QUANTITATIVE CEREBRAL CIRCULATION STUDIES WITH SODIUM PERTECHNETATE

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A small general-purpose computer interfaced with a gamma scintillation camera was used to compare the integrated counting rates measured over specific regions of the cerebral cortex from the time of intravenous injection of ^{99m}Tc-pertechnetate up to the time of peak radioactivity. The initial slope describing the rate of arrival of the tracer at various regions of the cortex was also measured, and comparisons were made between corresponding regions over each cerebral hemisphere. In 50 persons without evidence of cerebrovascular disease, the right/left ratios were 1.00 ± 0.10 (1 s.d.). Seventy-four percent of 23 patients with clinical evidence of cerebrovascular accidents had right/left ratios that were beyond 2 s.d. of the normal mean. The sensitivity of the method was increased by viewing the images before selection of the areas of interest by means of a light pen, compared to analyzing the entire cerebral hemisphere. While validation of the method will require extensive study in many patients suspected of cerebrovascular disease, our initial results suggest its potential value.

With the stimulus and insight provided by the classic studies of Kety and Schmidt in 1945, clinical investigators have continued to search for a simple method of measurement of cerebral blood flow that would achieve the widespread clinical usefulness of techniques such as brain scanning, cerebral arteriography, and pneumoencephalography. Such studies should prove useful in the diagnosis and care of patients with cerebrovascular thromboembolism, transient ischemic attacks, subarachnoid hemorrhage, trauma, and arteriovenous malformations. Much attention has been given to measurements of regional as well as total cerebral blood flow for several reasons: (A) Variation in blood flow between the two cerebral hemispheres of the brain in the same individual is likely to be less than differences in total cerebral blood flow between individuals; (B) Many important diseases affect regional cerebral blood flow and may be detectable by regional measurements even if not by measurement of total cerebral blood flow.

A technique frequently used for measuring cerebral blood flow is based on measurement of the mean transit time of a freely diffusible indicator, such as ^{133}Xe (*1,2*). Because of the necessity of carotid artery puncture with threading of a catheter into the internal carotid artery, the technique cannot be used as a screening method or for monitoring critically sick patients. The work of Mallet and Veall (*3*) followed by that of Obrist, et al (*4*) and Austin, et al (*5*) documented the feasibility of using an inhalation or an intravenous method of administering the xenon tracer without the need for carotid artery puncture.

While these modified techniques based on ^{133}Xe may achieve more widespread use in the future, another approach—the use of nondiffusible indicators such as sodium pertechnetate—is gradually being taken by others. Such studies have intrinsic appeal since this agent is widely used for brain scanning, and cerebral circulation studies could easily be performed on a routine basis if only an intravenous injection were required.

In a previous report we described the clinical use of the nondiffusible tracer, sodium pertechnetate, combined with the scintillation camera (vertex view) in the differential diagnosis of patients suspected of cerebrovascular disease or mass lesions of the brain (*6*). In essence, our results indicated that, while far from ideal, useful information could be obtained

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in a significant number of patients. Mass lesions nearly always were found to have a blood flow that was equal to or greater than that of surrounding brain while areas of the brain involved in thromboembolism had evidence of decreased circulation.

In the present paper we wish to describe our subsequent results using a computer-assisted quantitative method of data analysis to supplement subjective interpretation of the serial images.

PATIENTS AND METHODS

Fifty patients in the present study had no clinical evidence of cerebrovascular disease. Twenty-eight of these had an average age of 60 years nad hypertension or elevated serum cholesterol; these were studied as part of a survey to evaluate screening procedures in the detection of cerebral ischemic disease. The other 22 patients without evidence of cerebrovascular disease had been referred for brain scans because of the suspicion of cerebral neoplasia, and often had seizure disorders, headache, or psychiatric disturbances. Their average age was 36 years.

Twenty-three patients with overt cerebrovascular accidents were studied. All were thought on clinical grounds to have involvement of the territory of either the internal carotid or middle cerebral artery. Patients with evidence of cerebral hemorrhage, i.e., red blood cells in the cerebrospinal fluid, were excluded. The average age of this group was 65 years; 12 were female and 11 male. Seventeen of the 23 patients were studied within 3 weeks of the acute episode. The other six had severe residual neurological abnormalities from cerebrovascular accidents suffered from 2 to 18 months before the study; five had had previous studies at the time of the acute episode.

A Nuclear-Chicago Pho/Gamma III scintillation camera was used with either a 4,000 parallel-hole collimator or 17,000-hole high-sensitivity collimator. The vertex (or top) view was routinely obtained so that the regions of the anterior, middle, and posterior parts of the middle cerebral artery in both cerebral hemispheres could be viewed simultaneously. Activity in the patient's shoulders and trunk was shielded from the detector by flexible lead sheets. A bolus of 20 mCi of ^{99m}Tc-sodium pertechnetate in a volume of 0.8–2.0 ml was injected intravenously using the Oldendorf technique. Cranial activity was recorded in serial one to two second frames in a 64 × 64 matrix format by means of an image display and analysis (IDA) system interfaced to the gamma scintillation camera (*7,8*).

ANALYSIS OF DATA

The data were displayed from magnetic-tape buffer as either separate 1- or 2-sec images or in various

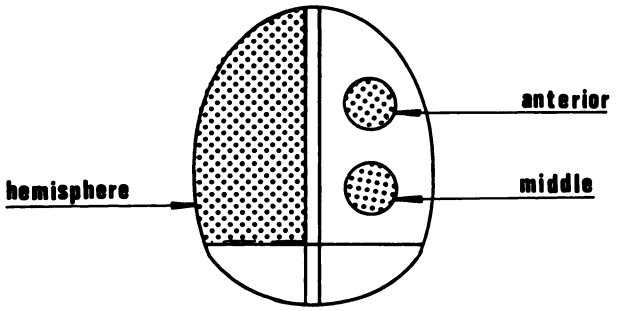

FIG. 1. Diagram of vertex view showing regions selected (dotted areas) for quantitation. Three regions illustrated were selected for each hemisphere making total of six regions.

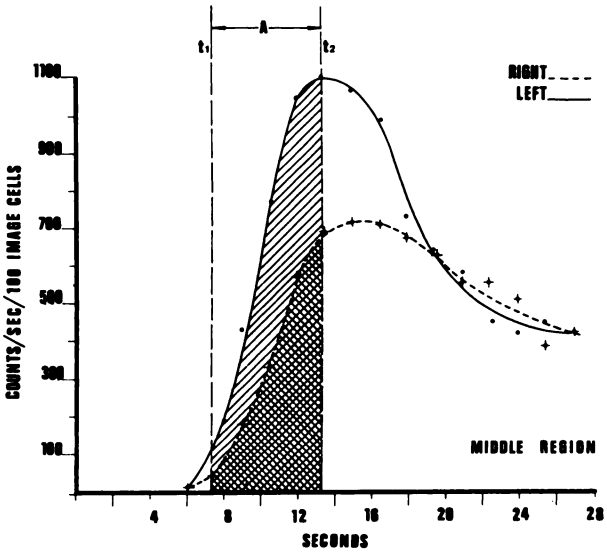

FIG. 2. Time-activity curves for left and right middle regions in patient with left hemiparesis. Areas under curves estimated by summing counts in interval "A". t_1 is time at which counting rate became 2× that of background activity; t_2 is time of earliest peak among the selected regions.

combinations of time intervals. Image contrast could be continuously varied by the observer while viewing the images. Images were photographed from the display monitor on 35-mm film. The details of the Image Display and Analysis (IDA) system have been described previously (*9,10*).

Although quantitative information could be obtained from any area of the images, six areas of interest were selected routinely. Regions comprising 50–60 image cells totaling about 5 cm^2 in area were flagged with a light pen in the anterior and middle portions of each hemisphere (Fig. 1). Exactly corresponding regions in the opposite cerebral hemisphere were selected by automatic computer programs. Care was taken to avoid flagging venous

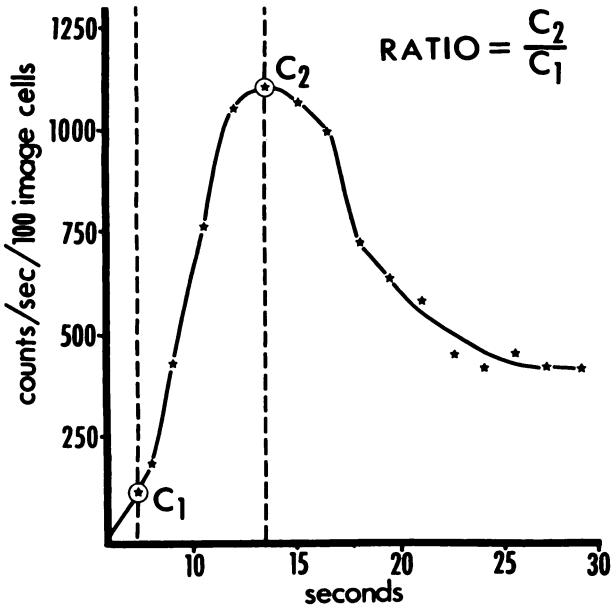

FIG. 3. Time-activity curve showing time interval in which maximum counting rate (C_2) and minimum counting rate (C_1) were identified. Ratio, C_2/C_1, is determined for each image cell and displayed with light intensity proportional to numerical value.

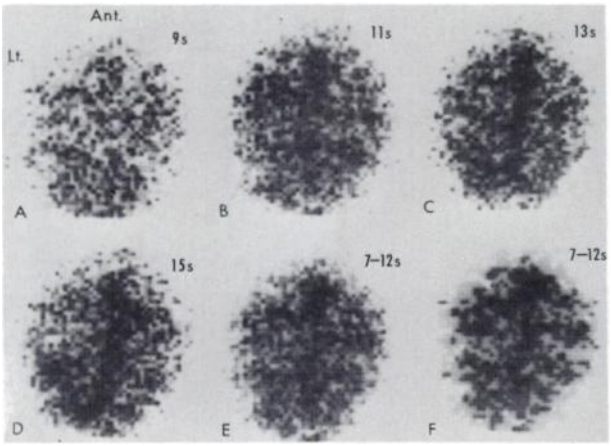

FIG. 4. Cerebral transit study in patient without cerebrovascular disease. (A–D) Serial two second images photographed from display monitor; time in seconds after injection. (E) Summed image for time interval 7–12 sec. Right/left ratios were: anterior region 0.98, middle region 1.04, hemisphere 0.93. (F) "functional" image interpreted as symmetrical.

sinuses. Total hemispheral activity was delineated by the placement of one horizontal and two vertical cursors with exclusion of superior sagittal and transverse sinus activity. A previously stored image of a sheet source of ^{99m}Tc activity ("flood field") was employed to correct the observed counts in each region for field nonuniformity of the scintillation camera. Corrected counts were normalized to 100 image cells to allow comparison of equally sized areas between the hemispheres.

Figure 2 illustrates typical time/activity curves which were plotted from the corrected normalized counts obtained over the middle region of each hemisphere. Our data analysis was not based on the measurement of mean transit time but is more closely related to the microsphere distribution method of measuring relative regional blood flow which will be considered in the discussion.

The microsphere method has been applied successfully to studies of the distribution of pulmonary arterial, coronary, and peripheral blood flow, but its extension to the study of the brain has been limited by potential toxicity. Therefore, we have attempted to apply the same principle to the use of a nondiffusible indicator, i.e., sodium pertechnetate, limiting the observations to the period when only a small fraction of the activity has crossed the vascular region being observed.

The initial accumulation of activity in each region was taken as the area under the time-activity curves

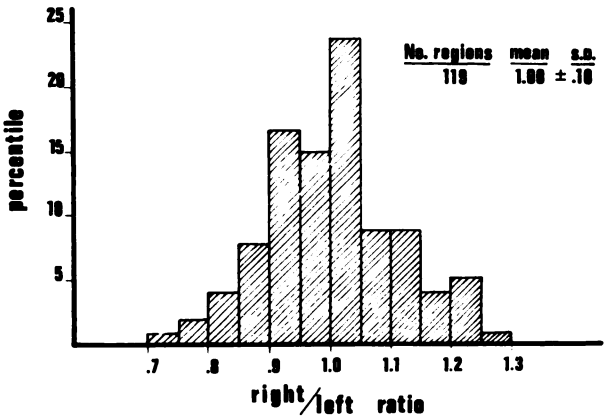

FIG. 5. Distribution of right/left ratios for anterior, middle, and hemispheral regions in 50 patients without cerebrovascular disease.

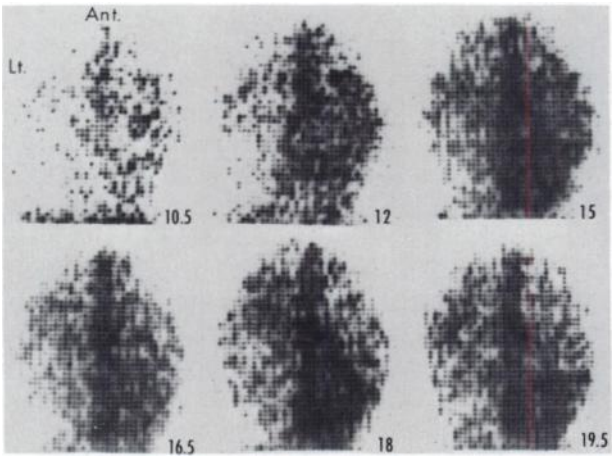

FIG. 6. Selected serial 1.5-sec images in patient with right hemiparesis. (Upper row) decreased activity in anterior portion of left hemisphere. (Lower row) delayed increase in relative activity in anterior portion of left hemisphere.

TABLE 1. PATIENTS WITHOUT CEREBROVASCULAR DISEASE

	Average age (years)	Right/left ratios for summed counts to earliest peak (mean ± 1 s.d.)					
		Anterior		Middle		Hemispheral	
		No.	Region	No.	Region	No.	Region
Selected normals (28 persons)	60	26	1.00 ± .12	27	0.99 ± .10	26	1.03 ± .06
Referred for brain scans (22 patients)	36	12	1.01 ± .16	20	1.01 ± .12	8	.99 ± .09
Total (50 patients)		38	1.00 ± .13	47	1.00 ± .11	34	1.02 ± .07

from the time the activity was twice background up to the time of the fastest peak. These are indicated in the figure as the sum of the counts accumulated within the interval "A" (Fig. 2), starting from the time the counting rate rose above background (t_1) to the time (t_2) of the earliest peak among the selected regions being compared.

The same time interval was used to integrate the accumulated counts in all regions. The right/left ratio of the summed counts was then determined for the anterior, middle, and total hemispheral portions of the cerebral hemispheres as seen in the vertex view.

A second type of analysis was related to the slope of the ascending portion of the time/activity curve. Within the same time interval selected for the right/left ratio determinations, the maximum and minimum counting rates were identified for every image cell in the 64 × 64 matrix, and the ratio between the values displayed as an image where the film density was directly proportional to the ratio values (Fig. 3). These "functional" images (*8*) were then viewed with and without contrast enhancement.

RESULTS

In all 50 patients without cerebrovascular disease the distribution of activity between the two cerebral hemispheres in serial 1–2-sec images (Fig. 4) appeared symmetrical. The right/left ratios of the accumulated counts up to the time of the earliest peak for anterior, middle, and hemispheral regions averaged 1.00 ± 0.10 for 119 regions (Table 1 and Fig. 5). The functional images also showed symmetrical distribution of the ratios in all 50 patients.

Among the 22 patients who had been referred for brain scans because of suspected intracranial pathology, normal ratios were obtained in 21; one patient had increased peripheral activity attributed to skull metastases.

PATIENTS WITH CEREBROVASCULAR DISEASE

All 23 patients in this group had hemiparesis or hemiplegia. Eleven were also aphasic or dysphasic.

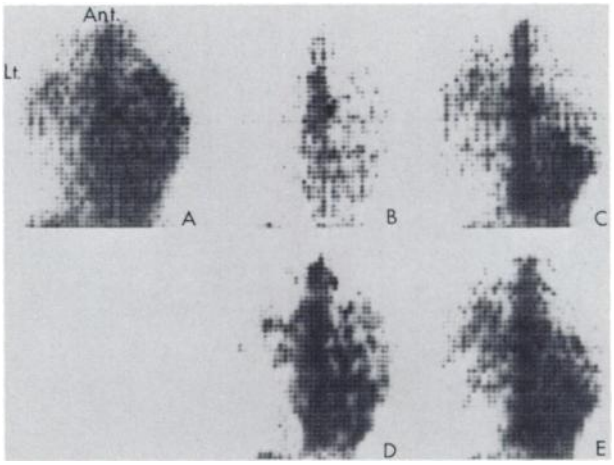

FIG. 7. Same patient as in Fig. 6. (Upper row) Summed images for intervals 7.5–15 sec (A and B), and for 15–22.5 sec (C). A and B differ only in amount of contrast selected. Right/left ratio for time interval 7.5–15 sec were: anterior region 1.31, middle region 1.56, hemisphere 1.50. (Lower row) "functional" images for interval 7.5–15 sec (D), and 15–22.5 sec (E).

An example of the serial scintillation camera images photographed from the display monitor of the IDA system is shown in Fig. 6; the processed images are seen in Fig. 7. The distribution of the right/left ratios of the counts accumulated up to the time of the earliest peak in the 23 patients is shown in Fig. 8. In the hemispheral region 11 patients (48%) had ratios outside 2 s.d. of the mean of patients without cerebrovascular disease, while in the anterior or middle regions, 17 patients (74%) had ratios outside the 2 s.d. normal range. The right/left ratios for the six patients who had abnormal values in the smaller subregions, but normal values in the total hemisphere, are seen in Fig. 9.

In 15 of the 17 patients with abnormal right/left ratios there was less activity in the hemisphere clinically affected. The other two patients had higher activity in the hemisphere thought to be involved on the basis of clinical examination alone. The functional images were also abnormal, i.e., they showed asymmetry in the 17 patients with abnormal right/left ratios.

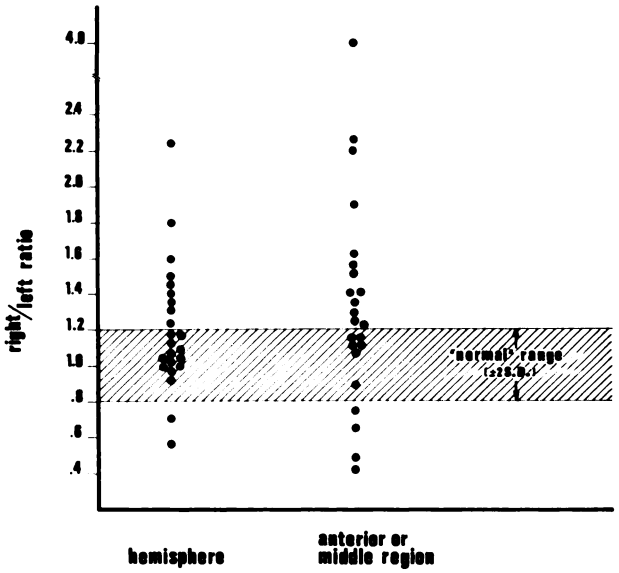

FIG. 8. Right/left ratios for summed counts to first peak in 23 patients with cerebrovasular accidents. Shaded area shows range (±2 s.d.) in patients without cerebrovascular disease.

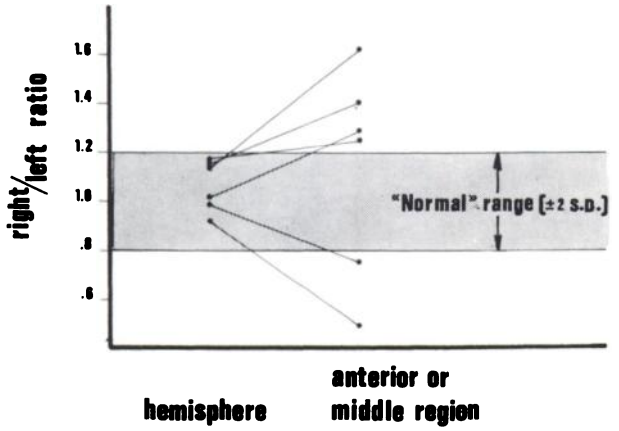

FIG. 9. Comparison of hemispheral vs. anterior or middle region right/left ratios. Shaded area as in Fig. 8.

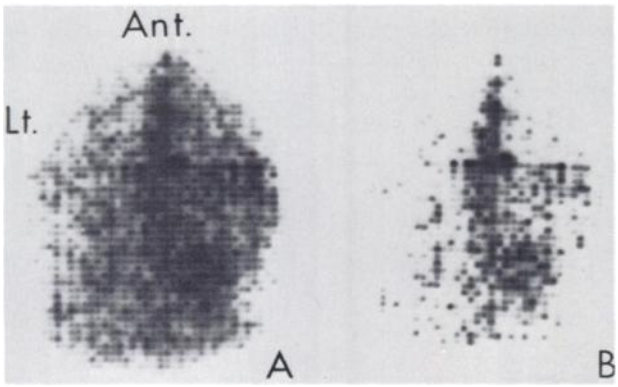

FIG. 10. Effect of contrast enhancement on summed image for interval 7.5–15 sec in patient with right hemiparesis. (A) normal contrast, (B) increased contrast. Decreased activity in left hemisphere more prominent in B.

DISCUSSION

Many applications of radioactive tracers to the study of blood flow (F) are based on measurement of the transit times of various indicators across the region of interest (*11,12*). Each component of the circulation is characterized by the mean transit time (T) of the specific indicator used to evaluate the system.

The basic equation that defines the mean transit time is $T = V/F$ where the volume V depends on the indicator used. In the case of a nondiffusible indicator such as labeled red blood cells, the volume V indicated in the equation is the blood volume of the system; in the case of a diffusible indicator such as xenon, the volume of distribution V corresponds to the entire mass of the organ including its blood content. Pertechnetate ion, the tracer used in the present study, is more diffusible than red blood cells but less diffusible than xenon. Objections have been raised to the use of nondiffusible indicators such as pertechnetate for study of the cerebral circulation, related to the fact that the data are thought of in terms of transit times.

As can be seen in the basic equation, mean transit time reflects both blood flow and the volume of distribution of the indicator. As Lassen (*13*) has stated, "It is necessary to assign V an assumed value. It is on this crucial point that nondiffusible tracers are so clearly inferior to freely diffusible tracers. For nondiffusible tracers, where V is approximately equal to cerebral blood volume, V cannot be assumed to be constant. Variations of more than 100% between the volume of an engorged vascular system and a collapsed one are certainly to be expected. For this reason, one cannot expect to gain reliable information to blood flow from transit time studies with nondiffusible tracers (e.g., ^{99m}Tc, IHSA, etc.)."

Such objections are probably valid if we analyze the data in terms of transit times. However, we prefer to restrict our use of the term *transit time* only when measurements are made of the concentration of the indicator at the outflow of the system, i.e., after it has crossed the region of interest. For example, this is what Kety and Schmidt measured in their original nitrous oxide method of measuring cerebral blood flow.

The method that we have proposed in this paper is an extension of the principle described first in 1956 by Sapirstein (*14*) which states that an adequately mixed indicator injected into the left heart is initially distributed to various organs in proportion to their blood flow. Potassium-42 and ^{86}Rb were used for this purpose by Sapirstein since these ions are believed to be completely extracted by organs other than the

brain during their initial circulation, and thus their distribution reflects the distribution of cardiac output during the initial 60 sec after injection.

The principle has been applied recently in the use of radioactive tracer microspheres to study the circulation to all organs in experimental animals and to the lungs, heart, and extremities in man. Such radioactive microspheres are trapped by the first capillary bed they encounter. The principle is as follows:

If the blood flowing through an organ is completely cleared of injected microspheres during the first passage of blood through the region, the number of microspheres trapped in the organ is given by the following equation:

$$q = f \int_0^\infty C(t)\, dt \qquad (1)$$

where q is the particles trapped in the organ, f is the blood flow to the organ, and C(t) is the concentration of particles in the blood at time t. If we compare one region with another, the ratio of $q_1/q_2 = f_1/f_2$.

According to the Stewart-Hamilton principle, cardiac output is expressed by the following equation:

$$Q = CO \int_0^\infty C(t)\, dt \qquad (2)$$

where Q is the amount of indicator injected and CO is cardiac output. The following equation is derived from Eqs. 1 and 2:

$$\frac{f}{CO} = \frac{q}{Q} \quad \text{or} \quad f = CO \times \frac{q}{Q}. \qquad (3)$$

Therefore the fraction of cardiac output to an organ (or f/CO) is obtained by measuring the radioactivity of each organ after the injection of radioactive microspheres into the left heart and the injected dose of microspheres. If cardiac output is measured, absolute blood flow to an organ can be obtained.

The method that we have described using pertechnetate can be assumed to be valid insofar as the results are identical with those obtained with microspheres. We assume that the time/activity curve shortly after injection of pertechnetate is identical with simultaneously injected microspheres during the initial 12–16 sec after injection since neither tracer leaves the area being examined during that period. Thus, the recorded activity is independent of the volume of the region. By analogy the method is similar to the counting of the times of arrival of persons at the entrance to a bridge, which is analogous to a region of the brain. In contrast to the situation where we measure the time of arrival of the persons on the *opposite* side of the bridge (which would be related to the length of the bridge), the rate of arrival at the bridge is independent of the bridge itself. The difference between pertechnetate and microspheres is that in the case of the latter, the drawbridge is open, whereas microspheres accumulate on the bridge rather than cross it as pertechnetate does.

Preliminary observations suggest that for the first 10–20 sec after injection the behavior of pertechnetate is similar to that of microspheres. These results will be presented in detail elsewhere.

Monitoring the time course of the passage of intravenously injected bolus of radioactive material through the cerebral circulation by subjective interpretation of serial scintillation camera images has been shown to be an aid in the differential diagnosis of arteriovenous malformation, cerebral neoplasms, and occlusive cerebrovascular disease (*6*). An important advantage is that the procedure can be followed by a conventional brain scan and does not require any additional administration of radioactivity. Such studies have been found to help in the interpretation of both normal and abnormal brain scans (*15–19*). In our initial experience based on subjective interpretation without quantification, 57% of patients with acute cerebrovascular accidents involving the territories of the internal carotid or middle cerebral arteries had visible decreases in activity in the hemisphere clinically affected (*6*).

There are several important advantages in being able to supplement the information provided by the images alone with the quantitative data that the computer can provide. Although in the clear-cut case the differences in the time-course of the activity across the regions of the cerebral cortex are apparent on simple inspection of the images, quantification aids in the establishment of criteria based on statistical evaluation of the results which in turn facilitates interpretation.

Particularly with small regions, significant differences may be missed by simple inspection of the images. An additional advantage is that corrections can be made for nonuniformity of the field responsiveness of the scintillation camera, and the observer is not limited to the technical factors such as dot density that usually are preselected before the performance of the study. The computer display permits a complete range of contrast enhancement of both the raw and processed data together with the capability of quantification.

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