Measurement of Regional Cerebral Blood Flow With $^{133}$Xenon and a Multiple-Crystal Scintillation Camera

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Abstract: Measurement of Regional Cerebral Blood Flow With $^{133}$Xenon and a Multiple-Crystal Scintillation Camera

A method was devised to measure gray and white matter cerebral blood flow simultaneously in multiple regions of the brain using $^{133}$Xenon and a multiple-crystal scintillation camera. Following magnification cerebral arteriography, $^{133}$Xe was injected into the internal carotid artery and the washout of tracer was monitored with a scintillation camera which consists of 294 individually collimated NaI (TI) crystals. These data, obtained from each crystal overlying the brain, were processed by a weighted least-squares nonlinear regression technique. The blood flow rates of the rapid and slow compartments were calculated by the Kety-Schmidt formula along with 95% confidence limits for each measurement.

In four patients, local increases or decreases in regional cerebral flow were correlated with areas of pathology. In one patient with a cerebral arteriovenous malformation, regions of local shunting of tracer were identified. Application of a three-compartment analysis to these curves permitted estimation of the magnitude of shunting along with gray and white matter flow in the lesion. The increased discrimination provided by the multiple-crystal camera and the estimates of measurement accuracy obtained by this mathematical analysis may facilitate more precise localization of regional blood flow abnormalities in intracranial disease.

Additional Key Words: nonlinear regression analysis, gray and white matter perfusion arteriovenous malformation

Since 1961, a variety of attempts have been made to assess regional cerebral blood flow by external monitoring of the washout from the brain of a radioactively labeled inert gas. Using a single external detector, Lassen and Ingvar and co-workers were able to estimate average capillary blood flow in both gray and white matter of one cerebral hemisphere by applying a two-compartmental model to the analysis of a single washout curve of $^{86}$Kr or $^{133}$Xe after tracer injection into the internal carotid artery. More recently, attempts have been made to monitor cerebral perfusion in spatially discrete regions of the brain by use of multiple detectors or a scintillation camera.

Each of the reported methods, however, fails to utilize all of the information which might be obtained from such studies. Inherent in the washout curves obtained in these studies is information about the blood flow rates in anatomically localized, discrete compartments, gray and white matter, as well as information concerning how accurately these flow rates have been determined, i.e., confidence limits for the flow estimates. The techniques which use only one detector to obtain a washout curve for an entire hemisphere yield only an average flow rate for a large area of the brain. Published studies using multiple detectors or a gamma camera provide measurements in localized areas of the brain, but more information might be obtained from the data if a more complete data analysis was performed. Height-area or initial slope analysis can measure the average flow rate in the region under study but can give no specific values for gray and white matter. Compartmental analysis of the tracer curves by graphical peeloff techniques yields flow rates for white and gray matter but gives no confidence limits for these measurements. Confidence limits which provide a quantitative index of measurement accuracy are important in assessing the significance of flow differences found in various regions of the brain.

The present report describes a method for the quantification of regional cerebral gray and white matter blood flow rates in multiple areas of the brain at the time of arteriography. The approach is an
extension of previous work which developed methodology to evaluate regional myocardial perfusion in man10,11 and a form of nonlinear regression analysis for estimation of the parameters of multieponential renal $^{133}$Xe washout curves.17 The technique involves injecting $^{133}$Xe into the internal carotid artery and the external monitoring of tracer removal from a cerebral hemisphere by means of a multiple-crystal scintillation camera and a multichannel collimator. The data are analyzed by a weighted least-squares technique which determines the rate constants and zero-time intercepts as well as the confidence limits of the washout curves from multiple areas of the brain. Local gray and white matter perfusion rates are calculated by the Kety-Schmidt formula, and the pattern of regional cerebral flows so obtained is compared to each patient's cerebral arteriogram. Results obtained by this procedure in four patients who underwent cerebral arteriography are presented to illustrate the method.

**Methods**

**ARTERIOGRAPHY**

Cerebral arteriography was performed for a variety of clinical indications by either direct carotid puncture or selective catheterization from the femoral artery. Patients were sedated with meperidine and diazepam. A catheter was passed into the right or left internal carotid artery either directly or retrograde from the femoral artery for injection of contrast material. In addition to standard anteroposterior and lateral films, magnification cerebral arteriograms also were taken using an $x$-ray tube with a 0.2 mm focal spot. Upon completion of arteriography the patient was wheeled to the radioisotope facility for blood flow studies which were performed eight to ten minutes later. Informed written consent was obtained from all patients for the administration of radioxenon according to a protocol approved by the Human Investigation and Joint Radioisotope Committees of the Columbia-Presbyterian Medical Center (New York, New York).

**TRACER ADMINISTRATION**

The patient's head was positioned in contact with the detector of the multiple-crystal camera so that the sagittal plane was parallel to the surface of the collimator. Radioactive point-source landmarks were placed at the outer canthus of the eye, the external auditory meatus and the vertex; after their positions were recorded and stored on magnetic tape they were removed. A sterile aphyrogenic solution of $^{133}$Xe dissolved in 0.9% saline and containing 15 to 25 mCi was aspirated into a syringe from which all air had been displaced by saline rinsing. The syringe was then attached to a three-way stopcock at the free end of the intracarotid catheter and the radioactive solution was flushed through by a rapid bolus injection of saline. The catheter, left in situ during the 15 minutes of data recording, was periodically flushed with saline to prevent clotting.

**DETECTION OF RADIOACTIVITY**

The 81 kev $\gamma$-radiation, emitted by $^{133}$Xe as it diffused rapidly into brain tissue and was washed out as a function of nonradioactive cerebral capillary blood flow, was monitored by means of a multiple-crystal scintillation camera (Baird-Atomic Digital Autofluoroscope, Model 5600). This instrument's detector is composed of 294 individual NaI(Tl) crystals arranged in a matrix of 14 rows and 21 columns. Each crystal, measuring $1.1 \times 1.1 \times 3.5$ cm, is individually shielded and optically connected to a photomultiplier tube which defines the position of incoming radiation in an X-Y coordinate scheme. Each pulse resulting from interaction of incident radiation was subjected to pulse-height analysis (the window used for these studies was 65 to 250 keV); anticoincidence circuits eliminated pulses due to random coincidence, Compton scatter, or optical cross talk. Pulses meeting these criteria were accumulated in one of two core memories contained in the machine. At the end of a preselected time interval (six seconds in the present studies), the data were recorded on magnetic tape for permanent storage.

Machine performance was tested before each study by repetitive countings of a standard $^{60}$Co pool. The counts recorded in successive counting intervals were compared with the Poisson distribution by Pearson's chi-square test. This test consists of determining the number of crystals which showed a counting variation greater than the 95% value for the chi-square. Normally 12 to 18 exceeded this value (the expected value is 14.7), with the individual crystals varying randomly from one test to the next.

**SCINTILLATION CAMERA CHARACTERISTICS**

Two of the most important considerations in using a gamma camera for dynamic radionuclide studies are instrument dead-time and the problems in spatial resolution caused by counts arising from regions adjacent to the region viewed by an individual scintillation crystal. The dead-time of the system is identified as the minimum time interval between two photon interactions in the detector that will allow the system to resolve both events. The dead-time of the present instrument was as assessed by using $^{60}$Co point sources to determine the effect on the count rate recorded by a single crystal of increasing the total count rate recorded by the entire detecting instrument to very high levels. Repeated measurements yielded an average dead-time of 22 $\mu$sec for the instrument used in these studies. Because the counts observed in recording intervals in which the total counting rate exceeded 2,000 cps were significantly reduced by the dead-time, a correction was introduced to estimate the true count rate (vide infra).

**COLLIMATION**

A 1 1/2-inch multichannel collimator was used for the studies. The effective resolution of the multiple-crystal scintillation camera is determined by the thickness of the collimator and the distance of the collimator face from the radioactive source.18 Static studies were performed with the multiple-crystal camera used in these studies by placing a bar source of $^{133}$Xe under one column of crystals in the detector and observing the number of counts recorded in adjacent columns. Count overlap, the ratio of counts in adjacent rows to counts in the primary row, was insignificant (< 3%) at distances under 5 cm and rose to 16% at 8 cm. However, when similar studies were performed with the $^{133}$Xe source immersed in water to simulate a situation in which tissue Compton scatter might be present, the count overlap was...
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20% at a 2-cm distance.* These observations suggest that measurements of regional cerebral blood flow from gray matter will be spatially well resolved, while measurements from white matter at greater depths will show an appreciable degree of regional smearing.

DATA PROCESSING

The primary data recorded on magnetic tape were counts detected in six-second intervals from each of 294 separate crystals. The tapes were read at the Columbia University Computer Center on an IBM 360/91 computer. The counts recorded by each crystal were first corrected for the differing efficiencies of the multiple crystals. (The correction to be applied was determined by repetitive counting of a uniform 60Co pool.) The counts from each crystal then were corrected for the dead-time of the instrument by standard means:

\[
\text{counts}_i = \frac{\text{counts}_{o,i}}{1 - \left(\frac{\tau}{t}\right)}
\]

where \(\text{counts}_i\) is the actual counts reaching detector \(i\), \(\text{counts}_{o,i}\) is the observed counts from detector \(i\), \(\tau\) is the dead-time of the instrument, and \(t\) is the sampling time. After the dead-time corrections had been applied for every time interval of the study, each crystal was analyzed to determine its peak counting rate. Crystals with peak counting rates less than 15% of the hottest crystal were excluded from further analysis. The data from each crystal were then normalized to a peak counting rate of 1,000 and punched out on cards with identification information. In addition, a printout of the positions of the radioactive markers and a printout of peak counting rates of all crystals were produced. In these and other printouts, the data obtained from each crystal were located in a position corresponding to the position of the crystal in the 21 \(\times\) 14 array of the gamma camera.

The processed data then were used as input to a non-linear regression program previously reported. Each data point was weighted for its relative accuracy, assuming the counts followed the Poisson distribution. An iterative technique was used to fit the sum of two exponentials to the data from each crystal. The program starts with initial parameter "guesses" corresponding to normal flow rates reported for man.* Convergence upon a final fit was rapid, requiring eight to ten iterations on an average. Fitting the data obtained from 100 crystals in one study required approximately three minutes of CPU time on an IBM 360/91. Blood flows for both compartments (gray and white matter) for each crystal were calculated by the Kety-Schmidt formula* along with their 95% confidence limits.* In addition, plots of data (counts per peak counts versus time) from individual crystals and the parameters of the equation fit to the data were produced on semilogarithmic paper using a computer subroutine and Hewlett Packard plotter.

Mathematical Treatment

The mathematical model proposed by Ingvar and Lassen to fit washout curves of radioactive inert gases from cerebral tissue is a parallel flow compartmental model with compartment I representing gray matter and compartment II representing white matter.* Thus, the data are expected to be fitted by the sum of two exponentials, \(A_i e^{-k_{i1} t} + A_2 e^{-k_{i2} t}\), where the \(k_i\)'s reflect the clearance constants of tracer removal and the \(A_i\) the relative proportion of tracer delivered to the compartment. Nutrient cerebral blood flow is calculated:

\[
\text{Flow}_i = k_1 \times \lambda_i
\]

where \(\lambda_i\) is the blood:cerebral tissue partition coefficient for \(^{133}\)Xe in compartment \(i\).

In order to test the assumption that the washout curves were biexponential, the data from each crystal on three patients were successively fit by one, two and three exponentials. The best fit was assessed by an F-test on the weighted residual error as:

\[
F = \frac{(Q_i, - Q_i) / (n_p - n_p_i)}{Q_i / (n_x - n_p)}
\]

where \(n_p\) is the number of parameters for fit \(i\), \(n_x\) is the number of data points, and \(Q_i\) is the residual error of the \(i\)-th fit. The F-test was used in each case to judge whether adding an exponential term significantly reduced the error associated with fitting the data. In every case the two-exponential fit was significantly better than the one-exponential fit at the 95% level, while the three-exponential fit never significantly reduced the error.

Confidence limits calculated in this way assess the reliability of the flow measurement obtained by an individual crystal. Previous workers who have attempted to provide confidence limits for blood flow values by means of serial studies in the same patient* provide only estimates of the average reliability of the technique. Attempts to assess accuracy of measurement from selected portions of the washout curve* give only rough estimates of the confidence limits for a flow measurement.
From the parameters of the biexponential fit of the data recorded by each crystal, a mean flow also was calculated as:

$$\frac{(A_1 + A_2)}{(A_1 + A_2)} = \frac{\text{Flow}_1}{\text{Flow}_2}$$

This approach to an average flow is similar to height-area analysis in that $$(A_1 + A_2)$$ represents the initial height and $$(A_1 + A_2)$$ is the area under the washout curve scaled by the $A_i$'s for each compartment. The difference is that the height and area are computed from the fitted parameters and are therefore model-dependent, whereas in traditional height-area analysis these quantities are computed numerically and are model-free.

In several patients regional shunting of 133Xe was detected in areas of the brain corresponding to the sites of arteriovenous malformations. 133Xe washout curves from the crystals overlaying the malformations were analyzed as the sum of three exponentials with the first exponential corresponding to the shunted isotope. The relative amount of shunt flow viewed by each crystal then was calculated from the zero-time intercepts as $A_3/(A_1 + A_2 + A_3) \times 100$. In addition, white and gray matter blood flows were calculated compartment washout curves, the area of the shunting by each crystal was proportional to the number of crystals with these characteristics and the extent of shunting in each region from the zero-time intercepts obtained by analysis of three term curves.*

### Correlation With Cerebral Angiography

As noted above, prior to each study radioactive markers were placed over the external auditory meatus, the outer canthus of the eye and the vertex, and their positions were recorded on magnetic tape. Upon completion of the study computer printouts of regional perfusion data were magnified and aligned with the ipsilateral cerebral arteriogram of the patient using these three landmarks, and the regional perfusion data were correlated with vascular anatomy by printing them onto the arteriogram or a tracing of the arteriogram.

Observations made in four patients are presented in order to illustrate information that can be obtained.

### Results

Figures 1 and 2 contain data from the cerebral blood flow study of a 27-year-old woman who was evaluated because of psychomotor seizures. The magnification of the cerebral arteriogram was normal. A washout curve recorded by an individual crystal from the study is illustrated in figure 1. Both the primary data and the biexponential fitted line are shown. Although a peak count rate of 30,000 counts per minute was observed, considerable scatter was noted in points at the tail of the curve, which indicates that the relative accuracy of the measurement is smaller toward the tail than at the initial portion of the curve. As outlined previously (Methods), the data were weighted by the reciprocal of the variance of the expected data point (assuming that the errors followed a Poisson distribution) in order to obtain meaningful parameter estimates from the entire tracer washout curve. Compartment I flow (gray matter) was 81 ml/100 gm per minute and compartment II flow (white matter) was 17 ml/100 gm per minute. The scatter in the data about the fitted line permitted estimation of the confidence limits for the parameters, i.e., a measure of measurement accuracy (9 ml/100 gm per minute for compartment I and 2 ml/100 gm per minute for compartment II of this curve). Figure 2a shows serial scintiphotographs of 133Xe distribution in the brain. Figure 2b shows the cerebral perfusion pattern obtained when the regional compartment I (gray matter) flow rates were superimposed on the patient's cerebral arteriogram. Figure 2c shows the corresponding pattern obtained using the compartment II (white matter) flow rates. Compartment I flow rates (from 126 crystals) averaged 71.7 ± 8.3 ml/100 gm per minute in this patient; compartment II flow rates averaged 18.2 ± 2.9 ml/100 gm per minute. These are comparable to normal values for gray and white matter reported by other workers. The coefficient of variation of local perfusion rates was 12% for compartment I and 15% for compartment II in this study. The coefficients of variation for the measurements (accuracy terms) were 5% and 7%, respectively.

Figures 3a, b and c show three single crystal washout curves obtained from a 133Xe study of a 27-year-old woman with a large arteriovenous malformation in the occipital region, which was supplied by branches of the left posterior, middle and anterior cerebral arteries. The washout curve of crystal #138 (fig. 3a), which viewed uninvolved brain tissue, was fitted best by a biexponential curve. There was no evidence of shunting. Compartment I flow was 64, and compartment II flow was 16 ml/100 gm per minute. In contrast, crystals #92 (fig. 3b) and #93 (fig. 3c), which overlay the arteriovenous malformation, recorded tracer curves which revealed an initial shunt slope. These curves were analyzed as the sum of three exponentials. The percent of shunting was 20.9% and 53.4% in the two crystals, respectively. The gray and white matter flow rates calculated from $k_1$ and $k_2$ of these triexponential curves were similar to those measured in gray and white matter of uninvolved brain (fig. 3a). These probably reflect tracer washout.

*The accuracy of the information obtained from zero-time intercepts is less than that obtained from the rate constants of tracer clearance. While the intercepts are proportional to the relative amount of tracer (and by inference the fraction of blood flow) distributed to each compartment, they also are proportional to the efficiencies with which tracer in each compartment is viewed externally. Thus, if the efficiencies with which compartments are viewed are very different, inaccurate estimates may be obtained for the extent of shunting even though the presence or absence of shunting can be detected. If an erroneously slow injection of tracer produces an initial plateau or a rounding of the initial portion of the curve, the zero-time intercepts is less than that obtained from the rate constants of tracer clearance.
The $^{133}$Xe washout curve recorded by a single scintillation crystal. The scatter of observed counts is greater at the tail of the curve. Compartment I (gray matter) flow was 80.2 ml/100 gm per minute; compartment II (white matter) flow was 16.8 ml/100 gm per minute. Mean flow in the region viewed by this crystal was 40.8 ml/100 gm per minute.

FIGURE 2a

Shows sequential scintiphotographs of $^{133}$Xe as it arrived and washed out from the left cerebral hemisphere.
The pattern of local cerebral gray matter flow rates has been superimposed on the normal cerebral arteriogram of patient R.F.

The pattern of local cerebral white matter flow rates has been superimposed on the same arteriogram.
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from normal brain tissue within and/or overlying the malformation. Figure 4 shows the cerebral arteriogram and perfusion pattern obtained from a study of this patient prior to percutaneous embolization of the malformation.

Regional cerebral blood flow measurements may be useful in the diagnosis of brain tumors\(^{22-24}\) and may facilitate understanding of some of the pathophysiological processes associated with them. Figure 5 shows the cerebral arteriogram and the compartment I perfusion pattern obtained from the study of a 31-year-old man with a large temporal lobe glioblastoma. The patient, who had suffered from psychomotor seizures for eight years, had an unremarkable physical and neurological examination except for a right superior quadrantanopia. Compartment I blood flow rates in the eight crystals overlying the tumor averaged \(78.4 \pm 6.2\) ml/100 gm per minute, whereas the compartment I blood flow rates in the remaining brain tissue averaged \(65.7 \pm 10.5\) ml/100 gm per minute. The increased tissue blood flow in the tumor was statistically significant (\(P < 0.01\)). The compartment II flow rates recorded by crystals over the tumor averaged \(23.5 \pm 2.6\) ml/100 gm per minute, a value not significantly above that of the remaining brain tissue, \(19.1 \pm 3.7\) ml/100 gm per minute.

The study depicted in figure 6 shows the cerebral perfusion pattern obtained in a 52-year-old patient eight days after an occlusion of the middle cerebral artery. Compartment I flow rates were significantly reduced to \(34\) ml/100 gm per minute in the area supplied by the occluded artery and averaged \(47\) ml/100 gm per minute for the remainder of the cerebral hemisphere, a significant difference (\(P < 0.001\)). Although the compartment I flow rates in this patient showed a total variation of 30%, the variation in the measurements was 8%. In the area of diffusely reduced flow, two crystals showed perfusion rates of \(44\) and \(46\) ml/100 gm per minute. Laminagrams taken of the vasculature in this region showed an area of increased vasculature typical of "luxury perfusion" (fig. 7).\(^{25,26}\)

**Discussion**

The present method for studying regional cerebral blood flow in man is an attempt to extract the maximum amount of information about the cerebral circulation which can be obtained using inert gas tracer techniques. This is accomplished by: (a) selective magnification cerebral arteriography to define anatomical features and to fix their geometry, (b) the use of a multiple-crystal scintillation camera to localize blood flow to small, well-resolved regions, and (c) computer weighted least-squares analysis of individual crystal washouts to obtain "best" flow estimates of gray and white matter perfusion and confidence limits for each observation.

The advantages of this technique are derived from the equipment used and the extent of the information obtained by fitting the parameters of a model by a least-squares procedure rather than by alternative forms of analysis.
\[ A_0 = 0.208 \]
\[ k_0 = 28.673 \]
\[ A_1 = 0.651 \]
\[ k_1 = 0.776 \]
\[ A_2 = 0.139 \]
\[ k_2 = 0.102 \]

\[ % \text{SHUNT} = \frac{A_0}{A_0 + A_1 + A_2} \times 100 \times 20.9 \% \]

\[ FLOW_1 = 62.0 \text{ ml/min/100 gm} \]
\[ k_1 = 0.776 \]

\[ FLOW_2 = 15.3 \text{ ml/min/100 gm} \]
\[ k_2 = 0.102 \]

\[ % \text{SHUNT} = \frac{A_0}{A_0 + A_1 + A_2} \times 100 \times 20.9 \% \]

\[ A_0 = 0.533 \]
\[ k_0 = 26.209 \]
\[ A_1 = 0.372 \]
\[ k_1 = 0.732 \]
\[ A_2 = 0.094 \]
\[ k_2 = 0.126 \]

\[ % \text{SHUNT} = \frac{A_0}{A_0 + A_1 + A_2} \times 100 \times 53.4 \% \]

\[ FLOW_1 = 58.5 \text{ ml/min/100 gm} \]
\[ k_1 = 0.732 \]

\[ FLOW_2 = 18.9 \text{ ml/min/100 gm} \]
\[ k_2 = 0.126 \]

\[ % \text{SHUNT} = \frac{A_0}{A_0 + A_1 + A_2} \times 100 \times 53.4 \% \]

\[ 18^\circ \text{Xe washout curves from crystals overlying the arteriovenous malformation of the patient are shown. Statistically, these tracer washout curves were fitted best by three exponential curves. The percentage of tracer shunted through the malfunction was calculated from the zero-time intercepts of the three exponentials. Gray and white matter flow rates were calculated from } k_1 \text{ and } k_2 \text{ of these curves.} \]
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The gray matter flow rates calculated from the biexponential curves are superimposed on the arteriogram of the patient with an arteriovenous malformation. The circles represent crystals from which three exponential curves were recorded (e.g., figs. 3b and 3c).

MULTIPLE-CRYSTAL SCINTILLATION CAMERA

Multiple-crystal scintillation cameras offer several advantages over single-crystal cameras for dynamic studies of radioactive tracer clearance from multiple regions of the brain. Single-crystal cameras suffer not only from nonuniformity of response in different regions of the crystal, but also from mispositioning of radioactive events at high count rates which may induce spatial distortion. This distortion has been reported to be a complex nonlinear process which varies with count rate, therefore, attempting to correct for these effects in rapid dynamic studies presents difficulties. Multiple-crystal cameras avoid these problems by employing many individual crystals connected by light pipes to photomultipliers arranged in an X-Y coordinate system to insure correct positioning of the radioactive events.

Finally, the maximum number of counts which can be recorded by a single-crystal camera is limited primarily by the characteristics of the NaI (TI) crystal, whereas the maximum number of counts which can be recorded by a multiple-crystal camera is limited by the speed at which the electronics can process events arising from separate crystals. Recent improvements in the electronics of the multiple-crystal scintillation camera have resulted in an instrument which can record 200,000 cps after injections of 99m technetium intravenously. Such increases in total count rate should improve the accuracy of measurements of tracer clearance from small areas of the brain.

COLLIMATION

The area viewed by each element of a multiple-crystal matrix or by one region of a single crystal is determined by the collimator used. The importance of collimation is twofold: (1) it determines the extent of the area viewed and, thus, the ability to detect local flow abnormalities, and (2) it influences the accuracy of flow estimates which can be obtained in the region viewed by controlling the degree to which counts arising from adjoining regions with different blood flow rates are detected by the primary crystal. If a significant number of counts within the field of view of a single crystal (or one area of light defined by computer in a large single crystal) arise from an adjacent area with a different perfusion rate, significant errors can be introduced into measurements of tracer washout from the regions of the tissue under study. An overlap of counts of 20% between regions with different 133Xe
In the region of the brain tumor (circled), local gray matter blood flow rates were significantly increased.

Regional cerebral blood flow rates were significantly reduced distal to the occluded middle cerebral artery.
The laminogram of the region distal to the occluded middle cerebral artery (compare with fig. 6) revealed an area of increased vasculature (upper left). Local gray matter flow rates in this region (43 and 44 ml/100 gm per minute) were higher than in surrounding brain tissue.

Clearance rates can induce directional changes and errors of up to 10% in the calculated rate constants. Static studies of the point spread function of $^{133}$Xe performed with the present collimator suggest that error due to overlap of field of view or due to tissue Compton scatter is negligible at the brain surface (gray matter) but probably is significant in more central regions of the cerebral hemisphere under study (white matter). Use of a more sensitive instrument with $2^\circ$ collimation and of $^{133}$Xe in the future may obviate these problems.

**Mathematical Analysis**

Several forms of analysis have been used in the study of regional cerebral blood flow, thus creating confusion as to the best method of procedure to use in these studies. The different methods will be discussed in terms of their theoretical and practical advantages and their limitations with respect to the form of analysis used in the present studies.

The stochastic or model-free approach has been advocated by Zierler to calculate blood flow from tracer data obtained by external monitoring; this approach has the advantage of not assuming that the washout curve has a particular form. The mean transit time $t$ is the area under the washout curve from time zero to time infinity divided by the peak height of the curve, i.e., $A/H$; the average blood flow per 100 gm of tissue viewed is calculated as $100 \times \lambda/t$, where $\lambda$ is the average blood:tissue partition coefficient. The area $A$ may be computed numerically, which means that the data need not be fit to a given mathematical model.

In practice, however, this approach has several inherent difficulties. The washout curve cannot be observed to time infinity; this necessitates either: (1) that the curve must be extrapolated beyond the observation time, e.g., monoexponential extrapolation, or (2) that an approximation must be used, such as height-area analysis for ten minutes of the curve. The latter approach systemically overestimates blood flow while monoexponential extrapolation of the curve assumes a given function for the washout curve and, therefore, much of the model-free appeal of the approach is lost. In addition, an average $\lambda$ must be assumed which depends upon the relative amounts of white and gray matter viewed; this cannot be determined a priori. Another problem is encountered when poor injection techniques cause the tracer not to enter as a bolus and the washout curve has an initial plateau. In this case the washout curve exhibits an initial rounded portion with a prolonged period before the washout of tracer begins. In order to use the peak height in height-area analysis it must be assumed that the entire dose instantaneously equilibrates with brain
tissues viewed by the detector so that peak height of the tracer washout curve externally measures the entire dose. If there is an initial plateau, the peak height underestimates the dose and thus underestimates the flow. Finally, height-area analysis yields only an estimate of mean blood flow and, therefore, does not allow for determination of changes in flow which may occur separately in gray or white matter.

Analysis of the initial slope of the cerebral washout curves also has been used as a measure of average blood flow in the brain.\textsuperscript{9-11, 28} Theoretical studies have indicated, however, that mean flows calculated from the initial slope of inert gas curves equal true mean flow only when the system under study is loaded with tracer to a uniform initial concentration.\textsuperscript{5-21} In the case of a bolus injection, this condition is not met and the initial slope yields a number which is intermediate between the fastest and slowest flow components. If the two compartmental model proposed by Ingvar and Lassen for the brain is correct, the initial slope is just \((A_1 k_1 + A_2 k_2) / (A_1 + A_2)\). The intercepts in this case are proportional to the total flow delivered to each compartment rather than proportional to the volumes of each compartment, which would be the case if the tissue had been loaded with tracer until equal initial concentrations in both compartments were attained. In addition, as mentioned previously, the intercepts also are proportional to the efficiency with which each compartment is viewed when the tracer removal is monitored externally. Thus, it may be entirely fortuitous if initial slope analysis yields mean flow. (This criticism does not mean to imply, however, that initial slope analysis is not useful in assessing such phenomenon as tissue shunts, or relative mean perfusion rates in different brain areas, but, the quantitative significance of the data obtained is limited.)

Compartmental analysis of the local cerebral washout curves of \(^{133}\text{Xe}\) was the approach used in the present study (e.g., figs. 1 and 3). Implicit in compartmental analysis is the assumption that there exists in the brain two homogeneous flow compartments (gray and white matter) which are viewed by each crystal over the brain and that diffusion equilibrium exists for both tissues.\textsuperscript{3} These assumptions are obviously a simplification of the real situation in which there may be a range of blood flows within the white and gray matter viewed by each crystal. However, the flow estimates obtained are average flows for each of the compartments in the area of brain viewed by each crystal (fig. 2). The importance of compartmental analysis lies in separating the components of gray and white matter blood flow in each region; these may be very different (e.g., figs. 2a or 2b). Any non-homogeneity of flow within one of the compartments is reflected in the broader confidence limits for the individual flow estimate obtained. In addition, a mean flow rate for the area viewed by each crystal may be calculated from the parameters of the fitted curve which were obtained by compartmental analysis (e.g., fig. 1). This approach to obtaining a mean flow has the advantage of using the estimated parameters to calculate both the area to time infinity and the initial height of the curve; thus, some of the practical difficulties with numerical computation of these quantities commonly encountered in height-area analysis are avoided.

Compartmental analysis of each tracer curve in these studies was performed by a nonlinear least-squares regression analysis which fit a biexponential equation to the entire washout curve.\textsuperscript{9} The alternative approach of performing compartmental analysis by graphical peeloff techniques is deficient in several respects. These techniques are subjective, and they assume all data points have equal variance. In the case of cerebral washout curves the relative accuracy of the parameter estimates is much smaller for the tail end of the curve than the beginning because there is greater scatter in the data at the tail of the curve (figs. 1 and 3). Furthermore, the assumption that all of the data are equally accurate leads to inaccurate parameter estimates. Finally, graphical techniques for analysis of multieponential tracer curves cannot provide confidence limits for individual measurements. Thus, the accuracy of individual determinations is unknown, which in turn makes it difficult to attach significance to the regional blood flow differences found in an individual patient.

The advantage of the technique described in this report is that it provides parameter estimates which are best, minimum variance estimates, by simultaneously treating the entire curve and weighting each point by its relative accuracy. In addition, the ability to assign confidence limits to the flow estimates provides a criterion by which one can assess whether differences in flow between individual regions are real or result from an inaccurate measurement, i.e., if the 95% confidence limits for two crystals do not intersect, then the probability is 95% that the flows are different. This ability provides a powerful tool for evaluating regional cerebral blood flow changes due to disease.

The ability to obtain confidence limits for individual measurements is useful in differentiating biological heterogeneity of cerebral blood flow rates from measurement variation. The total observed variation of the blood flow rates is represented by the variance of the calculated local flow rates, which includes both the true biological heterogeneity of flow and measurement inaccuracy. If the confidence limits for the observed local blood flow rates, calculated from the observed variance of flow rates, significantly exceed the measurement confidence limits, calculated from the scatter in the data, true heterogeneity of cerebral blood flow exists. Thus, this technique may provide an approach to the problem of quantitatively assessing true heterogeneity of cerebral blood flow.
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Measurement of Regional Cerebral Blood Flow With $^{133}$Xenon and a Multiple-Crystal Scintillation Camera

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