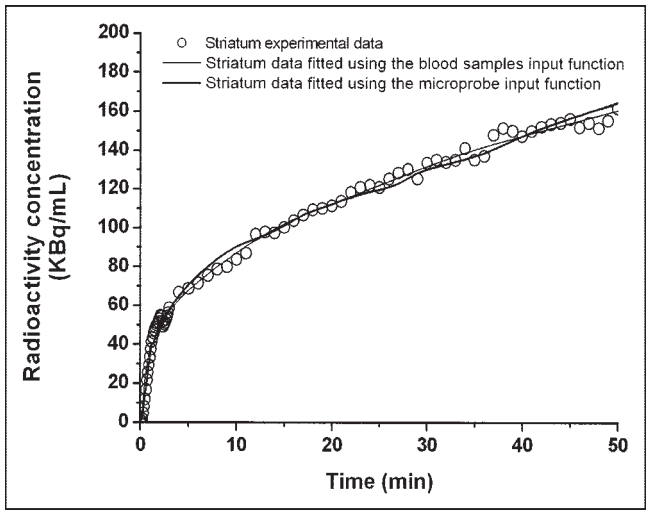

FIGURE 6. Time–activity curve for ^{18}F-FDG accumulation in the striatum fitted using either blood sampling or the β-microprobe arterial input function.

TABLE 1
Kinetics Rate Constants for ^{18}F-FDG in Striatum

Animal no.	Kinetics rate constants (blood/microprobe)			
	K1 (min^{-1})	k2 (min^{-1})	k3 (min^{-1})	(K1 × k3)/(K2 + K3)
1	0.104/0.102	0.119/0.119	0.054/0.056	0.032/0.032
2	0.050/0.048	0.091/0.089	0.056/0.049	0.019/0.017
3	0.065/0.05	0.016/0.011	0.086/0.050	0.023/0.016

input function is blood sampling, usually taken from the catheterized femoral artery of rats. This work is labor intensive, and the subsequent loss of blood may lead to hemodynamic instability. Several alternative techniques have been developed to avoid this procedure. Some of these techniques rely on automatic sampling and radioactivity counting of small blood volumes (*13*,*15–19*). Although these techniques allow standardization of the process and minimization of staff exposure to radioactivity, all require blood withdrawal unless a shunt system is used (*20*,*21*). Furthermore, 2 difficulties are inherent in the use of long catheters to drive the blood from the artery to the detection system. First, the dispersion function of the blood sampling system must be taken into account, and second, possible adsorption of the tracer on the catheter wall may lead to incorrect evaluation of radiotracer concentration. As an alternative, an input function derived from PET images has been proposed for rats and mice. Attempts to determine the input function from PET images of mice were not entirely convincing (*22*), but ^{18}F-FDG blood input functions have successfully been derived from left ventricle images of the rat heart (*23*). However, this required the use of a small-animal PET camera dedicated to cardiac studies (with electrocardiography-gated acquisition) and careful analysis of the signal to deal with motion artifacts and spillover.

The aim of the present study was to propose a simple and sensitive approach for in situ input function measurement that would overcome these limitations. The method has adequate sensitivity and therefore a high temporal resolution, which allows accurate determination of the whole-blood time–activity curve, including the first minutes after bolus injection of PET tracers. This high temporal resolution may also be useful for tracers labeled with short-period isotopes, especially flow studies with $H_2{}^{15}O$ (half-life = 2 min). Because blood sampling is not required, blood loss is minimal, making the method convenient for multiinjection experiments, which have proven to be powerful for determining complex pharmacokinetic parameters but require the successive measurement of at least 2 input functions.

In situ measurements, however, present inherent problems. As evaluated by Monte Carlo simulations, the probe position relative to the artery and the artery diameter are uncontrolled parameters and prevent direct quantification of the whole-blood time–activity curve. To obtain a quantitative input function, it is necessary to renormalize the measured time–activity curve to a late sample. Nevertheless, this does not interfere with the experimental scheme, since at least 1 blood sample is necessary to control the physiologic parameters of the animal throughout the experiment. Another difficulty is that the measured input function is the whole-blood time–activity curve, whereas compartmental modeling requires the plasma time–activity curve. For ^{18}F-FDG, if a standardized injection protocol is used, a simple correction based on the time course of the plasma-to-blood ratio is achievable (*21*). The weakest point in our technique is the necessity of subtracting background signal from the ^{18}F-FDG accumulation in surrounding tissues. However, it was possible to position a background probe above the femoral artery to ensure proper background subtraction. This point should be less critical for other PET tracers labeled with ^{18}F, ^{11}C, and ^{15}O that do not accumulate as much FDG in the tissues surrounding the femoral artery. Another point that might be of concern is the length of the probes. Because sensitivity increases linearly with probe length, the level of recorded counts in the present study indicates that probe length could be reduced to 3 cm without compromising the input function measurements.

CONCLUSION

The use of 2 positron-sensitive probes allowed accurate determination of the input function after bolus injection of ^{18}F-FDG, provided background suppression was accurate. The high temporal resolution prevented the peak of radioactivity in blood from being missed, as sometimes occurs with blood-sampling techniques. The proposed technique is accessible to any laboratory technician accustomed to placing catheters in rats and does not require blood collection, thus avoiding blood loss. This latter point should be of great interest for multiinjection experiments, which require the measurement of successive input functions. The technique offers sensitivity and temporal resolution adequate for accurate kinetic measurement of radiotracers in the blood compartment. Therefore, the β-microprobe system allows simultaneous measurement of blood and cerebral tissue time–activity curves after a single injection of a PET tracer in the animal.

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