Methodologic Factors Affecting PET Measurements of Cerebral Glucose Metabolism

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Measurements of cerebral glucose utilization rates in similar populations of human subjects under similar conditions vary considerably because of methods used in data collection and analysis. Using data acquired in two patients, we evaluated the effects of time schedule of data collection, region of interest size, method of attenuation correction, and input function shape on $LCMR_{glu}$ determined by dynamic positron emission tomographic scanning and calculation of rate constants. These different strategies of data acquisition and analysis produced variations of 3 to 14% in calculated $LCMR_{glu}$. These factors, in conjunction with the well described effects of instrument resolution and sensitivity may account for data discrepancies in the literature.

J Nucl Med 27:1358–1361, 1986

In recent years, numerous laboratories have published data concerning positron emission tomographic (PET) measurements of cerebral glucose utilization using the tracer [^{18}F]2-fluoro-2-deoxyglucose (FDG). While the biologic modeling assumptions used have been similar, various technical factors involved in these experiments have differed. Results for calculated local cerebral metabolic rates of glucose ($LCMR_{glu}$) differ from laboratory to laboratory by 20 to 30% for identical brain regions of similar subject populations as summarized by Heiss et al. (*1*). In particular, $LCMR_{glu}$ values obtained in our laboratory were higher than values obtained elsewhere (*1*). While factors such as instrument resolution (*2*), angular and transverse sampling (*3*), and geometric-anatomic effects (*4*) have been discussed, methodologic issues involved in data collection and analysis have received less attention. Using data from two healthy control subjects, we evaluated the effect of the different techniques used by different groups on the derived local glucose metabolic rate magnitudes. These experiments provide a plausible explanation for differences in reported $LCMR_{glu}$ values.

Received Sept. 5, 1985; revision accepted Feb. 19, 1986.

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MATERIALS AND METHODS

The procedure for the measurement of $LCMR_{glu}$ at our institution involves the i.v. injection of 5–10 mCi of FDG as a 5–10 sec bolus with rapid sampling of arterialized venous blood (*5*). The Donner 280-crystal tomograph (resolution 8 mm full width at half maximum) is used to collect tomographic data from the brain in order to obtain brain time-activity curves for the calculation of rate constants for transport (k_1^* and k_2^*) and phosphorylation (k_3^*) of FDG. Since dynamic data are collected for only the initial 40 min after isotope injection, k_4^*, the rate constant for dephosphorylation of FDG, is not included in the analysis. PET data are collected at 5-sec intervals from 0–2 min, at 15-sec intervals from 2–5 min, at 60-sec intervals from 5–15 min, and at 300-sec intervals from 15–40 min. The effective slice thickness used is 10 mm. The statistical quality of the data thus obtained is dependent upon region size and duration of counting. For small volumes (~2.5 cc) the statistical uncertainty of the tomographic counts in the region is on the order of 10% for the 5-sec data files, and drops to 5 and 1% for the 15 sec and 60 sec files, respectively. For larger volumes (~12.5 cc) the uncertainties are ~5% for early counting times and <1% for later times.

Arterialized blood samples are collected from a vein of a warmed hand (*5*) approximately every 3 sec for the first 2 min, followed by progressively longer intervals for 60 min. Emission data are corrected for attenuation using transmission data obtained in each subject with an external germanium-68/gallium-68 positron source. Regions of interest (ROIs) are

drawn on emission images using a standard anatomic brain atlas of tomographic sections (*6*). The regions are drawn within the boundaries of cerebral cortex and outline areas of highest activity (Fig. 1A). A nonlinear iterative least squares fitting procedure (*7*) is then used to estimate the rate constants k_1^* through k_3^* as well as fit for vascular fraction (f_v) and the time-offset (t_o) between tracer arrival in the brain and at the peripheral sampling site. We use the equation

$$Q(t) = s[f_v A(t - t_o) + (1 - f_v)(h \times A)(t)],$$

where Q(t) represents the activity in the ROI, s is a factor which scales blood activity to tomographic activity, A is the vascular concentration of tracer, h is the impulse response of the system which is determined by the rate constants as described by Sokoloff et al. (*8*) and "x" represents the convolution operation. We have previously demonstrated that values of f_v and t_o can be fit accurately when short initial sampling times are used (*9*). The product of $k_1^* \times k_3^*/(k_2^* + k_3^*)$ and the plasma glucose concentration is then used to determine $LCMR_{glu}$ for each brain region (*5,8*). Recent reports from our laboratory (*10,11*) contain additional information concerning our methods of data acquisition and analysis.

In this study we utilized data acquired from two male subjects who were free of significant medical and neurological illnesses and were 61 and 64 yr old. Five manipulations of data were performed—four changes in residue data were made on the original patient data, and one set of simulated data was used to show the effect of modified input data. The baseline data were manipulated in the following manner.

1. Data for minutes 0–5 were summed into five 60-sec time intervals in order to simulate a slower time collection protocol.

2. Data were summed, as in Part 1, above, and, in addition, data for minutes 0–3 were discarded.

3. Attenuation correction was achieved by the use of a constant attenuation equal to that of water. The attenuation volume was assumed to be 4.5 mm outside the skull to compensate for the known increase in the attenuation from bone (*12*).

4. ROIs were made significantly larger than those described above (Fig. 1B). Results of these manipulations were compared with values of $LCMR_{glu}$ obtained in our usual fashion.

5. A residue function was generated using previously published (*5*) average rate constants ($k_1^* = 0.102$, $k_2^* = 0.130$, $k_3^* = 0.062$), together with a tomographically determined left ventricular blood-pool time-activity curve which was collected using a protocol similar to that used for brain dynamic data. This residue function was then used with both the same left ventricular input function and an input function from "arterialized" venous blood (obtained concurrently in the same patient as the left ventricular input function) with the same least squares fitting procedure to estimate the model parameters (*13*). Results of $LCMR_{glu}$ determined in this manner using the two input functions were compared.

Each manipulation 1–5 was performed independently, and the same fitting procedure was used, with the exception that f_v and t_o were not fit for procedures 1 and 2, but utilized assumed values derived from the Donner method fit. In Cases 1–4, values obtained represent $LCMR_{glu}$ for the mean of left and right entire cortex (Fig. 1), while the simulation (Case 5) utilized input data from only one patient.

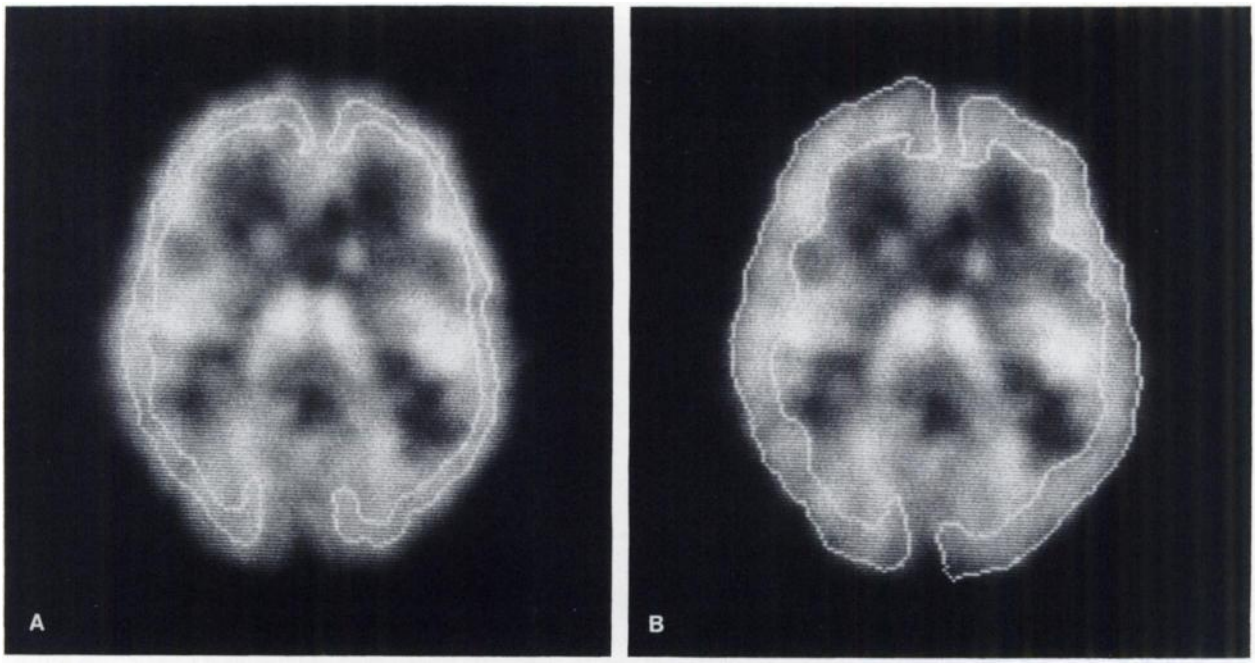

FIGURE 1
A: Right and left hemispheric cortical regions outlining areas of highest activity as normally used in our laboratory, with mean of 13.1 cc/region in this instance. B: Larger regions used in condition 4 as described in text, with mean of 29.6 cc/region

RESULTS AND DISCUSSION

Table 1 displays the effects of the various perturbations on the calculated $LCMR_{glu}$. All values for metabolic rates are estimated with a statistical uncertainty on the order of 1%. The use of temporal sampling at 1-min intervals produces a small diminution in metabolic rates, which is decreased further by discarding the first 3 min of data collection. While this technique has the advantage of eliminating the effect of the duration and size of the bolus injection, it underestimates the true metabolic rate by a small amount. As demonstrated by others (*8*), $LCMR_{glu}$ is a term which is quite stable regardless of the method used in its calculation. When time collection protocols are varied, effects on the actual rate constants are more significant, as has been elucidated by Mazoyer et al. (*9*). The use of slower time collection schedules also decreases the validity of the fit for t_o and f_v, forcing one to rely on assumed values. In addition, the model used for mathematic description of the data also has an important bearing on results obtained. A model which assumes that the activity value obtained for a given scanning time period represents the activity at the midpoint of that time period (the classic model), will lead to results that differ from those using an integral model which integrates activity over each time interval. Our simulations reported here use the classic model, and therefore the effects on determined metabolic rates which we found may result from biases due to the use of this model. The use of the classic as opposed to the integral model may result in differences of up to 10% in estimation of rate constants, and 3% in estimation of $LCMR_{glu}$ (*9*). Evaluation of these issues as well as the impact of different sampling strategies has recently been completed and allows one to quantitate the importance of variations in techniques comprising protocols used at present and proposed for the future (*9*).

The effect on $LCMR_{glu}$ produced by using a volume of constant attenuation is great, and will be further increased at brain levels with a high content of bone (such as the petrous ridge) or in patients with ventriculomegaly. We have not evaluated the effect of the chosen attenuation coefficient on the calculated metabolic rate, nor have we examined the effect of the shape or the size of the volume of constant attenuation.

The effect of region size is important, particularly when one considers the folded geometry of the cortical ribbon relative to the resolution of the tomograph. As region size increases, the activity sampled consists of more surrounding tissues, which, in the case of cortex, is the metabolically less active white matter, skull, and scalp. This produces underestimation of cortical metabolism. In addition, the use of nonanatomic ROIs (such as geometric shapes superimposed on cortex) can result in larger partial-volume effects which will also significantly lower metabolic rates.

Input function shape is also quite important when metabolic rates are calculated from dynamic PET data. Arterialized venous blood is an acceptable input function when used with the operational equation 5 for calculation of metabolic rates since this method utilizes the integral value of the function and is relatively insensitive to its shape. Determination of rate constants from fast dynamic data, however, requires a function which closely approximates the true brain input. Simulation 5 demonstrates that blurring the input function by using arterialized venous blood rather than a true arterial input will alter the value of the determined metabolic rate due to errors or differences in the determined rate constants.

It is particularly valuable to interpret the data obtained in our laboratory in light of the combined effects of these separate experiments. Laboratories using techniques 1 through 4 will derive results ~18 to 20% lower than ours. In addition, the use of arterial as opposed to arterialized blood with the dynamic PET method will lower results by an additional 14%. These factors are likely to account for the higher metabolic rates which are obtained with our rate constants.

We do not attempt to ascertain the accuracy of various methods here. Nevertheless, using our methods

TABLE 1
Rates of Cortical Glucose Utilization (Mean of Right and Left Entire Cortex in mg/100 g brain/min) Using Methodologies Described in Text*

		1	2	3	4	5
	Donner method	1-min time files	0–3 min discarded	Constant attenuation	Large regions	Arterialized input
$LCMR_{glu}$	3.51 (3.10, 3.91)	3.39 (2.94, 3.84)	3.33 (2.86, 3.79)	3.17 (2.74, 3.60)	3.32 (2.94, 3.69)	†
% Change		↓3.4	↓5.1	↓9.7	↓5.4	↑14

* Actual values for each patient given in ( ).

† For comparison between left ventricular and arterialized venous inputs, $LCMR_{glu}$ obtained with average rate constants was 3.29. Identical values were recovered when left ventricular input was fit with generated residue function. This is compared with higher value of 3.75 which was obtained using arterialized venous blood. This latter value is 14% higher than "true" value of 3.29.

of data collection in six healthy elderly subjects with a recently experimentally determined value for the lumped constant of 0.52 (*14*), we found a cortical $LCMR_{glu}$ of 8.13 mg/100 g/min (s.d. = 1.44) and a white matter $LCMR_{glu}$ of 2.96 mg/100 g/min (s.d. = 0.77). Assuming a 50–50 gray-white mixture (*15*) this yields a value of 5.54 mg/100 g/min, in good agreement with an average value of 5.38 mg/100 g/min found by others using the A-V extraction method and summarized by Phelps et al. (*5*).

The experimental issues of sampling time protocol, region size, attenuation correction method, and input function shape are interrelated. As these methodological aspects differ from one laboratory to another, differences in metabolic rates which may become quite large are expected. In addition, the nature of the model used will also affect experimental outcomes. It is clear that when one is comparing measurements of cerebral glucose utilization obtained in different laboratories, it is important to specifically note the experimental designs and methods of data collection and analysis.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Service of the United States Veterans Administration, by the Director, Office of Energy Research, Office of Health and Environmental Research of the United States Department of Energy under Contract No. DE-AC03-76SF00098, and by Public Health Service Grant Nos. 8605 and 8633 to R.H.H.

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