Measurement of Total Cerebral Blood Flow in the Monkey by External Monitoring of Cesium-131

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ABSTRACT

A modification of the $^{42}$K fractionation technique has been developed which permits rapid, repeated measurement of cerebral blood flow by external isotope monitoring without jugular or carotid puncture. $^{131}$Cs, an isotope with distribution characteristics similar to those of $^{42}$K, has been used in this study. Cerebral blood flow measurement involves determination of the peak cephalic activity of an intravenously injected bolus of $^{131}$Cs by digital rate counting in a well-scintillation crystal that encloses the head. If the entire fraction of the isotopic bolus entering the head appears in the cerebral circulation before significant venous loss of $^{131}$Cs begins, the ratio of peak cephalic activity to total injected activity will represent the cephalic portion of the cardiac output. Since cerebral capillaries are not very permeable to $^{131}$Cs, activity remaining in the head after decay of peak cephalic activity will represent uptake by noncerebral cephalic tissue, and the peak activity can be corrected to yield only the cerebral cardiac output fraction. Total cerebral blood flow calculated from $^{131}$Cs injection was compared with measured bilateral internal jugular flow obtained by cannulation of the jugular veins. In anesthetized rhesus monkeys, the average ratio (calculated flow/measure flow) was $1.05 \pm 0.06$.

ADDITIONAL KEY WORDS

potassium-42 cardiac output brain extracranial blood flow

With the pioneering introduction of the inert gas diffusion (diffusible tracer) method for the measurement of cerebral blood flow by Kety and Schmidt (1), study of the intact cerebral circulation first became practical. However, several drawbacks to the use of the inert gas method have prevented its widespread clinical application: (A) puncture of a jugular vein or carotid artery is usually necessary; (B) it yields only flow per unit weight of tissue, and not absolute flow (2); (C) at least three volumes of distribution are found for inert gases in cerebral tissues (3), necessitating complex computer solutions to determine blood flow from indicator uptake curves; and (D) large inaccuracies in the calculated flow may result if inert gas equilibrium between tissue and venous blood is not reached (4).

Because of these inherent difficulties, gamma-emitting, nondiffusible tracers have been used in the study of the cerebral circulation by external isotope monitoring (5, 6). The curves obtained from the nondiffusible indicators have been used to obtain indices of cerebral circulation, rather than actual flow measurements, due to the uncertainty in the determination of the precise volume actually included in the field of the scintillation detector. In addition, the contribution of the extracerebral cephalic circulation to the total cephalic circulation cannot be readily ascertained. Sapirstein (7) combined two isotopic indicators, $^{42}$K and $^{131}$Iodo-antipyrine, in an attempt to separate the extracerebral cephalic and cerebral portions of the flow as...
determined by the use of the gamma-emitting isotopes. $^{42}$K was used to measure the extra-cerebral cephalic flow since it is not taken up to any appreciable extent by the cerebral tissues (7, 8), whereas $^{131}$I-iodo-antipyrine was used to measure the total cephalic flow. The difference between the flows was attributed to true cerebral blood flow. A well-counter large enough to accommodate an entire human head was used in these experiments. Since the cerebral flow is obtained as the difference between the antipyrine and $^{42}$K flows, inclusion of excess noncerebral tissue should not invalidate the cerebral flow measurement.

This latter method represents an improvement over the nondiffusible indicator techniques because provision is made for estimation of the contribution of noncerebral cephalic flow to the total measured cephalic flow. The drawbacks of this method are the requirement of double injection of isotope, and the difficulty in analysis of the uptake curves of the diffusible indicator, iodo-antipyrine, to yield total cephalic blood flow.

It should be theoretically possible to simplify the cerebral blood flow procedure by taking advantage of the differential diffusion characteristics of $^{42}$K in the cerebral and noncerebral cephalic circulation, and thus, obtain true cerebral flow with a single indicator injection. In this method, the cerebral circulation is separated from noncerebral cephalic circulation by differentiating between the transient indicator-dilution passage of the bolus of isotope and the isotope activity remaining following the passage of the bolus. The former, presumably passing through nonpotassium exchanging capillaries, is attributed to the cerebral circulation, and the latter to the noncerebral cephalic circulation. This report will discuss the theoretical development for the measurement of total cerebral blood flow, and will also describe the validation experiments that were carried out.

**Theoretical Considerations**

The failure of $^{42}$K to enter cerebral tissue to any appreciable extent following intravenous isotope injection has already been established (7, 8). Most other tissue shows an extraction ratio of one for approximately 60 sec after a single intravenous injection of a bolus; that is, the venous loss of tracer from most tissues in the first seconds following tracer circulation through the tissue is negligible compared with the amount of tracer in the tissues (9). The observation that the clearance of $^{42}$K is nearly complete following intravenous injection has been used as the basis of the potassium fractionation technique for the measurement of regional blood flow (9, 10). The ratio of isotope activity recovered from the region or organ under study to the total injected isotope activity yields the fraction of the cardiac output perfusing the organ or region. This technique yields only nutritive blood flow; shunt flow passing through non-equilibrating channels is not measured. The $^{42}$K fractionation technique has been validated for a variety of dissimilar organs and tissues (9-13). Thus, in tissues in which the capillaries are readily permeable to $^{42}$K, the 30 to 60 sec fractional uptake following rapid intravenous injection of a bolus will represent the fractional cardiac output perfusing the tissue. This might also be reasonably expected to be true for most of the noncerebral structures of the head such as skeletal muscle, fat and bone (10, 12, 13).

Since $^{42}$K is not taken up by cerebral tissues, total counts measured from the head following injection of a bolus should have an indicator-dilution component. The rapid passage of the $^{42}$K bolus with a low extraction ratio ought to have the general appearance of a conventional indicator-dilution curve recorded from a systemic artery. It is apparent, however, that under certain conditions, the peak of the indicator-dilution curve above the subsequent equilibrium cephalic counting rate will be related to the fractional cardiac output perfusing the brain. The conditions necessary for this latter statement to hold are as follows:

A. The uptake of the radioisotope tracer by cerebral tissue should be small when compared with the total amount of isotope contained within the cerebral circulation at the
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time corresponding to the peak of the isotope dilution curve.

B. The extraction ratio of tracer by the noncerebral cephalic tissues should be nearly one for approximately 60 sec following arrival of the bolus in the cephalic circulation.

C. Tracer recirculation should be minimal.

D. The duration of the isotopic arterial bolus within the cerebral blood vessels should be less than the cerebral circulation time to that the entire fractional bolus of isotope is contained within the cerebral circulation at some discrete time following the injection of the bolus.

E. The counting efficiency of the external monitoring system for isotope within the well crystal should be uniform. The usual assumptions regarding uniform mixing of the injected bolus of isotope in the vascular system must also be made.

If the above restrictive conditions apply, and the entire head is enclosed within a well crystal, then the following relationship will hold:

\[ \frac{\text{cerebral blood flow}}{\text{cardiac output}} = \frac{q_0}{I_o} \]

where \( q_0 \) = peak value of the indicator-dilution curve above the equilibrium cephalic counting rate following passage of the bolus.

\( I_o \) = total injected isotope activity.

The ratio \( q_0/I_o \) will be denoted as the fractional cerebral isotope uptake. Multiplying the fractional cerebral isotope uptake by the cardiac output yields total cerebral blood flow.

Methods

SCINTILLATION CRYSTAL AND SINGLE-CHANNEL AMPLIFIER-ANALYZER

A scintillation crystal 8 inches in diameter by 5 inches deep with a 4-inch well which can completely enclose the head of a rhesus monkey was fabricated for this study by the Harshaw Chemical Company. Three photomultiplier tubes were attached to the crystal. The output from the photomultiplier tubes was coupled to a single-channel Baird Atomic amplifier-analyzer, which also supplied the high voltage to the photomultiplier tubes. No decrement in count rate due to resolving time of the amplifier crystal assembly was noted until the observed count rate exceeded 5,000,000 count/min.

NUCLEAR DATA RECORDING

Sapirstein (10) found that the \( ^{42}\text{K} \) activity in the brain had dropped to low levels at 5 to 10 sec following intravenous injection. It thus became apparent that if the rapid phase of the cerebral \( ^{42}\text{K} \) bolus were to be preserved, a rapid recording procedure would be necessary. An initial choice of a digital rate recording system was made because of the absolute count-rate lag inherent in conventional ratemeter circuits. Since the precise length of the digital time interval that would give optimal results was difficult to predict, a PDP8/S, \(^3\) 12-bit, 4000-word computer was used for collection of the analyzer output from the well crystal; therefore, the data collection rate and duration is under program control and can be readily altered. The counting interval was 100 msec. The output of the single-channel analyzer was stored in a 12-bit buffer register constructed of Flip-Chip Modules which could be gated, read, and cleared by the PDP8/S. A thirteenth bit was arranged for detection of overflow of the primary buffer register. The buffer was interrogated at 100-msec intervals; the actual gating, read, and clear time being only 4 \( \mu \)sec, so that counting was essentially continuous.

EXPERIMENTAL PROCEDURE

In these experiments, \(^{131}\text{Cesium (Cs)} \), an isotope whose biological distribution volume is similar to that of \(^{42}\text{K} \), has been used for the determination of cerebral blood flow. One problem with the use of \(^{42}\text{K} \) is the difficulty in obtaining adequate shielding of the 1.3- and 1.5-Mev gamma rays. In addition, \(^{42}\text{K} \) decays by emitting many strong beta particles, as well as the gamma rays. \(^{131}\text{Cs} \) decays by electron capture, yielding a 29.4-kev xenon x-ray. This monoenergetic gamma ray improves the counting efficiency that can be achieved, and is readily absorbed by simple shielding. In addition, the physical half-life of \(^{131}\text{Cs} \) is 9.7 days, which is more convenient for experimental use than \(^{42}\text{K} \) with a 12.4 hr half-life.\(^2\)

Figure 1 shows the instruments used for the fractional cerebral blood flow and cardiac output determinations. The isotope-dilution technique previously validated by Conn (15) was used to determine cardiac output; the dilution curve was obtained by continuous blood sampling from a catheter placed in the descending aorta through a femoral artery.

The radioactive isotope was injected through a small bore polyethylene cannula (PE 190, i.d.

\(^3\)Digital Equipment Corporation.

\(^2\)The biological half-life of cesium is estimated to be 13 days in the rat and 100 days in man.
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FIGURE 1
Schematic representation of the instruments used for the external isotope monitoring method for the measurement of cerebral blood flow. See text for details.

≈ 0.047 inches) inserted into a femoral vein and advanced in the inferior vena cava to the level of the right heart. Using a micrometer syringe that could dispense small volumes with 1% accuracy, the catheter was filled with a precisely measured volume of isotope. The injection of a bolus was achieved by rapidly injecting 2 ml of saline solution into the catheter previously loaded with the isotope. The same bolus of isotope was used for obtaining both the cerebral blood flow fraction and the cardiac output. Arterial blood was drawn through a cuvette mounted on a shielded scintillation crystal-photomultiplier assembly which was coupled to a nuclear ratemeter, and the dilution curves were recorded on a strip chart recorder. The animal was placed so that the entire head was within the well-scintillation crystal. The actual amount of isotope injected was determined by counting a known amount of the injected isotope activity, usually between 10 and 20% of the total injected dose, in a phantom head placed within the well-crystal detector.

The validation experiments were carried out in rhesus monkeys because their internal jugular veins almost exclusively drain the cerebral circulation (16, 17). Male monkeys weighing approximately 2 kg were anesthetized with sodium pentobarbital (30 mg/kg ip). Both internal jugular veins were cannulated, and direct measurements of cerebral blood flow were made by timed collection of jugular venous outflow in a calibrated reservoir. The blood was returned to the circulation via a cannulated femoral vein. Heparin (10 to 20 mg) was given as an anticoagulant. High molecular weight dextran (Cutter Laboratories), 6% in normal saline, was used initially to fill the reservoir and pump system (25 ml), and to replace blood loss during the surgical preparation.

Respiratory rate and blood pH, Pco2 and Po2 were also measured in some of the animals.

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In 2 animals, the arterial Pco₂ was intentionally increased by ventilating the animals with gas mixtures of 5% CO₂-95% O₂ and 10% CO₂-90% O₂.

**Results and Discussion**

Adequate cerebral counting with respect to time resolution and signal to noise ratio was obtained in monkeys when we injected 10 to 30 μC of ¹³¹Cs. As many as 5 to 6 injections of isotope could be made within a 2-hr period with satisfactory technical results obtained in all cases. All cerebral isotope recordings were continued for 38 sec following rapid intravenous injection of a bolus of the isotope. Figure 2 shows a time-activity plot obtained in an early validation experiment. Figures 2 through 6 have been plotted on a digital plotter from the punched paper tape output from the PDP8/S. The peak height of the cerebral isotope curve above the equilibrium counting rate (q₀) is shown in Figure 2. The fraction of the cephalic uptake attributed to extracerebral structures is designated λ₀. Several minor procedural difficulties were encountered in obtaining the equilibrium counting rate after passage of the cerebral bolus of isotope. Because of these difficulties, a least squares statistical fitting procedure for obtaining q₀ was applied to the data. This tech-

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**FIGURE 2**

Curve of isotope activity recorded from the well-crystal assembly enclosing the head following rapid intravenous injection of ¹³¹Cs. The count intervals are 100 msec in duration. The height of the curve peak above the equilibrium count rate after bolus washout is shown as q₀ and the noncerebral cephalic isotope uptake as λ₀.

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The analytic routine improves the precision of measurement of \( q_0 \), but the results obtained usually agree within a few percent with those obtained by direct inspection of the data. The main value of this analytic routine is that it identifies experimental curves that may give erroneous estimates of the fractional cerebral flow.

The general shape and form of the cerebral isotope curve shown in Figure 2 agrees with the theoretical expectation. The rapid passage of the bolus of isotope through the cerebral circulation is shown clearly, as is the uptake of isotope (\( \lambda_0 \)) by noncerebral cephalic tissues. Figure 3, obtained later in the same experiment following obstruction of the cannula draining one jugular vein, shows the effect of markedly reduced cerebral flow on the shape of the cerebral isotope curve; \( \lambda_0 \) is greatly reduced and the cerebral isotope washout is markedly delayed. The same total activity of \( ^{131} \text{Cs} \) was injected for both experiments.

The effect of increased arterial \( \text{PaCO}_2 \) on cerebral blood flow was studied in 2 animals. The upper panel in Figure 4 shows an isotope curve in a monkey with an arterial blood \( \text{PCO}_2 \) of 39.5 mm Hg and a pH of 7.28. The lower panel shows the isotope curve obtained in the same animal when it breathed 90% \( \text{O}_2 \)-10% \( \text{CO}_2 \); the \( \text{PCO}_2 \) was increased to 75 mm Hg and the pH decreased to 7.07. The same dose of isotope was injected in both experiments. The absolute magnitude of \( q_0 \) has almost doubled, while \( \lambda_0 \) has decreased approximately 10%. The calculated cerebral blood flow was 55 ml/min when the \( \text{PCO}_2 \) was 39.5 mm Hg and 102 ml/min when \( \text{PCO}_2 \) was 75 mm Hg. With hypercapnea, the cerebral blood flow accounted for one-third of the total cardiac output. Under these circumstances, a large fraction of nonextracted \( ^{131} \text{Cs} \) recirculates, and a recirculation peak in the cephalic isotope curve can be clearly seen. In a second monkey, an increase in arterial \( \text{PCO}_2 \) from 38.2 to 47.5 mm Hg, with a decrease in pH from 7.36 to 7.32, resulted in an increase in calculated cerebral blood flow from 36 ml/min to 48 ml/min.

The restrictive conditions necessary for the ratio \( q_0/\lambda_0 \) to estimate accurately the fractional cerebral blood flow have been studied as they apply in the experimental situation. The applicability of the five conditions listed...
Upper panel, curve of isotope activity. Arterial blood = $P_{CO_2}$ 39.5 mm Hg, $P_{O_2}$ 60 mm Hg and pH 7.28. Lower panel, curve from same monkey during inhalation of 10% $CO_2$-90% $O_2$. Arterial blood = $P_{CO_2}$ 75.0 mm Hg, $P_{O_2}$ 345 mm Hg and pH 7.07.
A. Information regarding the $^{131}$Cs uptake by cerebral tissues was obtained directly by measuring isotope uptake in the brain. Following termination of the isotope blood flow determinations, the cerebral tissues were removed, weighed, and total isotope activity was counted. Table 1 shows the results of these measurements. Isotope uptake is expressed as a fraction of the total injected activity. In these animals the mean $^{131}$Cs uptake of the cerebral tissue was less than one-half of a percent of the total injected dose. Since the cerebral isotope fraction usually was in the range of 10 to 15% of the injected dose, uptake of $^{131}$Cs by cerebral tissues represents a minimal (2 to 3%) error in the estimation of cerebral flow.

B. It is difficult to obtain a direct estimate of the $^{131}$Cs extraction ratio for the noncerebral cephalic tissues. The only evidence bearing on this point is indirect. The blood flow rates commonly reported for skeletal muscle...
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Semilogarithmic plot of the downslope of the curve shown in Figure 5. The equilibrium count rate following passage of the bolus of isotope has been subtracted from all points plotted in this figure. Zero time is taken at the point where the downslope of the curve begins. Also shown in this figure is the standard error of the count rate at 1-sec intervals and the curve obtained by the method of least squares.

are an order of magnitude lower than those reported for cerebral blood flow. If the noncerebral tissues lose a significant amount of isotope at a much different rate than does cerebral tissue, the downslope of the cephalic isotope washout curve could be resolved into two exponential components. Figure 5 shows a cephalic isotope curve following common carotid artery injection. The average count rate from 25 to 28 sec was not significantly different than the average count rate at 35 to 38 sec (P > 0.1), indicating that no relatively slow rate of isotope washout was present. Figure 6 shows a semilogarithmic plot of the downslope of the curve in Figure 5. The equilibrium counting rate at 25 to 35 sec has been subtracted from the downslope. The downslope has been fitted with a single exponential line by the method of least squares and no remarkable deviation from the single exponential line is evident. Undoubtedly, some loss of isotope by cephalic noncerebral tissues does occur. However, because of the relatively low blood flow in these tissues, the loss occurs so slowly that an effective extraction ratio for $^{131}$Cs of approximately unity for the first seconds following passage of the bolus of isotope is obtained.

Isotope-dilution curve obtained by measurement of arterial blood isotope activity following the intravenous injection of $^{131}$Cs. The semilogarithmic extrapolation of the downslope of the curve is shown by the dashed line. The background recorded after the passage of the bolus of isotope with no blood in the scintillation detector is also shown.

C. Figure 7 shows a typical cardiac output curve recorded following the intravenous injection of $^{131}$Cs. The recirculation peak, seen at about 15 sec is only 4 sec in duration, and only 6% of the magnitude of the peak count rate. Most of this recirculating isotope probably represents the venous return of cerebral isotope. In all experiments, the recirculation peak seen was of small magnitude, the highest observed being that seen in the lower panel of Figure 4.

D. Stable peak plateaus lasting at least 400 msec were recorded in most experiments (see Figs. 2 and 4). This finding supports the conclusion that the bulk of the initial bolus of isotope has entered the cephalic circulation.
Simultaneous recording of cephalic, jugular venous and arterial isotope activities following intravenous injection of $^{131}$Cs. The arrow shows the time of isotope injection. The arterial and venous curves are corrected for catheter delay time. The arterial catheter was placed at the level of the diaphragm.

Before significant venous loss begins. However, the presence of the peak plateau does not rule out the possibility that significant arterial isotope inflow is balanced by isotope loss in venous blood. In one experiment, arterial blood at the level of the diaphragm and jugular venous blood were sampled during an isotope head scan. Figure 8 shows the relationships between cephalic, arterial, and jugular venous isotope activity. The entire arterial bolus enters the cerebral circulation before isotope activity loss into jugular venous blood becomes significant. Thus, the fractional bolus of isotope brought to the cephalic circulation by the fraction of the cardiac output perfusing the head appears intact, without venous loss, in the field of the well-scintillation detector.

E. To eliminate the effects of geometry of distribution of isotope within the head, the efficiency of counting should be uniform within the well-scintillation detector. Uniformity was studied by placing a fixed amount of isotope in a container within the well, and then increasing the volume of distribution of the isotope within the container by adding water. Figure 9 is a graph of added volume to relative count rate for a constant quantity of isotope. Water was added in 10-ml increments. The well crystal does not exhibit entirely uniform counting characteristics, but for a 10% change in volume at 70 ml total volume, there was less than a 1% change in count rate. The 70 ml volume was the volume of the phantom head used in counting. As the volume increased over 100 ml, the rate dropped more rapidly because the volume was not as completely contained within the well. One attempt to compensate for this effect is to use a phantom head for standard isotope counting that is approximately the size of a monkey’s head. This effect would be minimized in a situation...
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Plot of actual count rate versus increasing volume of distribution of a fixed quantity of isotope within the well-scintillation detector.

in which changes in blood flow were being studied, in which case the volume of distribution of isotope would be almost identical from experiment to experiment. In the range of sizes of animal heads studied, this effect introduces an error in estimation of the total injected isotope dose that in all cases was less than 2%. With careful matching of phantom head to animal head size this error can probably be further reduced.

The restrictive conditions for the application of the $^{131}$Cs isotope technique for the measurement of cerebral blood flow appear to be reasonably well fulfilled and the external isotope monitoring method should thus give an accurate estimate of total cerebral blood flow. In six experiments, the results of the isotope method for cerebral flow measurement were compared with the directly measured internal jugular vein flow. The results of these experiments are shown in Table 2. In all cases except experiment 6, the isotope flow measurements were higher than the directly measured flow rates. A possible explanation for this observation is that the total internal jugular flow may not represent the entire cerebral flow, since venous drainage is possible via other channels. However, in spite of the consistent difference between directly measured and calculated cerebral blood flow, the agreement of the average measured values is close. The ratio of observed to calculated flow is not statistically significant from 1.0 ($P > 0.1$).

Blood flow through shunts will pass through channels that are essentially nonpotassium equilibrating. If the mean transit time through these channels is sufficiently short so that the isotope has left the crystal field before the cerebral isotope peak is seen, this type of flow will not be misinterpreted as cerebral flow. In the case where the transit times through the shunt paths are long, this flow will be measured as cerebral blood flow. If significant shunt flow occurs, a washout component due to this flow should allow resolution of the downslope of the cerebral isotope curves into two exponential components. As previously noted, the downslope of almost all curves could be fit by a single exponential curve. Some deviation from the single exponential curve might be concealed, however, in the method of least squares because of the statistical variability of the count rate. The existence of a 10% shunt flow might be concealed

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by the variability in the data, and hence, cannot be ruled out. The reasonable agreement between the directly measured jugular flow and the calculated cerebral flow also tends to eliminate the possibility that any major component of the cerebral isotope curve is due to flow through shunt channels.

The results obtained in this study suggest that cerebral blood flow can be satisfactorily measured by external isotope counting following rapid intravenous injection of a bolus of $^{131}$Cs. The fraction of the cardiac output perfusing cerebral tissue is obtained by differentiating between the extraction characteristics of $^{131}$Cs in the cerebral and noncerebral cephalic circulations. Cardiac output was calculated in this study by the measurement of the isotope dilution curve obtained by sampling of arterial blood. If cardiac output were measured by a noncannulating procedure, such as the isotope surface counting method discussed by Johnson et al. (18), only a single venous puncture would be necessary to obtain total cerebral blood flow via the external isotope monitoring technique. The isotope dose necessary to achieve adequate technical resolution of the cerebral curves is small, being in the range of 10 to 20 μc of $^{131}$Cs. This technique is well suited for studies in man since discomfort to the patient is minimal, the procedure is brief, requiring only 30 sec/determination and repetitive measurement can be made with ease.

Acknowledgments

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