FDG-PET in Early Infancy: Simplified Quantification Methods to Measure Cerebral Glucose Utilization

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For further insight into the physiology and pathogenesis of the developing brain, quantification of the cerebral glucose metabolism is needed. Arterial blood sampling or sampling of great volumes of blood is not justified for the purpose of PET studies in children. Therefore, we have developed simplified PET approaches to analyze brain FDG examinations during infancy. **Methods:** The study consisted of 18 FDG-PET examinations chosen from our research protocols concerning hypoxic-ischemic encephalopathy and severe neonatal hypoglycemia. The input function for graphical analysis according to Patlak was derived in two ways: (1) a combined time-activity curve derived from the left ventricular activity concentration (first 7–17 min of the study) and radioactivity concentration in venous whole-blood samples and; (2) activity concentration measured in whole-blood venous blood samples (arterial plasma in one case). As an alternative for semiquantitation, the standardized uptake values (SUV) were calculated and correlated to local cerebral metabolic rates for glucose (LCMRGlc). **Results:** The influx rate constants (Ki) and LCMRGlc values obtained using the combined curve versus venous curve did not differ statistically ($p > 0.05$). There was a good correlation between the SUV and LCMRGlc values ($r = 0.83$, $p < 0.001$). **Conclusion:** Local cerebral metabolic rates for glucose can be accurately calculated by using the combined curve (left ventricular activity concentration during first 5 min of the study and 2–3 venous whole-blood samples at the end of the study) for even the smallest pediatric patients. When blood samples cannot be obtained, SUV values provide an alternative for estimation of the cerebral glucose uptake and interindividual comparison of the patients.

Key Words: positron emission tomography; fluorine-18-fluorodeoxyglucose; infantile cerebral glucose utilization

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PET allows in vivo noninvasive measurement of the concentration of radiopharmaceuticals labeled with positron emitters (*1*). With the development of a method for deriving regional metabolic utilization rates from PET data, quantitation of tissue glucose uptake has become possible (*2,3*). The most frequently used tracer for the assessment of glucose metabolism is 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) (*2*). The graphical analysis according to Patlak et al. (3) and the deoxyglucose model developed by Sokoloff et al. (4) require an accurate measurement of the radioactivity concentration versus time in plasma. In these models arterial blood sampling during imaging has been used for measurement of the input function. Recently simplified methods have been reported in which the input function has been derived from the regions of interest (ROIs) drawn over dynamic PET images of the left ventricle (*5*) or on the thoracic aorta (*6*).

Only a few pediatric and even fewer neonatal PET studies with a complete quantitation of cerebral glucose metabolic rate have been presented so far (*7*). The problem in quantitative pediatric PET studies is justifying an invasive procedure in infants in order to obtain necessary clinical information. Furthermore, each invasive procedure puts the infant at risk. We think that it is unethical to take arterial blood samples from neonates for PET studies, nor is it possible to take large volumes of blood from these patients. The quantitation, however, of the cerebral metabolism is important to study the physiology and pathophysiology of the developing brain. The aim of this study was to develop and validate a simplified approach to making brain FDG-PET studies in small pediatric patients. For the input function in Patlak analysis, a combined blood time-activity curve derived from ROIs drawn on the left ventricle (LV) seen in PET images and from venous whole blood samples was obtained. Standardized uptake values (SUV) were also calculated and correlated to LCMRGlc in order to estimate the cerebral glucose uptake for interindividual comparison if no blood samples are available.

MATERIALS AND METHODS

Eighteen FDG-PET examinations of infants were selected from our ongoing research projects concerning hypoxic-ischemic brain injury and severe neonatal hypoglycemia. These projects were

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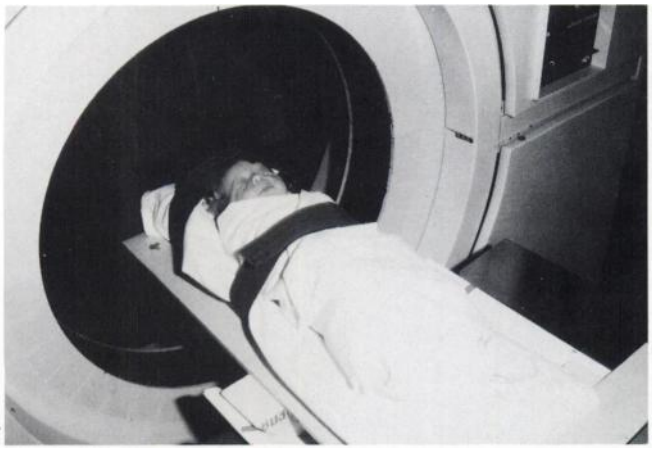

FIGURE 1. An additional plywood part of the tomograph bed with minimal attenuation specially constructed for PET studies of newborn infants.

approved by the Ethics Committee of the hospital and informed consent for the PET examinations was obtained from the parents. Of the 18 PET examinations, 9 were made during the neonatal period. The postconceptional age of the infant at the time of the examination was 38.4 ± 3.7 gestational wk and their weight was 3096 ± 848 g. The other nine examinations were made at age 3.3 ± 0.6 mo (corrected for gestation), and the weight of the infants was 6440 ± 890 g.

PET Tomography

Preparation of FDG. The FDG synthesis was a modification of the method reported by Hamacher et al. (*8*). Its radiochemical purity was better than 99% (*9*).

Image Acquisition. Image acquisitions were made with an eight-ring ECAT 931-08/12 tomograph (Siemens/CTI Inc. Knoxville, TN). The scanner gives images of 15 continuous planes with the spatial resolution of 6.5 mm FWHM inplane and 6.7 mm axially measured according to Spinks et al. (*10*). The axial field of view is 10.8 cm. The scanner was calibrated against the well counter (Bicron 3MW3/3P) with a known uniform solution of ^{68}Ge and water in a cylindrical phantom. The attenuation caused by the head and the body of the infant was corrected separately and individually with calculated method using mass absorption coefficient (0.095 cm^2/g). Transmission scans were not made to save time and to avoid superfluous radiation. A specially constructed plywood crib (an additional part to the tomograph) was used to decrease the attenuation of the bed (Fig. 1). The error between the measured and the calculated attenuation was estimated with a uniform phantom study (14-cm diameter). The estimated error for the heart was −7% and for the brain a maximum of 20% (for the lowest parts of the brain nearest to the crib and for a very small ROI).

Study Design. All PET examinations were carried out without sedation in the afternoon during postprandial sleep. Two venous catheters were inserted, one in a cranial vein for blood sampling and the other in the hand or foot vein for FDG injection. One infant had an umbilical arterial catheter for clinical reasons. A light, foam rubber holder was used to immobilize the head. FDG in physiological saline (3.7 MBq/kg) was intravenously injected during 10 sec. A dynamic heart scanning was simultaneously started and continued for 17 min (6 × 20 sec, 5 × 60 sec, 5 × 120 sec). In practice this turned out to be an unnecessarily long time and we changed the protocol during the study. For this reason the heart study lasted only 7 min (12 × 10 sec, 10 × 30 sec) for three infants. The heart study was made in order to measure the blood radioactivity from ROIs drawn on the left ventricle of the heart. After the heart study, a corresponding 20-min brain scan was made (10 × 120 sec). The exact starting time of the brain study varied due to the vigilance stage of the infant (average time, 33 min). As many venous whole-blood samples as possible were taken during the PET examination. At least one sample was always taken at the end of the study to get the end-point of the curve. An average of nine samples (range 2–16) were obtained using microtechniques (the total volume per patient did not exceed 5 ml). In six examinations, an average of 14 (range 11–16) samples were available to obtain a sufficient whole blood input function for graphical analysis. In one examination, 16 arterial blood samples (whole blood and plasma) could be obtained. The radioactivity concentration was measured with a well counter (3″ × 3″ NaI(Tl) crystal, Bicron 3MW3/3P) and the plasma was not separated because of the small volumes of each sample, except in the arterial case. The glucose level in whole blood was determined three times during the study (0 min, 20 min and at the end of the study) with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). The whole blood glucose value was multiplied by 1.05 to get the plasma glucose value. The average of these three measurements was used.

Image Processing. ROI analysis was performed on images which were reconstructed in a 256 × 256 matrix with a Hanning filter (0.5 cut off-frequency). The data were corrected for deadtime, decay and the calculated photon attenuation.

Heart Studies. Three circular ROIs (30–50 pixels) were drawn on representative transaxial mid-ventricular slices of the last frames of the dynamic scan, where the myocardium was visible. The appropriate localization of each ROI was also verified on the blood pool images at the beginning of the examination. The ROIs were drawn away from the apparent tissue edge of the myocardium in order to minimize spillover and overlapping of the myocardial wall. The ROI with the highest radioactivity concentration at the beginning of the study was chosen. The time-activity curve from the heart study (the LV curve) was combined with the time-activity curve obtained from the whole blood samples. This combined curve was fitted to a three exponential function with a nonlinear least-squares method. The original time-activity curves were inspected graphically. The part of the LV curve without suspected interaction from the myocardium and other tissues was included in fitting.

Brain Study. In the brain study, elliptical or circular ROIs were placed on each transaxial slice visualizing the frontal, sensorimotor (pre- and postcentral gyri), temporal, parietal and occipital cortex, as well as the thalamus, brainstem and cerebellum. The mean activity concentrations of these individual regions were calculated. Also, one ROI to represent the whole brain was drawn on the slice visualizing the thalami. Total number of ROIs varied from 60 to 80 and the number of pixels per ROI was 80–100.

Calculation of Regional Glucose Utilization. The differential equations governing the three-compartment FDG tracer-kinetic model have been described previously (*2,11*). The fitted combined input curves and tissue time-activity curves were analyzed graphically to quantitate the fractional rate of tracer phosphorylation K_i (*3*):

$$Ki = (k_1 \times k_3/k_2 + k_3),$$

TABLE 1
Ki and LCMRGlc Values of the Whole Brain ROI

	Ki			LCMRGlc*		
Study	Combined	Venous		Combined	Venous	
L00030	0.0134	0.0131		14.26	13.96	
L00041	0.0096	0.0097		10.22	10.35	
L00044	0.0116	0.0123		12.36	13.16	
L00045	0.0185	0.0182		20.25	20.01	
L00053	0.0159	0.0175		23.32	25.67	
L00056	0.0184	0.0196		20.06	21.37	
	Combined	Arterial Plasma	Whole blood	Combined	Arterial Plasma	Whole blood
L00126	0.0124	0.0113	0.0125	9.86	8.98	9.94

*μmole/min/100 g.

where k_1 is the transfer coefficient from vascular space into the tissue; k_2 is the initial clearance and efflux coefficient; and k_3 is the phosphorylation rate constant. The graphical analysis according to Patlak et al. assumes that the rate of dephosphorylation (k_4) is zero and that the tracer is irreversibly trapped into the cell (*3*). For FDG-PET studies less than 60 min duration, the necessity for fitting k_4 as an additional parameter has not been demonstrated (*12*).

The rate of glucose utilization is obtained by multiplying K_i by the plasma glucose concentration $[Glc]_p$, and dividing by a lumped constant term (LC) (*4*); i.e., the rate of glucose utilization = $([Glc]_p/LC) \times K_i$. The lumped constant accounts for differences in the transport and phosphorylation of FDG and glucose (*2*). The LC for the young adult brain has been measured to be 0.52 (*1*), which is the value used in this study.

To compare the K_i values and LCMRglc values based on the venous whole blood input function to those based on the combined input function, the Patlak analysis was calculated with whole brain ROI in those six examinations, where enough blood samples for the whole time of the study were available. In instances where arterial samples could be used, analysis was done with whole brain ROI using the arterial plasma and whole blood curves, and the combined curve as the input function.

Semiquantitative Analysis of the Cerebral Glucose Utilization. SUVs (*13,14*) of all brain regions were also calculated for each infant. SUV is defined as tissue radioactivity divided by intravenously administrated dose per patient's weight.

$$SUV = \frac{\text{Average Radioactivity in ROI (Bq/ml)}}{\text{Injected Dose [Bq]/Patient Weight (g)}}.$$

SUV values were obtained at 40–50 min after injection of the tracer.

Statistical Analysis

A paired t-test was used to test the difference between the K_i and LCMRGlc values obtained from Patlak analysis using the combined time-activity curve and the venous time-activity curve as the input function. The correlation between the LCMRGlc values and the SUV values was calculated by linear regression. A p-value <0.05 was considered statistically significant.

RESULTS

The plasma time integrals of the combined curves were 7.0% ± 6.3% higher compared to the venous input curves. The mean (± s.d.) percentage differences between the Ki and LCMRGlc values obtained from the Patlak analysis using the combined curve and the venous blood curve as the input function were 4.6% ± 3.2% (range 1.2%–6.5%) and 4.6% ± 3.3% (range 1.2%–7.6%). The mean differences were 0.000695 (± 0.000548) and 0.855 (± 0.780), respectively, which were not statistically significant ($p > 0.05$) (Table 1). The differences in Ki and LCMRGlc values obtained from the Patlak analysis of ROIs drawn on whole brain ROIs using the arterial plasma curve versus the combined curve as an input function was 8.9% and the difference between plasma curve versus whole blood curve was 9.6%, respectively. The corresponding difference between the whole blood curve and the combined curve was 0.08% (Figs. 2, 3). The blood glucose levels were quite stable during the whole study, the mean (± s.d.) value was 5.9 ± 0.94 mmole/liter.

The LCMRGlc values in individual brain regions of the infants varied from 3.9 to 37.0 μmole/min/100 g. The cortical LMRGlc values were 3.9–18.5 μmole/min/100 g during the neonatal period and 10.8–34.5 μmole/min/100 g in examinations made at the age of about 3 mo. The LCMRGlc values of the subcortical regions (thalamus, brainstem, cerebellum) were correspondingly 7.2–22.5 μmole/min/100 g and 11.9–37.0 μmole/min/100 g. There was a good correlation between SUV and LCMRGlc over all individual brain regions of the infants ($r = 0.83$, $p < 0.001$) as presented in Figure 4.

DISCUSSION

Research conducted over the past two decades has dramatically expanded our knowledge of those critical vascular and metabolic events that eventually lead to brain tissue injury arising from hypoxia-ischemia (*15*). Hypoxic-

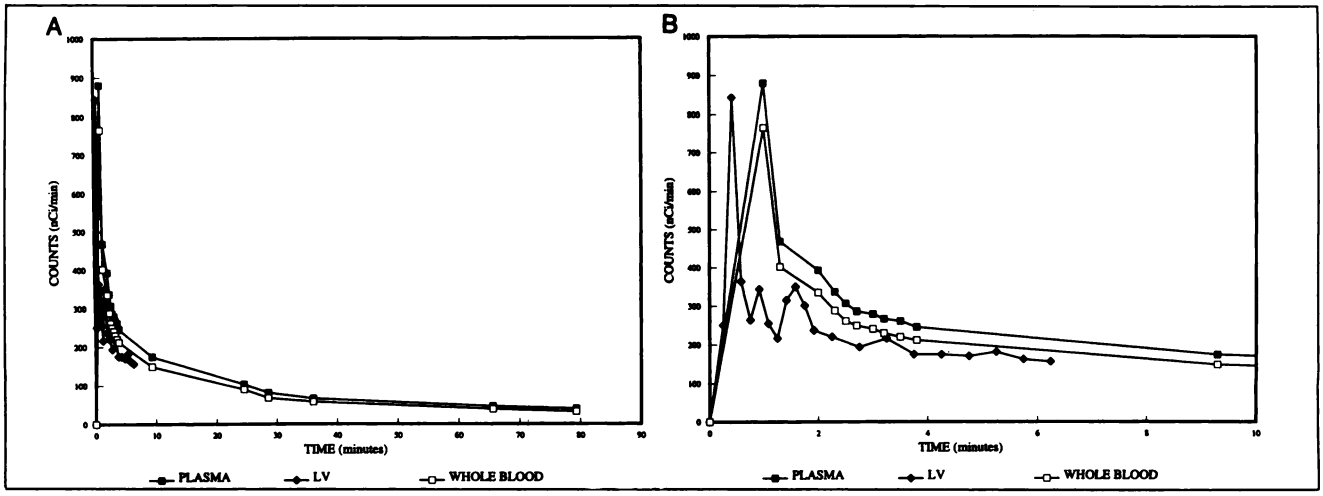

FIGURE 2. (A) Fluorine-18 radioactivity in plasma, whole blood and left ventricle blood pool. The differences in the peaks are due to delay and dispersion of the tracer and differences in whole blood and plasma. (B) The expanded peak region.

ischemia causes various biochemical alterations which can lead to the chronic neurological handicaps of cerebral palsy, mental retardation, learning disabilities and epilepsy. Based on animal studies, potential new modalities of therapy capable of preventing—or at least reducing—brain damage including calcium channel blockers, oxygen-free radical inhibitors and scavengers, excitatory amino acid antagonists have also been presented (*16*). PET offers a unique possibility and further insight into the various processes in the developing brain and can provide useful information about the long-term prognosis of a critically ill infant (*17–19*). PET is, however, a very techinally demanding procedure requiring blood sampling (usually arterial, which is especially invasive for small infants. Here we present a method which provides reliable LCMRGlc values for infants but does not require arterial blood samples.

According to Patlak, a proper input function is needed in graphical analysis to obtain the LCMRGlc values. This input function can be obtained in infants by combining the input function derived from ROIs drawn over dynamic PET images of the left ventricle during the first minutes of the examination and a few venous whole blood samples obtained during the last part (20–50 min) of the examination. The scanning of the heart without a transmission scan is possible in the PET studies of infants because of the small body dimensions and the high water content of the tissues.

In Patlak analysis, it is important to obtain the correct input function in the later phase from 15–60 min. Spillover from the myocardium to left ventricle may cause an increase in the radioactivity counts at that phase of the time-activity curve. This error can be avoided by using the LV curve only at the beginning of the examination, as we did in our study. A short heart scan, however, may not be enough for fitting and at least one sample at the end of the study is needed to ensure a proper curve is obtained.

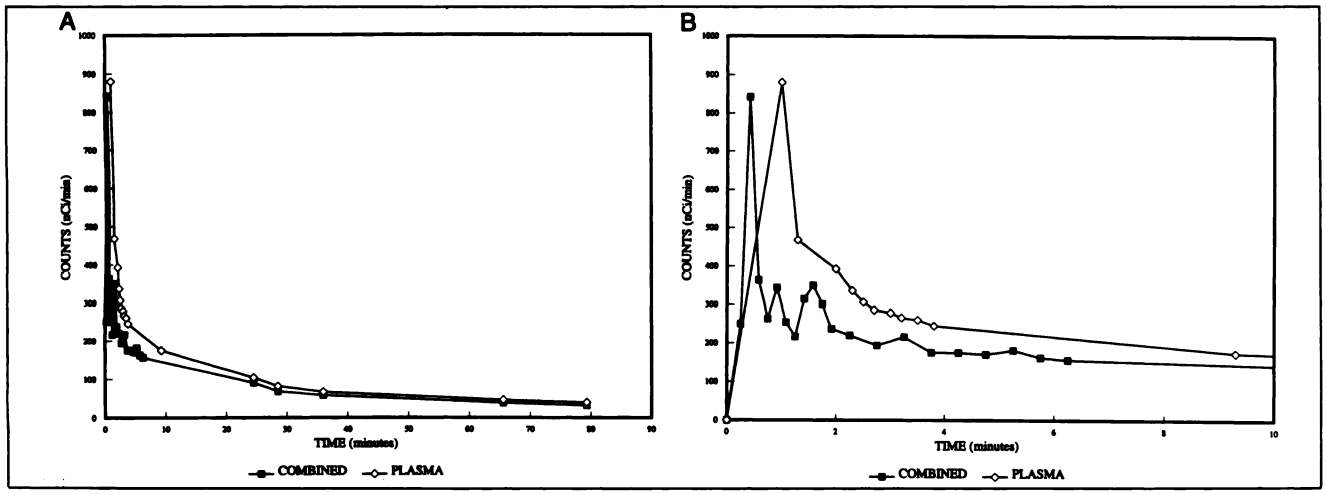

FIGURE 3. (A) The combined and plasma curves which are quite identical during the latter part of the study (>30 min) because there is no effect of the spillover in the combined curve. This is because the LV activity was used only during the first minutes of the study in the combined curve. The small difference is due to differences in whole blood and plasma. (B) The expanded peak region.

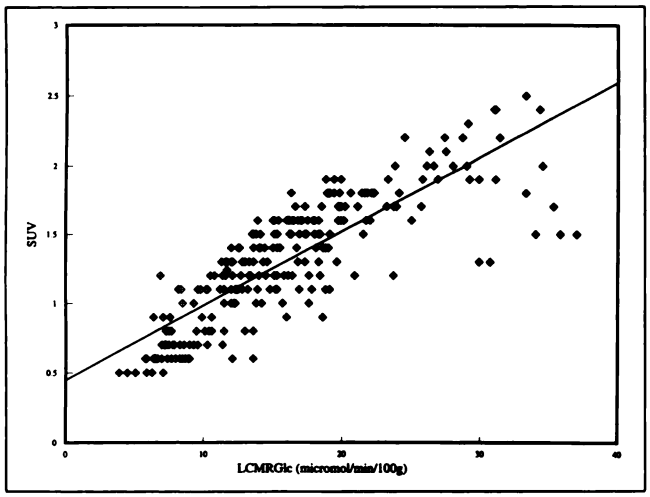

FIGURE 4. Correlation in all patients between the SUV and LCMRGlc values of all cerebral ROIs (n = 252), r = 0.83, p < 0.001.

Whole-blood samples were used instead of plasma samples for the combined curve. Although the whole blood activity concentration is initially less than the plasma activity concentration (causing lower maximum of the time-activity curve), Gamphir et al. (*5*) found the arterial whole blood and plasma radioactivities reach equilibrium very quickly, (Fig. 2), thus justifying the use of either the whole blood or the plasma time-activity curve as the input function. A difference of about 10% in Ki and LCMRGlc calculated from arterial plasma and arterial whole blood curves was found in our patient with the arterial catheter (Table 1). This difference agrees with a previous study in adults (*20*).

Because arterial sampling is not possible and enough blood to separate the plasma cannot be systematically obtained in small infants, venous blood samples were used in this study. It has been shown earlier by Teräs et al. (*20*) that Ki values calculated from arterial plasma and arterialized (heating the hand) plasma samples are almost identical. The venous samples from our infants were not arterialized, but the patient was warmly wrapped during the study. We think, however, that venous whole-blood samples can be used instead of arterial samples in infant studies to minimize the volume of blood needed and to make the study more noninvasive.

In this study, the infant LCMRGlc values were higher at the age of 3–4 mo than during the neonatal period. This phenomenon reflects the normal maturation of the brain, especially the cortex, known to occur during the first months of life along the psychomotor development of the infant (*7,17,19*). Our values concur with the those reported earlier by Chugani et al. (*7*), although his report included only a few children under 1 yr of age.

SUVs provide a semiquantitative method to analyze PET data (*13,14*). This method has been used in studies of adults, especially in oncology. A good correlation between SUV and Ki values of Patlak analysis has been found in tumors (*21*). We found a good correlation between the cerebral SUV and LCMRGlc (r = 0.83) in infants. The SUV method has been shown to affect the blood glucose level in the analysis of FDG-PET studies (*22,23*). Postprandial blood glucose levels, however, in infants seem to be stable, as demonstrated in this study (5.9 ± 0.9 mmole/liter). So if no blood samples are available, the cerebral SUV values can be used as an alternative for estimating the cerebral glucose utilization and interindividual comparison in infants.

This study demonstrates that the input function in neonatal brain FDG studies can be obtained by combining the time-activity curve derived from ROIs of the left ventricle of the heart and the time-activity curve obtained from a few whole blood samples. We recommend a protocol including heart scaning for 5 min and two to three blood samples in the latter part of the study. At least one blood sample is needed at the end of the study to obtain the end-point of the time-activity curve. According to Patlak et al., local cerebral metabolic rates for glucose can be calculated for even the smallest pediatric patients by using such an input function in graphical analysis. When blood samples cannot be obtained, standardized uptake values can be used as an alternative for estimating the cerebral glucose uptake and for interindividual comparison in infants. By using these simplified methods, cerebral metabolism can be studied in many disorders during the neonatal period to gain further insight into the developing brain.

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