EXTRACRANIAL MEASUREMENT OF REGIONAL CEREBRAL CIRCULATION

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Several parameters which reflect changes in regional cerebral circulation may be measured. Included among these are blood flow per unit volume of tissue, circulation time, and oxygen metabolism. Studies of extracranial measurement of regional cerebral blood flow (rCBF) have dealt primarily with the use of diffusible radionuclide-labeled tracers to measure blood flow per unit volume of tissue (*1,2,3,* and references therein). In order to determine what information could be gained about cerebral circulation from the use of nondiffusible tracers, intracarotid injection of ^{99m}Tc-sodium pertechnetate was used with a system for regional extracranial monitoring of radioactivity. Comparison studies were also made with the nondiffusible tracer ^{131}I-sodium iodohippurate. The present studies indicate that, at least during the first intracranial circulation following intracarotid injection, the pertechnetate compound also acts as a nondiffusible tracer.

The present report describes an evaluation of measurements made in normal subjects in terms of simple clinical indices of regional cerebral circulation. A more extensive analysis of the measurements in terms of a simple model of regional cerebral circulation is described in the following report (*4*).

METHODS

Detection equipment. The initial specifications for a regional external detector were that the maximum response come from a volume within one cerebral hemisphere and that the response be statistically significant. A tapered collimator was found to be the simplest and most effective design (*5,6*). A conical aperture in lead of 7.5 cm in length tapering from a diameter of 2.5 cm at the scintillation crystal to 1.25 cm at the collimator face provided the desired collimation for a single detector. The sensitive region defined by the collimator approximates a conical volume coaxial with the collimator axis, with a diameter of 1.25 cm at the collimator face and 5 cm at a depth of 7.5 cm (approximately midline of the head).

Preliminary investigations conducted with two such collimators were found to yield satisfactory results (*7*). A multi-collimator system consisting of six single conical openings in a lead block was used for the present investigation. The openings are arranged in two rows, each of three openings. Figure 1 illustrates the geometrical arrangement of one of the rows. The central axes of the outer collimators are aligned at an angle of 6 deg to the axis of the center collimator. This design brings the observed tissue volumes close together while allowing more shielding between collimators. The design also reduces the variation in volume of extracranial tissues viewed by adjacent detectors.

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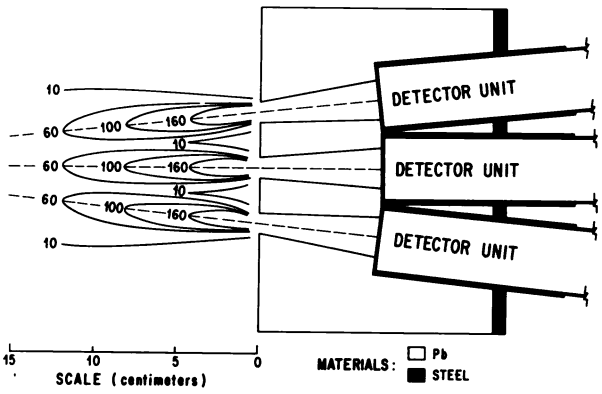

FIG. 1. Cross section of bank of three collimated detectors and isoresponse plot obtained with line source of ^{99m}Tc in air. Responses shown are relative to value of 100 on collimator axes at approximately 8 cm from collimator face.

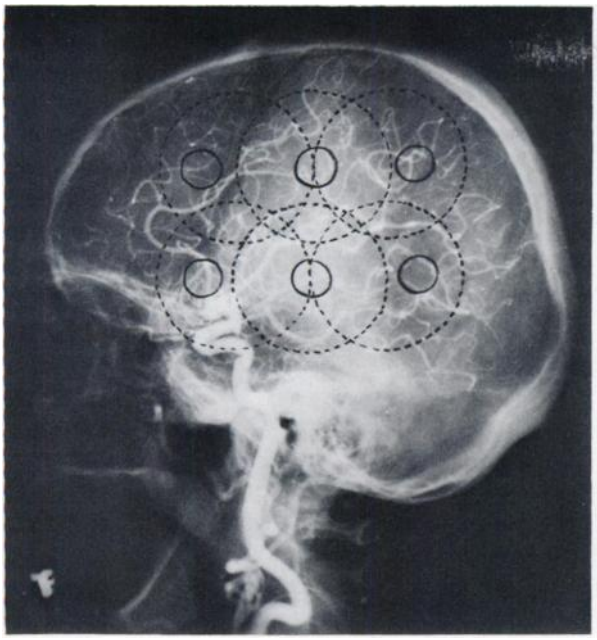

FIG. 2. Cross sections of conical volumes of cerebral tissue defined by six-unit collimated detector array positioned at left side of head. Geometrical extent of volumes is shown by solid circles at detector openings on scalp and dashed circles at sagittal plane.

An isoresponse plot of three of the regions determined with a ^{99m}Tc line source is shown in Fig. 1. For both ^{131}I and ^{99m}Tc, approximately 80% of the response of a detector comes from a volume which is not viewed by adjacent detectors. Each collimated detector views approximately 70–100 cm^3 of tissue in one cerebral hemisphere (*5*). Figure 2 shows the relationship of the six openings to the side of the head. The face of the lead block is flat and a note is made of any distance between a collimator opening and the scalp. This measurement is usually never more than a few millimeters for one or two of the openings and does not significantly alter the results.

Each detection unit consists of a 2.5 × 2.5-cm-diam NaI(Tl) crystal mounted on a Dumont 6467 photomultiplier and encased in a steel tube together with pulse-shaping electronics. A similarly constructed seventh detector with a 0.3-cm-diam × 0.6-cm-deep cylindrical aperture in lead is used for detection of the tracer bolus over the injection site in the neck.

Pulses from the seven detectors are recorded and stored by a portable seven-channel magnetic tape recording unit (*8*). The recording system is interfaced to a Digital Equipment Corporation PDP-7 computer for display and analysis of the data (*9*). For analysis, recorded counts are typically accumulated in 0.1-sec intervals and smoothed with a five-interval running average for display.

Selection of radionuclide. The nuclide ^{99m}Tc is advantageous for this type of study for a number of reasons. In addition to its ready availability in the pertechnetate form, the nuclide emits only gamma rays with an energy of 0.14 MeV. Gamma radiation of this energy is detected with a high intrinsic efficiency in NaI(Tl). As a consequence of the low radiation dose to the patient, repeated studies may be done. The energy is also such that gamma-ray absorption in bone, which rapidly increases with energy below about 0.1 MeV, is not a serious problem. However, the energy is low enough to allow adequate shielding between the regional detectors.

Clinical measurements. Biological data were obtained with strict adherence to the requirements of the committee on human investigations at the Massachusetts General Hospital. All studies were done at least 15 min after the time carotid angiography was performed as a necessary diagnostic procedure in the evaluation of the patient. Studies have been limited to adults with a presumptive diagnosis of cerebral vascular disease, cerebral trauma, or intracranial neoplasm. Thus the normal studies are selected from those patients who, on the basis of subsequent clinical and laboratory findings, prove not to have significant intracranial pathology.

Before the injection, the six-unit detection system is placed against the side of the head, and its position is carefully adjusted with respect to external landmarks. The seventh detector is then placed over the neck distal to the point of injection. Position of the detectors in relation to the lateral carotid angiogram is illustrated in Fig. 2. For cerebral angiography the needle is usually placed in the common carotid artery although selective internal carotid injection is used at times. A 500-μCi quantity of ^{99m}Tc-pertechnetate or 250 μCi of ^{131}I-iodohippurate is diluted with saline to a 1-cc volume and is placed in a flexible tube with a total volume of 2 cc. This tube is connected to the angiogram needle. The bolus is then injected by a 5-cc volume of saline with a rapid (1.0-sec) manual injection. Following the test, a sample of arterial blood is taken and analyzed for pCO_2, pO_2, and hematocrit.

Data analysis. An example of a typical observed activity* distribution obtained in a normal patient from a single detector is shown in Fig. 3. Following injection of the radionuclide-labeled tracer bolus at time $t = 0$, there is a short interval of time t_a (appearance time) before the tracer bolus arrives in a field of view of the detector. After onset of detected activity, the curve rises rapidly in a time t_b (buildup time) to a maximum. The activity then decreases

* Throughout this text, the term "activity" means detected counting rate expressed in counts per minute (cpm).

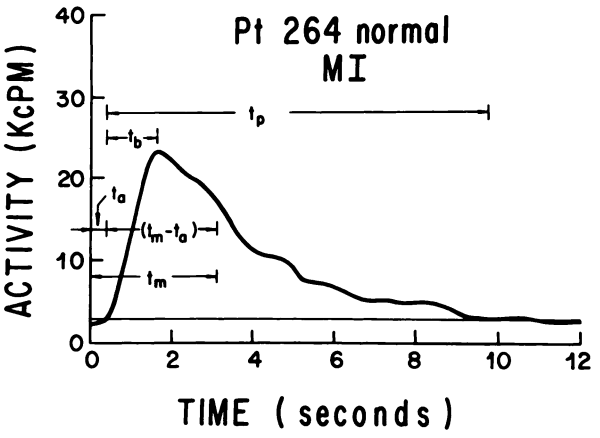

FIG. 3. Typical activity distribution obtained in middle inferior (MI) cerebral region of normal subject. Appearance time t_a, buildup time t_b, and passage time t_p are indicated, as well as mean time t_m and distribution mean ($t_m - t_a$).

more slowly, passing in some cases through a secondary maximum, and returns to a small flat background level. The total time of passage t_p of the activity from onset until return to flat background is designated as the passage time.

With the use of a nondiffusible tracer, the peak height of the activity distribution is quite sensitive to the conditions of injection as well as to the location of the monitored region with respect to the site of injection (i.e., sensitive to the dispersion of the tracer bolus before its entrance into the monitored volume). Therefore the peak height divided by the area under the distribution (*10*) is not considered a suitable index of rCBF in the evaluation of the present measurements.

The parameters of the regional activity distribution which may serve as suitable clinical indices of circulation are those which are independent of instrumental effects, such as the detection efficiency, and of effects of the method, such as injection artifacts. The most straightforward parameters are times determined directly from characteristic features of the curve (t_a, t_b, t_p). These times, however, will be dependent to some extent on the dispersion of the tracer bolus before entrance into the monitored volume as well as on the dispersion within the monitored volume.

In addition to these direct determinations, the time interval from injection to the centroid of the activity distribution can be determined. This is done by defining the mathematical moments of the activity distribution. The first moment about $t = 0$ is the center of gravity (centroid) of the curve. The first moment thus defined will be designated in this study as the mean time t_m of the region monitored but is not to be confused with the mean transit time as defined by other investigators (*10,11*).

The mathematical definition of the moments is expressed as

$$\mu_n = \frac{1}{A} \int_0^{t_a+t_p} t^n q_{obs}(t)dt \qquad (1)$$

in which μ_n is the moment of order n about $t = 0$ ($n = 1$ designates the first moment, i.e., $\mu_1 = t_m$), $q_{obs}(t)$ is the observed activity distribution as a function of time t, and A is the area under the activity distribution, or the sum $\int_0^{t_a+t_p} q_{obs}(t)dt$ of all the counts recorded during passage of the bolus.

The area A measured under an activity distribution which is obtained with an external detector has been shown to be proportional to the mean transit time as customarily defined (*10*). The measured value of A also depends upon the total amount of tracer entering the monitored regional volume as well as upon the detection efficiency. Since these factors may vary considerably in measurements made from patient to patient and from region to region in the same patient, we do not explicitly use values of A as indices of regional cerebral circulation in this study. However, the values of moments, as defined in Eq. 1, are not affected by changes in these factors (*4*).

The second moment, μ_2, is related to how the activity is distributed around the center of gravity of the measured distribution. The width (σ) of the distribution is given by the expression

$$\sigma = (\mu_2 - \mu_1^2)^{1/2}.$$

The skewness, $T_1 = [\mu_1 - (t_a + t_b)]/\sigma$, is a measure of deviation from symmetry about the center of gravity (*12*).

An additional quantity considered as an index of regional circulation is the mean time minus the appearance time ($t_m - t_a$). This time parameter, called the distribution mean, may be a more appropriate index of regional circulation than the mean time t_m, inasmuch as the time delay in arrival of the bolus at the monitored region is taken into account.

Other quantities were considered which have been shown to be sensitive in varying degrees to changes in the shape of indicator dilution curves caused by variations in flow, volume, and path length (*13*). However, none of these quantities proved to be of use in evaluating the present measurements.

RESULTS

Summary of normal studies. Seventeen patients have been studied to determine normal values for

the parameters being investigated. These cases were selected from over 200 studies in patients who, after a presumptive diagnosis of cerebral vascular disease, cerebral trauma, or intracranial neoplasma had been made, had normal angiograms and subsequent normal neurological examinations and tests. It is recognized that this is not an ideal group for the determination of normal values, but it appears to be entirely satisfactory as a basis for comparative studies.

In Fig. 4 a normal family of activity distributions recorded by the six detectors is displayed. The high peak in the anterior inferior distribution is related to the bolus in the carotid siphon and intracranial portion of the internal carotid artery.

Table 1 records the mean values and standard deviations of the various circulation time parameters in six cerebral regions of 17 normal subjects of mean age 43 years and range 20–63 years.

Several factors which are known to have some influence on cerebral blood flow were monitored. The arterial pCO_2 ranged from 33 to 49 mmHg, with an average of 41.9 mmHg and standard deviation of ±5.3 mmHg. There was no significant correlation with the time parameters over this range of values. The pO_2 ranged from 63 to 245 mmHg and, as would be expected from previous studies (*14*), this had no significant effect on the time parameters. The hematocrit, also within normal range, varied only slightly over the group of patients, and again there was no change in the time parameters related to the slight changes in hematocrit. However, of the seven times listed in Table 1, a definite dependence on age was observed in some of them, as had been anticipated from previous studies. Figure 5 illustrates the gradual increase with increasing age of several of the parameters obtained from measured activity distributions in the middle inferior region of the cerebral hemisphere. Similar dependence on age is observed in the parameters obtained in other regions.

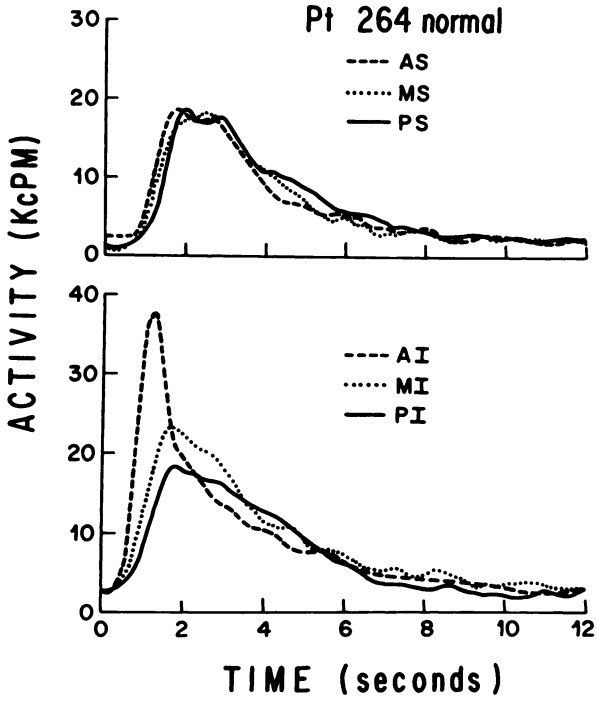

FIG. 4. Activity distributions measured in three superior (S) and inferior (I) regions [anterior (A), middle (M), and posterior (P)] of right cerebral hemisphere of normal 52-year-old man with normal circulation. Curves have been smoothed with 0.5-sec-wide running average.

TABLE 1. MEAN VALUES AND STANDARD DEVIATIONS OF REGIONAL CEREBRAL CIRCULATION TIME PARAMETERS IN 17 NORMAL HUMAN STUDIES

Parameter	Cerebral region*						Mean of six regions
	AI	MI	PI	AS	MS	PS	
Appearance time	0.3	0.3	0.5	0.5	0.5	0.7	0.5
t_a (sec)	±0.2	±0.2	±0.2	±0.2	±0.2	±0.2	±0.2
Buildup time	0.9	1.0	1.2	1.2	1.3	1.3	1.1
t_b (sec)	±0.4	±0.3	±0.5	±0.5	±0.5	±0.4	±0.4
Passage time	9.5	9.8	9.5	9.3	9.7	9.1	9.5
t_p (sec)	±2.3	±2.5	±2.5	±1.6	±2.8	±1.9	±2.2
Mean time	2.8	3.0	3.4	3.1	3.2	3.5	3.2
t_m (sec)	±0.4	±0.4	±0.5	±0.4	±0.3	±0.4	±0.4
Width	1.9	1.9	1.9	1.8	1.8	1.8	1.8
σ (sec)	±0.4	±0.4	±0.4	±0.3	±0.4	±0.4	±0.4
Skewness	0.9	0.9	0.8	0.8	0.7	0.7	0.8
T_1 (—)	±0.1	±0.1	±0.2	±0.2	±0.2	±0.3	±0.2
Distribution mean	2.5	2.6	2.8	2.6	2.7	2.7	2.6
($t_m - t_a$) (sec)	±0.4	±0.4	±0.5	±0.4	±0.3	±0.4	±0.4

* The cerebral regions are defined in Fig. 4.

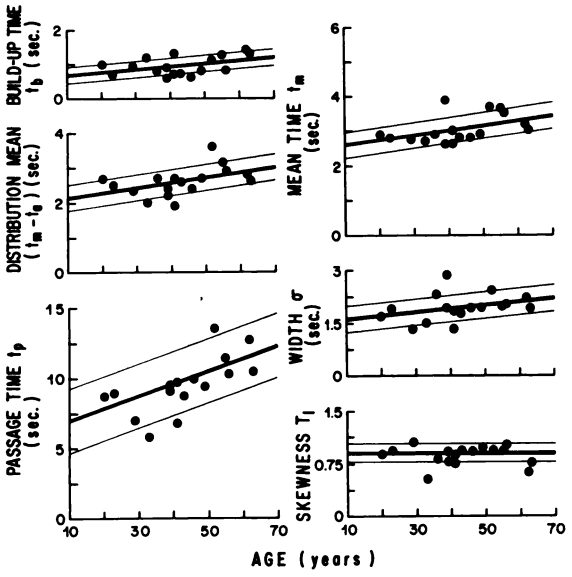

FIG. 5. Regional circulation time parameters in middle inferior cerebral region of normal subjects as function of age of subjects. Linear regression lines (heavy lines) and standard deviations (light lines) of values are also shown.

Comparison of ^{99m}Tc-pertechnetate and ^{131}I-iodohippurate. Previous reports have indicated that the pertechnetate ion may act as a nondiffusible tracer (*15*). Our data show that this is true, at least during the first intracranial passage of the bolus. In most patients the level of activity returns to a small background level after the bolus leaves. Since Oldendorf (*11,16*) has shown that ^{131}I-iodohippurate acts as a nondiffusible compound, a comparison was made between a group of seven normal studies made with the ^{131}I compound and a group of ten normal studies made with the ^{99m}Tc compound. No significant differences were found between the time parameters determined in the two groups studied. Consequently, the two groups have been combined in the present paper.

External carotid artery flow. Investigations into the contribution of activity in the scalp circulation to the recorded activity distributions were made since most of our injections were into the common carotid artery. Measurements with electromagnetic flow meters have shown that approximately 30% of blood in the common carotid artery enters the external carotid circulation (*17*). The design of the collimator used in the present measurements minimizes the scalp contribution from the field of view of a regional detector. Figure 6 compares two curves from the anterior inferior detector: one from a normal patient and the other from a patient with total occlusion of the internal carotid artery and no angiographic evidence of collateral circulation into the intracranial portion of the internal carotid artery. It is obvious that, even when the entire bolus enters the external carotid circulation, there is little influence on the recorded activity distribution.

Examples of abnormal studies. While it is not the purpose of this paper to discuss the findings in disease states, three selected examples of regional abnormalities noted in the study are used to illustrate the type of information that can be gained.

Case I, intracranial aneurysm. This 35-year-old woman had suffered two subarachnoid hemorrhages. She was unresponsive, with signs of left hemisphere damage. Angiograms revealed a left middle cerebral artery aneurysm with moderate spasm of the middle cerebral artery and evidence of Sylvian fissure hematoma. Figure 7 records the graphic display of the regional curves. A marked abnormality is apparent in the posterior inferior region. The specific time parameters recorded in Table 2 also indicate the regional localization of the abnormality in circulation.

Case II, cerebral contusion. A 21-year-old man injured in an automobile accident had difficulty with memory, slight left hemiparesis, and cortical sensory loss. Three days after the accident, angiography and a circulation study were performed. Although the angiogram was normal, a localized abnormality in circulation in the posterior inferior region was noted (Table 2).

Case III, intracranial occlusive disease. This 62-year-old man had the sudden onset of right hemiparesis and aphasia. Two days after onset, angiography revealed no definite abnormality although some observers thought that there was a possible slight decrease in filling of ascending frontal-parietal branches of the middle cerebral artery. Table 2 shows the localized abnormality in the anterior inferior and, to a lesser extent, in the middle inferior regions. These abnormalities are statistically sig-

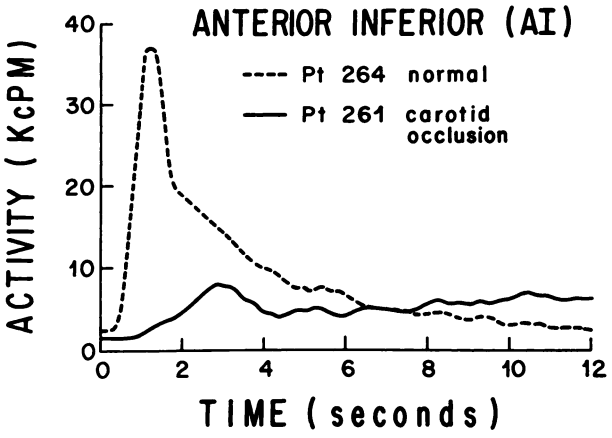

FIG. 6. Activity distributions measured in anterior inferior regions of normal subject (dashed curve) and patient with total internal carotid occlusion (solid curve).

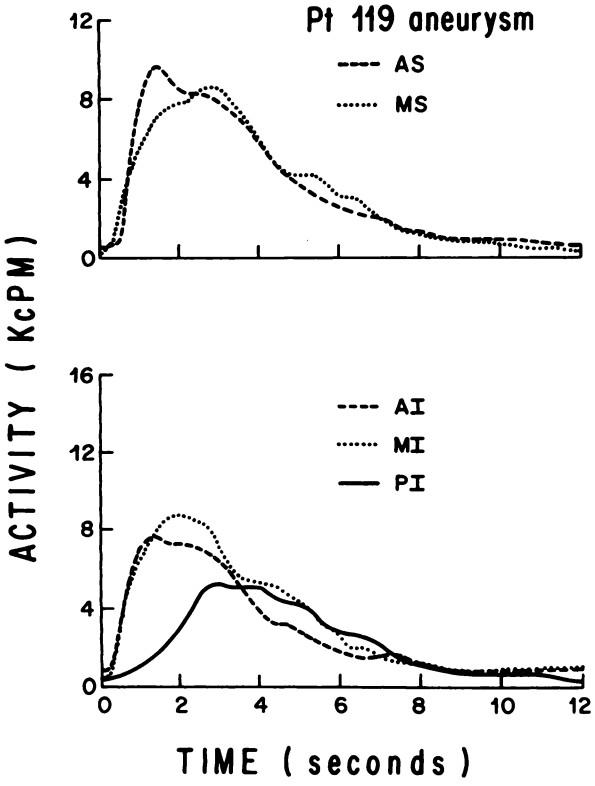

FIG. 7. Activity distribution measured in five regions of left cerebral hemisphere of 35-year-old woman with left middle cerebral aneurysm (Case I of abnormal studies).

nificant when compared with normal values. In addition, the width of the curve (σ) is relatively larger in the middle inferior region, perhaps indicating localized increased resistance in this region.

The values of pCO_2, pO_2, and hematocrit in these three patients were within the range of the 17 normal subjects, as given above.

DISCUSSION

Measurement of cerebral blood flow by means of either intravenous (*11,16,18*) or intracarotid injection (*16,19–24*) of nondiffusible radionuclide-labeled compounds has been reported. For the most part, these methods have involved measurement over most or all of one cerebral hemisphere and have not recorded regional changes. Oldendorf and Kitano (*11*) have pointed out that, to obtain curves with sufficient definition to see small regional abnormalities of circulation time in an area of pathology, a "very abrupt" input of tracer is needed and that this can be achieved only by carotid injection.

Our studies indicate that ^{99m}Tc-pertechnetate acts as a nondiffusible compound during the first intracranial circulation following carotid injection. Studies of cerebral circulation following intravenous injection of ^{99m}Tc-pertechnetate have been made using a gamma camera (*25–29*), various types of collimators (*15,30*), and an autofluoroscope (*31*). These

TABLE 2. REGIONAL CEREBRAL CIRCULATION TIME PARAMETERS IN THREE PATIENTS WITH FOCAL ABNORMALITIES

Parameter	Pt*	Cerebral region AI	MI	PI	AS	MS	PS
t_a (sec)	I L	0.3	0.3	0.6	0.5	0.3	†
	II R	0.5	0.6	0.9	0.7	0.7	†
	III L	0.3	0.4	0.4	0.4	0.5	0.6
t_b (sec)	I L	1.3	1.8	3.0‡	1.5	2.9‡	†
	II R	0.6	1.1	1.6‡	0.7	0.4‡	†
	III L	0.6	0.7‡	1.8	1.3	1.4	1.9
t_p (sec)	I L	10.1	11.5	10.4	10.6	10.1	†
	II R	12.1	11.0	11.8	9.7	10.9	†
	III L	9.2	8.9	8.1	8.3	9.2	7.8
t_m (sec)	I L	2.9	3.2	4.3‡	3.3	3.5	†
	II R	3.6	3.9	5.1‡	3.3	4.0	†
	III L	2.4‡	3.2	3.3	2.7	3.1	3.3
σ (sec)	I L	1.8	1.9	1.8	1.9	1.9	†
	II R	2.5	2.3	2.5	2.0	2.4	†
	III L	1.9	2.4	1.9	1.8	1.8	1.7
T_1 (—)	I L	0.9	0.9	0.9	0.9	0.4	†
	II R	1.0	1.0	1.0	1.1	1.2	†
	III L	0.8	0.9	0.6	0.6	0.7	0.4
$(t_m - t_a)$ (sec)	I L	2.6	2.9	3.7‡	2.8	3.2	†
	II R	3.1	3.3	4.2‡	2.6	3.3	†
	III L	2.1‡	2.8	2.9	2.3	2.6	2.7

* Left (L) or right (R) hemisphere; see text for description of patients.
† No measurement obtained.
‡ Values differ (>±2 s.d.) from normal values (Table 1).

techniques have made possible the measurement of circulation times or the display of sequential pictures which record gross changes in circulation over the cerebral hemisphere. It has not been possible to study detailed regional changes with these techniques.

The effect of increasing age on prolonging circulation times has been demonstrated in our studies. This fact has also been seen in the studies done following intravenous injection of ^{99m}Tc-pertechnetate (*26*) and ^{131}I-iodohippurate (*11,16*).

The effect of angiography on cerebral blood flow measurement has been studied by Potchen et al (*32*) for the diffusible compound ^{133}Xe. They found that if the blood flow study was done after the angiographic procedure, cerebral blood flow values, as determined from the peak height divided by the area under the first 10 min of the distribution, increased but returned to pre-angiographic values as early as 30 min after the injection of contrast substance. There have been no similar studies with nondiffusible tracers of the effect of angiography on the cerebral circulation. Although in the present study, the effect of angiography on the circulation time parameters was not explicitly investigated, a lapse of at least 15 min between injection of the contrast medium and the flow study was allowed to permit diminution of any possible effect due to the contrast medium.

Feindel and coworkers (*20*) have pointed out that, while studies employing nondiffusible compounds failed to measure absolute cerebral blood flow, studies using diffusible compounds may be insufficient when there is arterio-venous shunting or pooling of blood which may be associated with some intracranial pathology. In many instances, measurement of the timing and amount of blood passing through the vascular bed may be more appropriate.

Lassen (*33*) first used diffusible compounds to measure regional cerebral blood flow in man by external detection. Fieschi et al (*21*) have attempted to compare in the same patient measurements made by intracarotid injection of a nondiffusible and a diffusible tracer. These investigators concluded that there is a linear correlation between the circulation time and regional cerebral blood flow per unit volume of tissue. The regional circulation time could be used as an approximate index of regional cerebral blood flow when comparing normal values with changes during disease. However, changes induced in a given patient by pharmacological or physiological stimuli would be underestimated by the circulation time measurement because of changes in regional blood pool volume.

A primary advantage to the use of a nondiffusible indicator is that an independent measurement of regional blood volume can be made easily (*34,35*), provided the rate of clearance of the indicator from the total blood pool is negligibly small compared with the rate at which equilibrium concentration is reached. Since this criterion is not met with the use of pertechnetate or iodohippurate compounds, the use of a more ideal nondiffusible compound labeled with a short-lived radionuclide would be preferable.

Of particular importance is the development of techniques to measure all of the quantities relevant to cerebral circulation, i.e., flow per unit volume of tissue, circulation time, flow per unit blood volume, blood volume, and oxygen metabolism, in the same patient. This may soon be possible with the use of a short-lived, cyclotron-produced nuclide such as ^{15}O (*36*).

SUMMARY

A method for extracranial measurement of regional cerebral circulation using a nondiffusible compound has been investigated. The literature on the use of ^{99m}Tc-pertechnetate and nondiffusible tracers for measuring cerebral circulation is discussed. Our studies showed that, during the first intracranial passage following intracarotid injection, ^{99m}Tc-pertechnetate acted as a nondiffusible indicator. This radionuclide was used with a specially designed system of six regional detectors.

Significant circulation parameters measured with this method are defined and normal values determined from clinical investigations in a series of 17 patients. No significant effect on these parameters from external carotid circulation was demonstrated. Changes in these values with age are documented. Studies in patients with changes in cerebral circulation due to different etiological factors are discussed.

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REFERENCES

1. BROCK M, FIESCHI C, INGVAR DH, et al: *Cerebral Blood Flow. Clinical and Experimental Results.* Berlin, Springer Verlag, 1969

2. LUYENDIJK W: Cerebral circulation. In *Progress in Brain Research* vol 30, Amsterdam, Elsevier, 1968

3. MCHENRY, LC: Cerebral blood flow. *New Eng J Med* 274: 82–91, 1966

4. HOOP B, OJEMANN RG, BROWNELL GL: A stochastic model of regional cerebral circulation. *J Nucl Med* 12: 540–546, 1971

5. MILLER, CR: *The Measurement of Cerebral Blood Flow Using Radioisotopes and a Multi-channel Detection*

and Recording System. Thesis, Master of Science, Dept Nuclear Engineering, Massachusetts Institute of Technology, June 1964

6. WILLIAMS GF: *An Analysis of Regional Cerebral Blood Circulation Data Obtained by Radioisotope Indicator Dilution Methods.* Thesis, Master of Science, Dept Nuclear Engineering, Massachusetts Institute of Technology, Jan 1967

7. OJEMANN RG, MILLER CR, BROWNELL GL: Extracranial measurement of regional cerebral blood flow by intracarotid injection of RISA. *Surg Forum* 15: 407, 1964

8. BURNHAM CA, ARONOW S: A magnetic tape system for tracer studies. *Proc Ann Conf Eng Med Biol* 10: 52A3, 1968

9. WILENSKY S, ASHARE AB, PIZER SM, et al: Computer processing and display of positron scintigrams and dynamic function curves. In *Medical Radioisotope Scintigraphy* vol 1, Vienna, IAEA, 1969, pp 815–827

10. ZIERLER KL: Equations for measuring blood flow by external monitoring of radioisotopes. *Circ Res* 16: 309–321, 1965

11. OLDENDORF WH, KITANO M: Radioisotope measurement of brain blood turnover time as a clinical index of brain circulation. *J Nucl Med* 8: 570–587, 1967

12. VON MISES R: *Mathematical Theory of Probability and Statistics.* New York, Academic Press, 1964

13. THORBURN GD: Factors influencing the dispersion of indicator in dye-dilution curves in normal man. *Aust J Exp Biol Med Sci* 42: 543–560, 1964

14. REIVICH M: Arterial PCO_2 and cerebral hemodynamics. *Amer J Physiol* 206: 25–35, 1964

15. MARSHALL WH, LUKIS G, SAPIRSTEIN LA: Comparison of hemispheric blood flow using a new isotope technetium-99m. In *Research on the Cerebral Circulation,* Meyer JS, Lechner H, Eichhorn O, eds, Springfield, Charles C. Thomas, 1969, pp 121–131

16. OLDENDORF WH, KITANO M: Isotope study of brain blood turnover in vascular disease. *Arch Neurol* 12: 30–38, 1965

17. HARDESTY WH, ROBERTS B, TOOLE JF, et al: Studies on carotid artery flow. *Surgery* 49: 251–256, 1961

18. THOMPSON SW: Cerebral blood flow assessment with a radioisotope method. *Arch Neurol* 10: 26–34, 1964

19. VAN DER DRIFT JHA, SPARLING CM, VAN DEN BERG D, et al: Spontaneous occlusion of a carotid-cavernous shunt. *Neurology* 17: 187–193, 1967

20. FEINDEL W, GARRETSON H, YAMAMOTO L, et al: Blood flow patterns in the cerebral vessels and cortex in man studied by intracarotid injection of radioisotopes and Coomassie blue dye. *J Neurosurg* 23: 12–22, 1965

21. FIESCHI C, AGNOLI A, BATTISTINI N, et al: Mean transit time of a non-diffusible indicator as an index of regional cerebral blood flow. *Trans Amer Neurol Ass* 91: 224–226, 1966

22. BELL RL: Observations of cerebral arteriovenous transit times using radioiodinated human serum albumin. *J Nucl Med* 5: 9–15, 1964

23. FIESCHI C, AGNOLI A, GALBO E: Effects of carbon dioxide on cerebral hemodynamics in normal subjects and in cerebrovascular disease studied by carotid injection of radioalbumin. *Circ Res* 13: 436–447, 1963

24. FAZIO C, FIESCHI C, AGNOLI A: Direct common carotid injection of radioisotopes for the evaluation of cerebral circulatory disturbances. *Neurology* 13: 561–574, 1963

25. ROSENTHALL L: Detection of altered cerebral blood flow using technetium-99m pertechnetate and the gamma-ray scintillation camera. *Radiology* 88: 713–718, 1967

26. BURKE G, HALKO A: Cerebral blood flow with sodium pertechnetate Tc-99m and the scintillation camera. *JAMA* 204: 109–114, 1968

27. LAMBETH JT, GOTTSCHALK A: Correlation of cerebral blood flow dynamics with time lapse scintiphotography using the gamma camera with multichannel analyzer. *J Nucl Med* 8: 263, 1967

28. ARNOLD JS: Anger camera studies of cerebral blood flow. *J Nucl Med* 8: 264–265, 1967

29. POWELL MR, ANGER HO: Blood flow visualization with the scintillation camera. *J Nucl Med* 7: 729–732, 1966

30. BRITTON KE: A feasibility study of a screening test for abnormalities of carotid blood flow using technetium-99m. *J Neurol Neurosurg Psychiat* 32: 379–382, 1969

31. JACKSON GL, BLOSSER N: Nondestructive method for measuring cerebral hemispheric blood flow—a preliminary report using a gamma camera. *J Nucl Med* 10: 501–507, 1969

32. POTCHEN EJ, DAVIS DO, WHARTON T, et al: Regional cerebral blood flow in man. I. A study of the xenon-133 washout method. *Arch Neurol* 20: 378–383, 1969

33. LASSEN NA, HOEDT-RASMUSSEN K, SORENSEN SC, et al: Regional cerebral blood flow in man determined by krypton-85. *Neurology* 13: 719–727, 1963

34. GLASS HI, BRANT A, CLARK JC, et al: Measurements of blood volume using red cells labeled with radioactive carbon monoxide. *J Nucl Med* 9: 571–575, 1968

35. RISBERG J, ANCRI D, INGVAR DH: Correlation between cerebral blood volume and cerebral blood flow in the cat. *Exp Brain Res* 8: 321–326, 1969

36. TER-POGOSSIAN MM, EICHLING JO, DAVIS DO, et al: The measure in vivo of regional cerebral oxygen utilization by means of oxyhemoglobin labeled with radioactive oxygen-15. *J Clin Invest* 49: 381–391, 1970