Fluorine-18-Fluorodeoxyglucose PET to Determine Regional Cerebral Glucose Utilization: A Re-examination

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The [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) method for quantitative measurement of regional cerebral glucose utilization (rCMRglc) was first developed about 16 yr ago for use with single-photon emission scanning (*1*) and shortly thereafter adapted for use with PET (*2*). The procedures for its implementation were accommodated to the state-of-the-art resources and equipment then available. Since then, there have been major technological advances in instrumentation and new insights developed from its use which make possible alternative strategies for determining rCMRglc with [^{18}F]FDG and PET (*3*). This historical evolution has led to some confusion in the field about how best to apply the method, and after 16 yr of experience and new developments, it is time to re-examine the state of the field. The aim of this review is to examine recent developments that bear on optimal implementation of the [^{18}F]FDG method and to recommend standard procedures for data acquisition and analysis that may help to reduce variability and improve reliability of the values for rCMRglc obtained with the method.

HISTORICAL BACKGROUND

The [^{18}F]FDG method was derived from the autoradiographic [^{14}C]deoxyglucose ([^{14}C]DG) method for measuring local cerebral glucose utilization in animals (*4*). Carbon-14-DG was specifically chosen as the tracer, not by chance or fortuitous circumstance, but because its already well-known biochemical properties facilitated the design and analysis of a kinetic model that described the brain-plasma exchange of [^{14}C]DG and its phosphorylation by hexokinase in relation to those of glucose and could be readily implemented for use with quantitative autoradiography. The advantage of [^{14}C]DG over labeled glucose as the tracer is that the primary and secondary products of its phosphorylation, unlike those of glucose, are trapped in the tissue and accumulate where they are formed for reasonably prolonged periods of time. Models representing biological events in vivo almost never do, and never can, fully account for all potentially relevant factors and conditions and are consequently imperfect. The experimental procedure of the [^{14}C]DG method was designed to minimize possible errors arising from limitations and/or imperfections of the model. The rationale for the design is made clear by examination of the originally reported operational equation of the method (*4*). There have been a variety of mathematical rearrangements or forms of this basic equation, but the original version illuminates the roles and contributions of the various factors that go into the computation better; it also segregates the least reliable and error-prone model-dependent components into terms that can be identified and minimized. Regional cerebral glucose utilization is calculated as:

$$rCMR_{glc} = \frac{C_i^*(T) - K_1^* \int_0^T C_p^*(t)\, e^{-(k_2^*+k_3^*)(T-t)}\, dt}{\frac{\lambda V_m^* K_m}{\Phi V_m K_m^*}\left(\int_0^T \frac{C_p^*(t)}{C_p}\, dt - \int_0^T \frac{C_p^*(t)}{C_p}\, e^{-(k_2^*+k_3^*)(T-t)}\, dt\right)}, \quad \text{Eq. 1}$$

where C_i^* represents total concentration of ^{14}C in a homogeneous tissue in brain; C_p^* and C_p are the [^{14}C]deoxyglucose and glucose concentrations in arterial plasma, respectively; T is the duration of the experimental period following the pulse of tracer and t is the variable time; K_1^* and k_2^* are the rate constants for carrier-mediated transport of [^{14}C]DG from plasma to tissue and back again, respectively; k_3^* is the rate constant for phosphorylation of [^{14}C]deoxyglucose by hexokinase; λ equals the ratio of the distribution spaces of deoxyglucose and glucose in the tissue; Φ equals the fraction of glucose which, once phosphorylated, continues down the glycolytic pathway; V_m and K_m represent the maximal velocity and Michaelis-Menten constant of hexokinase for glucose and V_m^* and K_m^* are the equivalent kinetic constants of hexokinase for 2-deoxyglucose.

The numerator of the equation equals the total tissue concentration of labeled products of [^{14}C]DG phosphorylation formed in the tissue during the experimental period; this is determined as the difference between total radioactivity measured by quantitative autoradiography (C_i^*) less a term that represents the estimated free, unmetabolized [^{14}C]DG still remaining in the tissue at the end of the experimental period. In order to minimize the free [^{14}C]DG in the tissue and also the effects of errors in its estimation on the value of the numerator, a long period of tracer circulation after a pulse of [^{14}C]DG was adopted; the total tissue ^{14}C concentration measured autoradiographically then represents mainly labeled products of [^{14}C]DG phosphorylation. In the denominator of the operational equation, the integrated specific activity (ratio of [^{14}C]DG to glucose concentrations) in the tissue precursor pool is computed by subtracting from the integrated specific activity measured in the plasma, a term that corrects for the lag in equilibration of the tissue precursor pool behind the plasma. The magnitude and, therefore, effect of this correction term is also minimized by the use of the long period of tracer circulation after the pulse. Because the total ^{14}C concentration in the tissue and the integrated plasma specific activity are increasing while the

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correction terms that are subtracted from them are decreasing with time after a pulse, the effects of errors in the estimates of these correction terms diminish with time.

What is frequently overlooked or ignored is that the model was specifically designed for a homogeneous tissue where rates of blood flow, glucose metabolism, transport of glucose and [^{14}C]DG between tissue and blood, etc. are uniform. The estimations of the terms that correct for the free [^{14}C]DG in the tissue and the lag of the tissue behind the plasma (i.e., the terms with the exponential functions in the numerator and denominator) are based on rate constants that are evaluated by fitting procedures that apply only to homogeneous tissues. All the errors due to heterogeneity are contained in these terms. As the magnitude of these correction terms decreases with time after the pulse, errors due to heterogeneity diminish, and the calculated value for $rCMR_{glc}$ approaches the true average of the heterogeneous tissue properly weighted for the relative masses of the tissues comprising the mixture.

As desirable as it may be to minimize errors due to inaccurate estimates of the terms containing the rate constants, the experimental period cannot be extended indefinitely, because loss of labeled products does eventually become significant. Although attempts have been made to correct for loss of labeled products, the effects of product loss increase with time, making the calculated rate of glucose utilization increasingly sensitive to correction accuracy. An experimental period of 45 min was recommended for use with the [^{14}C]DG method in rats because it was shown experimentally to be long enough to minimize errors due to inaccuracies in the rate constants and yet short enough to avoid significant effects of product loss. Similar considerations are just as appropriate for the use of [^{18}F]FDG with PET.

When the [^{18}F]FDG method was first adapted for use with PET, only single-ring, relatively inefficient and slow PET scanners were available, and several hours were required to scan the entire brain. After approximately 2 hr following the pulse of [^{18}F]FDG, total tissue radioactivity began to decline, indicating loss of labeled products (*2,5*). Inasmuch as it was not always possible to limit the duration of the experimental period to times before product loss became significant, an additional first order rate constant, k_4^*, was added to the kinetic model of the [^{14}C]DG method to correct for loss of labeled product (*1,2*). This modified model (4K Model) incorporated an arbitrary and doubtful assumption that k_4^* was constant throughout the experimental period; i.e., that k_4^* was a first-order rate constant and that a constant fraction of the primary and secondary products of [^{18}F]FDG phosphorylation, predominantly [^{18}F]fluorodeoxyglucose-6-phosphate ([^{18}F]FDG-6-P), was recycling directly back to the precursor pool per unit time. This was the simplest assumption to make at that time, but not necessarily the most correct.

With the slow single-ring scanners, the strategy for determining the rate constants was the same as that for the [^{14}C]DG method; they were estimated in a separate group of subjects by non-linear least squares fitting of the model equation to the measured time courses of total ^{18}F activity in the tissues determined by brain scanning for extended periods of time (initially 3 to 14 hr.). The rate constants, thus estimated from several individuals, were averaged and the average population-determined rate constants were subsequently used with each new subject's measured final [^{18}F]FDG concentration in brain regions of interest (ROIs) and the time course of arterial plasma specific activity to calculate $rCMR_{glc}$ with the operational equation.

INFLUENCE OF TECHNOLOGICAL DEVELOPMENTS IN PET SCANNERS

Recent generations of scanners are more efficient and contain multiple-rings that allow many planes to be scanned simultaneously in much shorter time intervals, e.g., 30–60 min or less. Although there has never been any direct, objective demonstration that significant product loss occurs during such short time intervals, the 4K Model which includes k_4^*, the rate constant for product loss, continues to be widely used with these shorter duration studies; the only apparent justification for its use is that it results in better nonlinear, least squares fits of the equations of the 4K Model to the time course of total tissue radioactivity.

The advent of faster scanning capabilities with PET has also made possible rapid dynamic scans and the ability to estimate the rate constants in each individual subject at the time of the study, which obviate the need to use population average rate constants. It was expected that estimation of the rate constants in each individual subject would improve the accuracy and allow studies to be completed in shorter time intervals. Dynamic scanning capabilities also opened the possibility to use other types of analyses that were not based on any specific compartmental models; these include the multiple-time graphical analysis technique, i.e., Patlak plots (*6,7*) and the spectral analytic technique (*8,9*). Despite the speed and advantages of dynamic scanning, it did not fully obviate the need to address the following three major issues that are relevant regardless of the model used and the method of analysis of the [^{18}F]FDG data:

1. Effects of kinetic heterogeneity in the tissues on the evaluation of the rate constants and the calculation of $rCMR_{glc}$.
2. The time after the pulse for effective equilibration between tissue precursor pools and the arterial plasma to be achieved.
3. The time after the pulse when product loss begins to have significant effects on calculated $rCMR_{glc}$.

These factors are all interrelated. For example, the presence of heterogeneity in a tissue region of interest leads to overestimation of product loss when k_4^* is included in the kinetic model. Lack of effective equilibration between plasma and tissue precursor pools may be misinterpreted as evidence for product loss in Patlak plots because both phenomena lead to downward curvature of Patlak plots. An understanding of these issues is essential for evaluating the soundness of the alternative methods for analysis of [^{18}F]FDG data. These and other issues related to the lumped constant and to accurate measurement of the input function, are discussed below.

TISSUE HETEROGENEITY

The quantitative autoradiographic technique was originally developed for use with the indicator diffusion method for measuring local cerebral blood flow (*10*), which, like the deoxyglucose and [^{18}F]FDG methods, applies only to homogeneous tissue compartments. Autoradiography provided a means not only for localization but for visualizing and focusing the densitometric measurements on regions of tissue that were relatively homogeneous with, in the case of the [^{14}C]deoxyglucose method, a spatial resolution of 200 μm. PET provides localization, but it samples voxels of tissue blindly, and the regions represented in the reconstructed images are usually kinetically heterogeneous with respect to blood flow, tracer transport, metabolism and even structure. This deficiency is further aggravated by the limited spatial resolution of even the most advanced of the current generation of PET scanners. ROIs

generally contain mixtures of gray and white matter, and the most desirable solution is to determine average values of glucose utilization rates or parameter estimates that are properly weighted for the relative masses of the constituents in the mixed tissue.

The two most currently used kinetic models are the three-rate-constant model (3K Model), which assumes effective trapping of labeled products of [^{18}F]FDG phosphorylation for the duration of the experimental period, and the four-rate-constant model (4K Model), with the rate constant k_4^* included to correct for an assumed constant fractional loss of labeled product throughout the experimental period. Both assume homogeneous tissue compartments. Mathematical analyses and simulation studies have shown, however, that when these homogeneous tissue kinetic models are applied to heterogeneous tissues, the apparent rate constants for efflux of [^{18}F]FDG from the tissue, k_2^*, and for phosphorylation of [^{18}F]FDG, k_3^*, initially decline with time and become constant and equal to their true mass-weighted average values only after the experimental periods have been extended long enough for the tissue pools to reach equilibrium or steady state with the arterial plasma (*11*). PET studies have confirmed the decline is the estimates of k_2^* and k_3^* with increasing data collection time, at least until 45 min (*12*) or 120 min (*13*) after injection of [^{18}F]FDG. The best estimates of the mass-weighted average kinetic model rate constants for the 3K Model were reported to be those determined over an experimental period beginning at the time of tracer injection and continuing for a minimum of 60 min and a maximum of 120 min (*14*). When the 4K Model was used, the decline in the apparent k_3^* was compensated for by an overestimate of the rate constant for dephosphorylation of [^{18}F]FDG-6-P, k_4^*. The estimates of k_4^* fell progressively with increased scanning interval lengths, as would be expected if high estimates of k_4^* result more from tissue heterogeneity than from loss of [^{18}F]FDG-6-P, at least up to 120 min following a pulse of [^{18}F]FDG (*13*).

Overestimation of the rate constants k_2^*, k_3^*, and k_4^*, which occurs before all tissues that comprise the mixed tissue equilibrate with the arterial plasma, then results in overestimation of the rate of glucose utilization due to two factors. First, overestimation of k_2^* and k_3^* results in underestimation of free [^{18}F]FDG remaining in the tissue at the time of measurement. Second, overestimation of the rate constant k_4^* leads to overestimation of the amount of product lost. Both factors lead to an overestimation of the amount of product formed during the experimental period and, consequently, overestimation of $rCMR_{glc}$.

A compartmental model that explicitly considers tissue heterogeneity has been developed (*11*). Its use has established that the time course of radioactivity in heterogeneous tissues can be accurately described without any need for an assumption of loss of metabolic product in the first 120 min following the pulse of [^{18}F]FDG (*13*). The use of this "tissue heterogeneity model" to compute rCMRglc requires experimental periods long enough for tissue precursor pools to equilibrate with arterial plasma (*11*).

EQUILIBRATION OF TISSUE PRECURSOR POOLS WITH ARTERIAL PLASMA

An alternative to compartmental models is the multiple-time, graphical analysis of Patlak et al. (*6,7*) which applies equally well to heterogeneous as to homogeneous tissues (*15*). This analysis is based on the premise that, following equilibration between tissue and plasma, the apparent distribution space for total ^{18}F in the tissue, when plotted against the normalized integrated tracer concentration in arterial plasma, will increase linearly as long as there is no product loss. The slope of the linear portion of this graph is directly proportional to $rCMR_{glc}$. It should be emphasized that either lack of equilibration between the precursor pool and the arterial plasma in any of the tissues in the ROI or loss of metabolic products may cause nonlinearity of the graph. Application of this technique to the determination of $rCMR_{glc}$ is limited by the difficulty of objectively determining the appropriate linear segment of the curve, i.e., the starting time of the segment after which all the tissue pools can be considered to be sufficiently equilibrated with the arterial plasma and an upper time limit before product loss occurs.

Various time intervals have been used in Patlak graphical analyses. Gjedde et al. (*16*) used visual inspection and concluded that the Patlak plot was approximately linear between 10 min (real time) after the pulse and 40 min, the time at which they discontinued scanning. Wienhard et al. (*17*) chose the interval between 18 and 40 min for the Patlak analysis. Lammertsma et al. (*3*) systematically examined the effects of assumed equilibration times, i.e., the start time of the analysis, on curvature in the Patlak plot and found downward curvature in the graph of normalized whole brain tissue radioactivity for all time intervals between 1–50 and 38–50 min following the pulse of [^{18}F]FDG. They interpreted this as evidence for loss of product, but did not consider the possibility that all the tissue pools in the brain may not yet have equilibrated with the arterial plasma even more than 30 min after tracer injection.

The commonly observed persistent declines in the fitted values of k_2^* and k_3^* with increasing time when the compartmental models were used suggested that there were some tissue precursor pools in the mixed tissue that equilibrated only slowly with arterial plasma. Lucignani et al. (*14*) obtained more definitive evidence of slowly equilibrating compartments by examining Patlak plots for various time intervals; they found that, in most ROIs, values of $rCMR_{glc}$ calculated from the Patlak plot decreased until the start time of the plot segment exceeded ~45 min. Calculated $rCMR_{glc}$ then either stabilized or increased slightly in the intervals that began by ~45 min and ended by ~100 min postinjection. Further slight declines in calculated rCMRglc, statistically significant only in white matter, were observed in intervals ending between ~105 and 120 min when the study was terminated. These results indicated that the early declines in $rCMR_{glc}$ determined from the Patlak plot were due to lack of equilibration between tissue pools and the arterial plasma in the ROI because declines in the slope due to loss of metabolic product would not be reversible.

GLUCOSE-6-PHOSPHATASE ACTIVITY, LOSS OF METABOLIC PRODUCTS AND k_4^*

Nonlinear least squares fits of the 4K Model equations to the time course of measured total tissue radioactivity have consistently provided estimates of the rate constant k_4^* significantly greater than zero. In the early days of slow PET scanning, the least squares estimation was performed on time courses of tissue activity measured from the time of injection of the [^{18}F]FDG until as long as 14 hr later when product loss was clearly observable (*2,5*). Positive estimates of k_4^* could then be associated with product loss from the tissue, but not necessarily first-order loss because, at least with deoxyglucose, the label is distributed not only in deoxyglucose-6-phosphate, but also in substantial amounts in other products (*18*). Furthermore, as discussed above, k_4^* values significantly greater than zero at shorter experimental times have been shown to be associated with tissue heterogeneity that has not been taken into account in

the kinetic model. In fact, simulation studies showed that when the 4K Model is applied to kinetically heterogeneous tissues, nonzero estimates of k_4^* are found even in the total absence of any product loss (*11*).

Loss of labeled metabolic products of [^{18}F]FDG phosphorylation from the brain has been arbitrarily assumed to be due to glucose-6-phosphatase activity (*19*), although this has never been proven. This assumption is based on claims that the deoxyglucose method was invalid because of significant product loss due to G-6-Pase activity in the brain (*20–25*). These claims have been refuted and shown to be based on methodological deficiencies, misinterpreted observations and failure to consider the effects of tissue heterogeneity (*26–29*). Measured G-6-Pase activity has, in fact, been found to be very low in brain tissue (*4,30,31*). Furthermore, its cellular localization is on the inner membrane of the cisterns of the endoplasmic reticulum where it is separated from the cytosol in which [^{18}F]FDG-6-P is formed. A specific translocase that transports hexose-6-phosphates across this membrane is absent in the brain (*32*), thus limiting their access to the action of G-6-Pase. There are other potential pathways and/or mechanisms for product loss, but their role in brain remains to be identified.

SPECTRAL ANALYSIS

Compartmental analyses that describe the kinetics of tracer uptake and metabolism are based on the a priori definition of a kinetic model and nonlinear least squares algorithms to estimate the parameters of the model from the time courses of radioactivity measured in the arterial plasma and tissue ROIs. In contrast, the spectral analysis technique of Cunningham and Jones (*8*) requires no specific model assumptions and applies to a wide range of tracers utilized with PET. This technique can identify the number of components and the kinetic parameters from the acquired data. Results obtained with the spectral analysis technique in [^{18}F]FDG studies in normal human subjects confirmed the presence of kinetic heterogeneity and slowly equilibrating components in the data and the absence of significant product loss in the first 120 min following tracer injection (*9*).

LUMPED CONSTANT

The lumped constant is the constant of proportionality between the steady-state rates of [^{18}F]FDG and glucose phosphorylation in the brain. It is the physical constant used to convert rates of [^{18}F]FDG-6-P accumulation to rates of glucose utilization. The lumped constant for deoxyglucose has been shown to be relatively stable over a wide range of plasma glucose concentrations in normal brain. It is influenced mainly by plasma and tissue glucose levels, falling progressively but very gradually with increasing plasma glucose levels all the way to severe hyperglycemia (*33*). When glucose supply is limiting, however, such as in hypoxemia, ischemia or extreme hypermetabolism, the lumped constant may increase considerably (*34*). In such cases, it is important to estimate the value of the lumped constant locally, possibly from measurements of the brain uptake of methylglucose (*16,35*). Less than extreme changes in glucose metabolism have only small effects on the lumped constant (*36*).

A direct measurement of the lumped constant for [^{18}F]FDG in humans under normal physiological conditions has been reported in only one study (*37*). The lumped constant has also been estimated by normalizing the whole brain rate of [^{18}F]FDG-6-P accumulation by the average whole brain rate of glucose utilization determined by the Kety-Schmidt technique (*2,38*). As discussed previously, however, estimates of the rate of [^{18}F]FDG-phosphorylation are dependent on a number of factors, such as time of scanning and the kinetic models, as well as rate constants used (*13*). Uncertainties in the estimated rate of [^{18}F]FDG-phosphorylation translate into uncertainties in lumped constant estimates. There have also been attempts to estimate the lumped constant that are based on kinetic modeling of the relationship between glucose and [^{18}F]FDG (*19*). These estimates are also subject to uncertainties in the model, particularly one that does include intracellular and extracellular compartments for the distribution of the label. It is then particularly hazardous to model the lumped constant when glucose supply is limiting because significant differences between intracellular and extracellular glucose concentration are most likely to occur under these conditions.

INPUT FUNCTION

The time courses of arterial plasma [^{18}F]FDG and glucose concentrations are required for quantitative determination of $rCMR_{glc}$. Instead of sampling arterial blood, many PET centers sample so-called arterialized venous blood. Because of dispersion and delay, venous sampling introduces errors in the input function that are greatest at early times after the pulse and cause errors in estimation of the rate constants, particularly K_1^* and k_2^*. Venous blood sampling can also lead to errors as high as 14% in calculated $rCMR_{glc}$ (*39*), but errors could be much greater if the deviation between arterial and venous concentrations of [^{18}F]FDG increase due to muscle activity that stimulates muscle glucose metabolism. Provided that the muscle remains at rest, errors due to venous blood sampling may be least if the Patlak plot is used to calculate $rCMR_{glc}$, because it requires only the integral of the arterial plasma [^{18}F]FDG concentration, which is relatively insensitive to delay and dispersion, and the arterial plasma [^{18}F]FDG concentration at late times when the arterial plasma concentration has become relatively constant.

The time course of arterial plasma glucose concentration is also required for quantification. Glucose levels tend to rise during the scanning period, possibly due to stress. When the single-scan method is used to determine $rCMR_{glc}$, the operational equation allows proper weighting of the glucose and [^{18}F]FDG levels throughout the experiment because the equation includes the time course of the specific activity in arterial plasma which can be determined in each individual plasma sample. The glucose levels early in the experimental period, therefore, are more heavily weighted due to the high levels of [^{18}F]FDG at the early times.

IMPORTANCE OF ABSOLUTE QUANTIFICATION

The [^{18}F]FDG method was developed with the hope that a protocol to detect alterations in local cerebral energy metabolism would contribute to the identification of regions in the human brain involved in normal functions or those affected in neurological and mental disorders. Because of the close relationship between local functional activity and energy metabolism, evoked metabolic responses promised to be a potent tool to localize the sites of specific functions within the brain. It has, to a considerable extent, achieved these goals. The method has contributed to the characterization of postnatal development and differentiation in the human brain; premortem localization of changes in Alzheimer's disease, the timing of these changes and the premortem distinction of Alzheimer's from other dementias and the localization of changes in Parkinsonism, Huntington's disease and epilepsy. It has proved useful to determine location and grade of brain tumors, distinguishing between tumor recurrence and radiation necrosis and identify-

ing regions of viable tissue after stroke. It has also provided insights into some mental disorders.

For many clinical PET studies, when only localization of metabolic defects is the main purpose of the study, e.g., localization of tumor or of tissue affected by stroke, quantification may be unnecessary (*40*). Nor may full quantification be required in activation studies where only localization is the issue of interest. For many research questions, however, determining location is only part of the information; magnitude of the change is also important, particularly because changes in $rCMR_{glc}$ and the degree of functional activity are quantitatively related (*31*). Furthermore, without full quantification, it is often impossible to make comparisons between individuals and groups. Relative change in $rCMR_{glc}$ normalized to a reference, such as the whole brain average or specific regions like white matter, is inadequate because the reference structure may also change or many regions of the brain may be similarly affected. For example, in slow wave sleep, $rCMR_{glc}$ is reduced proportionately almost everywhere in the brain (*41,42*); normalization would lead to the erroneous conclusion that $rCMR_{glc}$ is unchanged in slow-wave sleep. In studies in which absolute quantification is needed, efforts must be directed at reducing variability due to methodological factors, and standardized protocols that take into account the current state-of-the-art should be adopted.

RECOMMENDATIONS FOR FLUORINE-18-FDG STUDIES

To minimize the effects of tissue heterogeneity on calculated $rCMR_{glc}$, the scan period should be delayed as long as possible following the pulse of [^{18}F]FDG to allow maximal equilibration of the precursor pools in the tissue with the arterial plasma and yet short enough to avoid significant product loss. The optimal time has been shown to be between 60 and 120 min following the pulse (*14*). Scanning after a long delay following tracer injection without the need to reposition the subject is now practical given advances that allow transmission scans after emission scans. We recommend that the 3K Model be used because inclusion of a k_4^* with scan data acquired over the recommended time period results in overestimation of $rCMR_{glc}$. Rate constants should also be determined over as long a time interval as possible; this makes dynamic scans for the determination of rate constants impractical as a routine procedure. In normal subjects, rate constants determined over 120 min were found to be optimal (*14*). The only estimates of rate constants in patients with substantially altered rates of glucose metabolism currently available are those determined over much shorter time intervals. These estimates were made before the influence of heterogeneity on the rate constant estimates was fully understood and, therefore, potential errors in their estimation should be considered when they are used. It remains to be determined whether population average rate constants determined in normal subjects can be used in these patients by prolonging the time between tracer injection and brain scanning to lessen the effect of rate constants on calculated $rCMR_{glc}$.

The most practical use of dynamic scanning is in combination with the Patlak plot applied to data acquired late enough for all tissue precursor pools to be in approximate equilibrium with arterial plasma but before significant product loss occurs. In the studies of Lucignani et al. (*14*) the Patlak plot provided estimates of glucose utilization that were relatively constant with time when applied to data acquired from scans starting not earlier than 45 min after tracer injection; data acquisition could be continued up to 120 min after tracer injection without evidence of significant effects of product loss. As was the case when a single scan was delayed after injection of tracer, repositioning the patient may not be necessary if transmission scans are obtained immediately prior to or immediately after emission scanning.

The finding of relatively long periods of stability, i.e., intervals during which tissue precursor pools are in approximate equilibrium with arterial plasma but before significant product loss occurs, also makes the use of lower [^{18}F]FDG doses possible. The lower counting rates in the tissues are compensated for by the increased duration of the scanning interval.

PET scanning of $rCMR_{glc}$ with [^{18}F]FDG may provide better spatial resolution than blood flow scanning with ^{15}O-water, but it still fails to provide imaging of uniquely defined anatomical structures. Each ROI represents a number of structures. To establish some degree of uniformity across studies from various laboratories, it is recommended that, in view of its widespread availability, MRI be used to create each subject's own brain atlas from which to define ROIs more precisely on the basis of anatomical structure.

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