Measurement of Blood Input Function in Animal

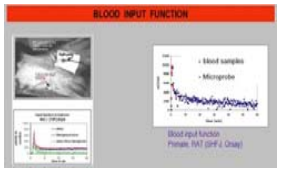
Doctoral Seminar Small Animal Imaging 1

Summer Semester 2008/2009

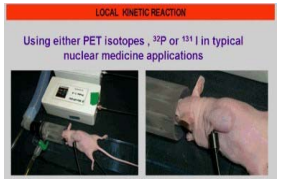
Blood Input Function

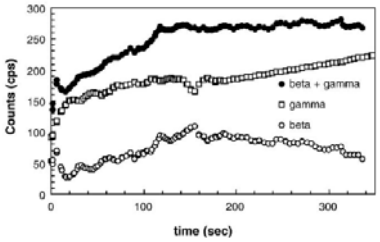
- Measurement of the blood activity concentration over time forms the basic element for tracer kinetic modelling
- Prerequisite for accurate determination of various biological parameter
- Several methods can be used to measure blood activity concentration

Beta Probe



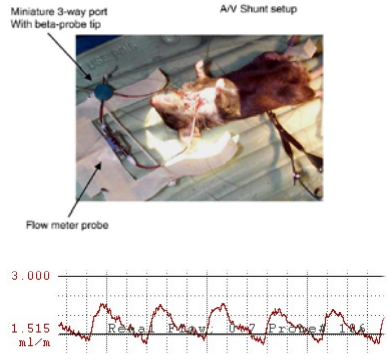
- Directly detect the activity contained within the blood as it passes through the blood vessel
- Probe is placed in direct contact with blood or blood vessel
- This method using scintillation detector





Arterial/Venous Shunt

- Catheter surgically inserted between the carotid artery and jugular vein
- Placement of catheter allows for fraction of blood to flow outside the body through the catheter



Arterial Blood Sampling

- Directly measured from rapid blood sampling in small amount at the time intervals from a major blood vessel
- Radiopharmaceutical is inserted via catheter in femoral or jugular vein
- Micropipette tube are pre- and post-weighted and counted in gamma counter for true counts
- Can measure blood flow as well as for substrate and metabolite

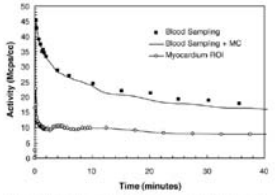


Fig. 3. Blood pool and myocardium time–activity curves obtained by serial blood sampling and with a ROI traced on the myocardium. The blood sampling curve corrected for metabolite is shown on the graph; this curve is identified as blood sampling+MC (metabolite correction).

Factor Analysis

- The blood input function is derived from dynamic images without the need for drawing ROIs
- FA describes the covariance relationship among many variables in term of few underlying, but unobservable

$$Y(p,t) = \sum_k I_k(p) C_k(t)$$

- FDG PET in heart : Myocardium, right ventricle and left ventricle
- Physiological time activity (TACs)

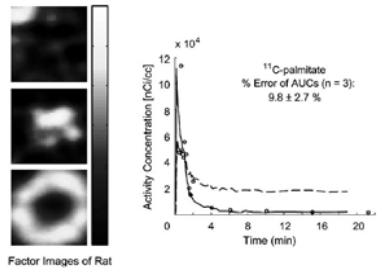


Fig. 4. Factor images for ^{11}C-palmitate and blood time–activity curve extracted by the factor analysis technique from a rat study. On the left, typical factor images for ^{18}F-FDG in rat showing the three compartments are shown: right ventricle (RV), left ventricle (LV) and myocardium (MY). On the right, blood sampling data (open circles) are compared to blood time–activity curve (solid line) for ^{11}C-palmitate in rat. Excellent correlation with the blood sampling technique is found as shown by the small relative difference of their respective AUC.

Image-based analysis with ROI

- Blood input function derived from dynamic PET images
- Direct measurements from images by ROI on LV or ascending aorta
- The accuracy of the measurements is affected by the spatial and temporal resolution of camera
- ROI traced in LV, the measure activity must be corrected by partial volume recover coefficient of LV (Rlv) and spillover activity from myocardium to LV (Sm-lv)

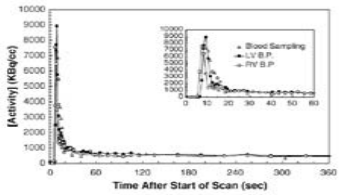
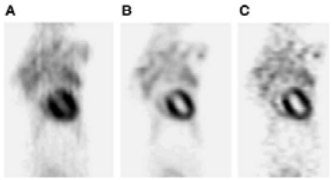


Fig. 5. Blood time–activity curves extracted from rat heart images. Forty-six megabecquerel (1.26 μCi) of ^{18}F-FDG was injected. The inset shows an expanded view of the early time point illustrating the temporal resolution of the scanner, which allows the separation of the RV from the LV blood input functions.

Cardiac Gating

- Dividing the heart cycle into several time bins in order to extract the diastolic phase
- Minimizes the spillover effect from activity in myocardium into the intra-ventricular blood pool



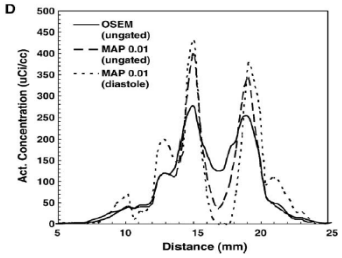


Fig. 6. Coronal images of mouse ^{18}F-FDG heart in a microPET-F120 scanner. (A) FORE+2D-OSEM, 4 iterations, 16 subsets; (B) 3D-MAP, 2 iterations (3D-OSEM) and 18 MAP iterations (beta=0.01, pixel size=0.4 mm); and (C) MAP [same parameters as (B)] but gated (diastolic phase). In (D), line profiles traced through the heart short axis show that the quantitative improvement is due to resolution gain offered by MAP and also by gating.

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

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The evaluation of every new radiotracer involves pharmacokinetic studies on small animals to determine its biodistribution and local kinetics. To extract relevant biochemical information,

Key Words: arterial input function; β-microprobe; ^{18}F-FDG; rat; kinetic modeling

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Aim of Study

- Evaluate the potential of an intra-arterial beta sensitive microprobe
  - 18-FDG input function
- Evaluate theoretic stability of the technique to measure tracer concentration
  - Monte Carlo simulation

Materials

- Beta -microprobe
- 18-FDG with activity in the range of 17.4 to 31.8 Mbq in 1 mL
- Blood flow using $H_2{}^{15}O$
- Wistar rats (IFFA CREDO)

Monte Carlo Simulation

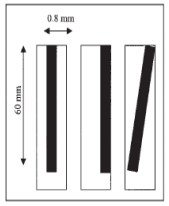

FIGURE 1. Probe positions used for the Monte Carlo simulation: probe axis aligned with artery axis (left), probe laid on artery wall (middle), and probe axis twisted at a 0.8° angle relative to artery axis (right).

Beta microprobe experimental setup

- Diameter probe 250 micro meter < diameter of femoral artery (between 0.2 – 1 mm)
- Activity detected from beta radioactivity in blood and accumulated radioactivity in surrounding tissue and artery walls
- Background is detected by second probe
- Each channel was calibrated using 18 FDG of known radioactivity concentration (in cps/kBq/ml)

Animal preparation

- Rat anesthetized
- Catheter were placed into the right femoral vein and artery for radiotracer injection and blood sample collection
- Beta probe first is inserted into the left artery
- Second probe inserted to artery is far surrounding tissue to obtain background signal
- Arterial blood samples was collected continuously for first 3 minutes after 18 FDG injection an increasing intervals up to 60 minutes

Compartment Modelling

- Animal is mounted in a stereotactic frame and craniotomy is performed for insertion of a microprobe
- 3 compartments (concentration FDG in plasma, in tissue, and FDG-6P in tissue) was used to determine the 18F-FDG kinetic rate constants in the striantum

Results

Monte Carlo Simulation

- Detected beta particle as a function of distance
- Efficiency of probe position in Fig. 1 are 14.5%, 10%, and 11.8%
- Calculate apparent sensibilities

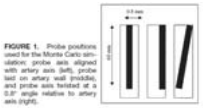

FIGURE 1. Probe positions used for the Monte Carlo simulation: probe axis aligned with artery axis (left), probe laid on artery wall (middle), and probe axis twisted at a 0.8° angle relative to artery axis (right).

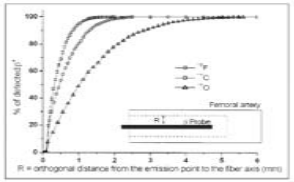

FIGURE 2. For ^{18}F-, ^{11}C-, and ^{15}O-labelled molecules, Monte Carlo evaluation of the fraction of detected signal corresponding to radioactivity in the femoral artery as a function of artery radius.

Measurement

- Artery Signal
- Background
- Input function in microprobe and blood sample

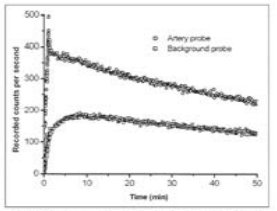

FIGURE 3. Raw time–activity curves recorded by the artery and background probes after bolus injection of ^{18}F-FDG.

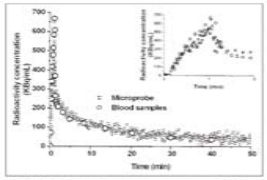

FIGURE 4. Arterial input functions determined with blood sampling or the β-microprobe. Graph shows 1 datum point every 10 s and then averaging of the data every 10 s. Inset zooms in on the first 2 min after bolus injection.

Compartment modelling

- TAC
- TAC as input function to compartment model

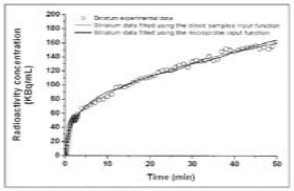

FIGURE 6. Time–activity curve for ^{18}F-FDG accumulation in the striatum fitted using either blood sampling or the β-microprobe arterial input function.

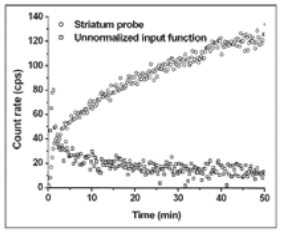

FIGURE 5. Simultaneous determination of arterial input function and striatum time–activity curves after bolus injection of ^{18}F-FDG.

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

Minimally Invasive Method of Determining Blood Input Function from PET Images in Rodents

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Aim of Study

- Investigating changes in organ function
  - ➔ Blood flow, glucose and free fatty acid metabolism
- Problem: micro blood sampling technique
  - ➔ Limited : number of blood sample, invasive
- Factor analysis non-invasive

Materials

- MicroPET R4
- Animals: 6 Spraque-Dawley rats (group 1) and 6 BALB/c mice
- 18-FDG : 26.8 + 4.5 Mbq (rats) and 24.1 + 3.8 Mbq (mice)

Methods

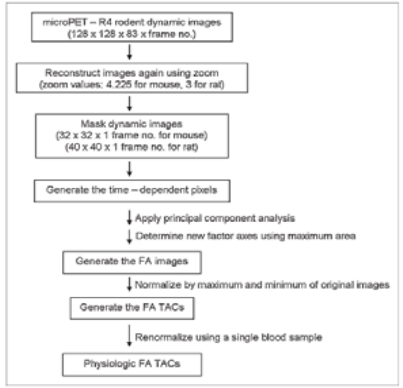

FIGURE 1. Flow chart of FA procedure used in this study. TACs = time–activity curves.

Result

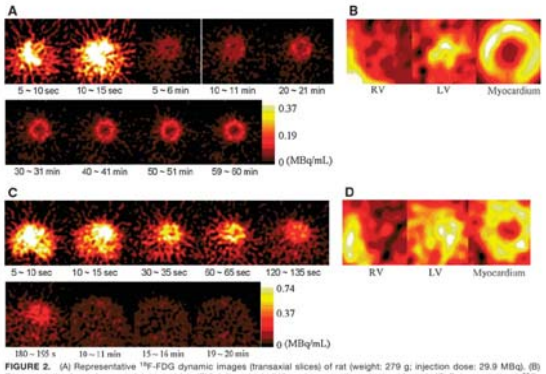

FIGURE 2. (A) Representative ^{18}F-FDG dynamic images (transaxial slices) of rat (weight: 279 g; injection dose: 29.9 MBq). (B) Representative factor images of right ventricle (RV), left ventricle (LV), and myocardium obtained from A. (C) Representative 1-^{11}C-acetate dynamic images (transaxial slices) of rat (259 g; 38.3 MBq). (D) Factor images of RV, LV, and myocardium obtained from C.

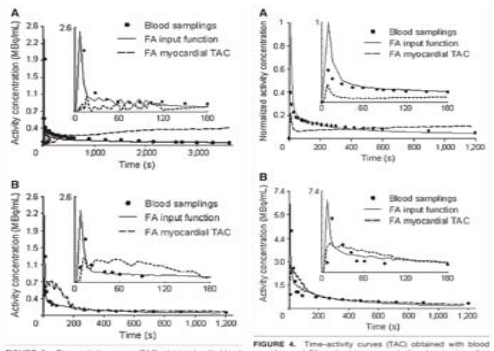

FIGURE 3. Time–activity curves (TAC) obtained with blood sampling and FA method in rat studies. Insets show first 3 min of time–activity curves. (A) Blood-pool input functions generated by blood sampling and FA method in ^{18}F-FDG rat study ($r = 0.96 \pm 0.01$, $n = 3$). (B) Blood-pool input functions obtained by blood sampling and FA method in 1-^{11}C-acetate rat study ($r = 0.97 \pm 0.02$, $n = 3$).

FIGURE 4. Time–activity curves (TAC) obtained with blood sampling and FA method in mouse studies. Insets show first 3 min of time–activity curves. (A) Input function and myocardial time–activity curve in mouse study with ^{18}F-FDG. FA input function was rescaled with blood sample obtained at 20 min after administration. (B) Input function and myocardial time–activity curve in mouse study with 1-^{11}C-acetate. It was not possible to extract myocardial time–activity curve by ROI method because of partial–volume effects and spillover.

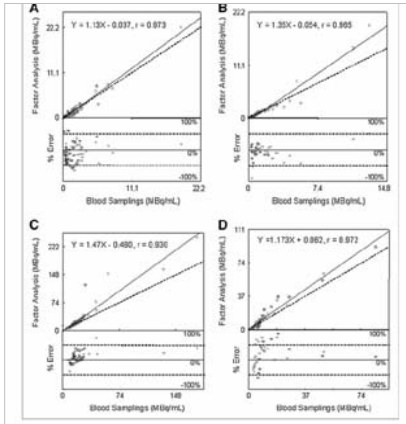

FIGURE 5. Linear regression line (—) and percentage error plot for input functions obtained from blood sampling and FA method. Percentage error was calculated from difference between FA values and blood sample values. Dashed line is unity line ($y = x$). (A) ^{18}F-FDG rat studies ($n = 3$). (B) 1-^{11}C-Acetate rat studies ($n = 3$). (C) ^{18}F-FDG mouse studies ($n = 3$). (D) 1-^{11}C-Acetate mouse studies ($n = 3$).

Conclusion

- Challenge to determine blood input function
- Monte Carlo simulation
- Measurement

Question?