REGIONAL CEREBRAL BLOOD FLOW ESTIMATION IN THE DIAGNOSIS OF CEREBROVASCULAR DISEASE

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Kety has stated recently: "In spite of whatever contributions they may have made to normal and abnormal human physiology, measurements of the total cerebral circulation have been of only limited value in the study of the individual patient with cerebrovascular disease. For diagnosis, localization, and evaluation of progress of the disorder in the individual patient, we are still in need of suitable methods" (*1*).

In this report we describe the results of a procedure that, while not the final answer, offers promise of providing a simple procedure that is helpful in the study of regional cerebral blood flow in man.

The method is a modification of Oldendorf's technique of measuring mean transit time (*2,3*), the major improvements being in the instrumentation and data processing. In essence, the gamma camera is utilized to monitor the passage of an intravenously injected bolus of ^{99m}Tc-sodium pertechnetate through the cerebral circulation to gain information about regional cerebral blood flow (*4,5*). The technique can be used with the conventional brain scan, and only a single, intravenous injection is required.

We have studied more than 400 patients to try to answer the following questions: (A) Can we improve our diagnostic accuracy in cerebrovascular disease? (B) Can we differentiate cerebral infarction from cerebral neoplasm?

TABLE 1. PATIENT CHARACTERISTICS

Patient classification	Number	Average age (range)	Males (%)	Number with contrast angiography
Cerebrovascular disease				
1. Ischemic stroke (includes embolic)	58	57 (9–83)	52	29
2. Hemorrhagic stroke	10	46 (29–65)	60	9
3. Transient ischemic attack	14	61 (46–74)	64	10
4. Chronic	26	67 (46–86)	50	7
Cerebral neoplasm and arteriovenous malformation	22	53 (26–70)	59	21
Other neurological diseases*	40	48 (11–85)	40	17
Asymptomatic	40	62 (49–72)	50	0
Total	210			93

* Includes idiopathic epilepsy, idiopathic papilledema, multiple sclerosis, brain abscess, and psychiatric disorders.

DESCRIPTION OF PATIENTS AND METHODS

Two hundred ten patients studied between July 1969 and April 1971 who had adequate clinical and laboratory data form the basis of this report (Table 1). Patients were classified as acute stroke if they had the abrupt onset of neurological deficit attributable to primary pathology of the cerebral vessels which persisted for more than 24 hr (*6*). Sixty-nine percent of the 68 patients in this group were studied within ten days of the onset of symptoms. Ten of the 68 patients had subarachnoid or intracerebral hemorrhage and were considered separately from those with ischemic strokes. Patients with residua from previous strokes or with findings attributable to diffuse cerebral atherosclerosis were considered chronic, and those with recurrent transient loss of function lasting minutes or hours were classified as transient ischemic attack. Subdivision was made into internal carotid and vertebrobasilar groups on the basis of clinical and contrast angiographic evidence.

Patients with primary cerebral neoplasia or arteriovenous malformations were considered together. All had histological and/or arteriographic confirmation of the diagnosis.

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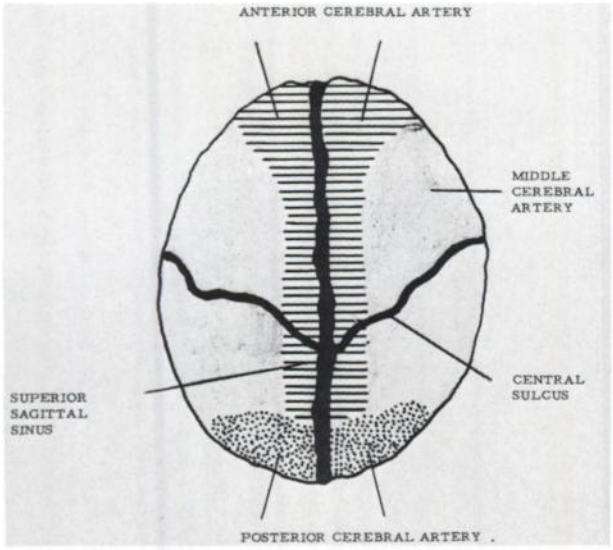

FIG. 1. Diagram of distribution of cerebral arteries as seen in vertex view.

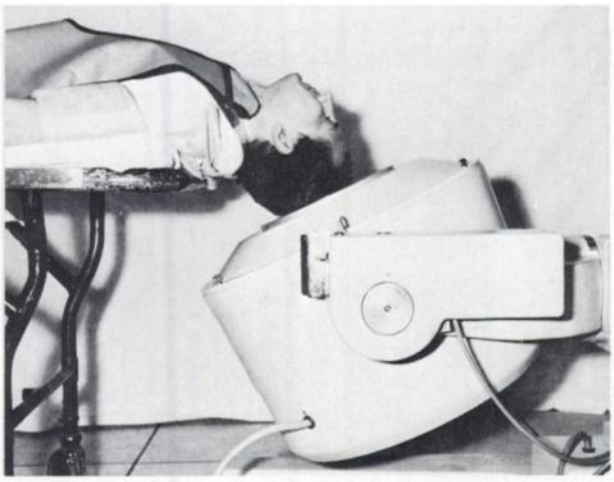

FIG. 2. Patient in position for regional cerebral blood flow estimation (rCBFe). Lead shields prevent neck and shoulder activity from being recorded.

Eighty patients without evidence of cerebrovascular disease were studied. Forty had a variety of neurological disorders such as generalized seizures, cerebral abscess, multiple sclerosis, and idiopathic papilledema. The other forty had diabetes, hypertension, or elevated serum cholesterol and were studied as part of a survey to evaluate screening procedures in the detection of cerebral ischemic disease.

The radioactive tracer studies and the contrast angiograms were reviewed separately without knowledge of the patients' clinical or laboratory data.

The vertex view was used since the major portion of the middle cerebral artery territory and portions of the anterior and posterior cerebral artery distributions are closer to the detector than in the anterior view (Fig. 1). The patient was studied in the supine position with his head hyperextended and positioned so that the orbito-meatal line was parallel to the face of the collimator of the scintillation camera (Fig. 2). Either a 4,000 or 17,000 parallel-hole collimator was used. Neck and shoulder activity was shielded from the detector by means of a collar filled with lead shot and with flexible lead sheets. Twenty millicuries of ^{99m}Tc-sodium pertechnetate in a volume of 0.5–2.0 ml were injected as a bolus into an antecubital vein using the injection technique described by Oldendorf (*7*). Serial 35-mm photographs were made of the scintillation camera image on Kodak RAR 2498 film with a Nikon F camera equipped with motorized film advance (*8*). In order to insure adequate statistics and temporal resolution, the first frame recorded the initial 6,000 counts reaching the cerebral circulation. Thereafter, successive 2-sec exposures were made for 40–60 sec from the time of injection. Without moving the patient, a final 350,000-count image was made after the tracer had equilibrated in the extracellular fluid. A conventional five-view brain scan was performed 1 hr after injection.

RESULTS

A typical regional cerebral blood flow estimation (rCBFe) in a person without cerebrovascular disease is illustrated in Fig. 3. The tracer appears first in the central portion of the territory of the middle cerebral arteries (Figs. 3A and B) and spreads anteriorly and posteriorly (Fig. 3C). In frames D and E the superior sagittal sinus, torcular Herophili, and sigmoid sinuses are visualized. Asymmetry was frequently noted in the venous phase (Fig. 3E) even in normal persons.

Acute stroke. Asymmetrical distribution of activity in the arterial-capillary phase lasting for at least 4 sec (two frames) was observed in 57% of the

TABLE 2. ACUTE STROKE

Patient category	Number	rCBFe* abnormal†	Brain scan abnormal	Contrast angiography: Number	Contrast angiography: abnormal
Ischemic stroke					
1. Carotid	47	27(57%)	15(32%)	23	17(74%)
2. Vertebrobasilar	11	2(18%)	1(9%)	6	2(33%)
Hemorrhagic stroke	10	5(50%)	3(30%)	9	8(89%)
Total	68	34(50%)	19(28%)	38	27(71%)

* Regional cerebral blood flow estimation.
† Unilateral decrease in activity.

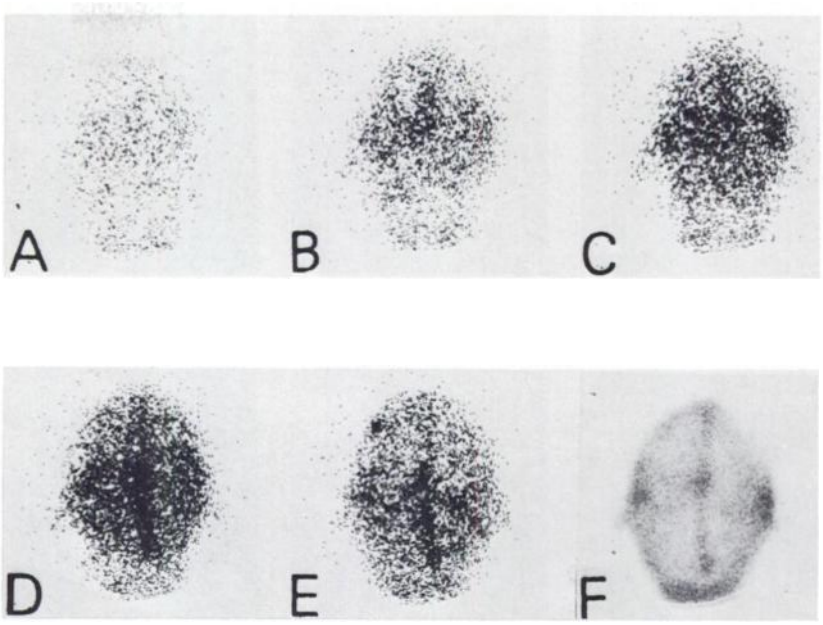

FIG. 3. Normal rCBFe. Frames A–E are sequential (but not consecutive) beginning 9 sec after injection. Frame F shows 350,000 count equilibration image.

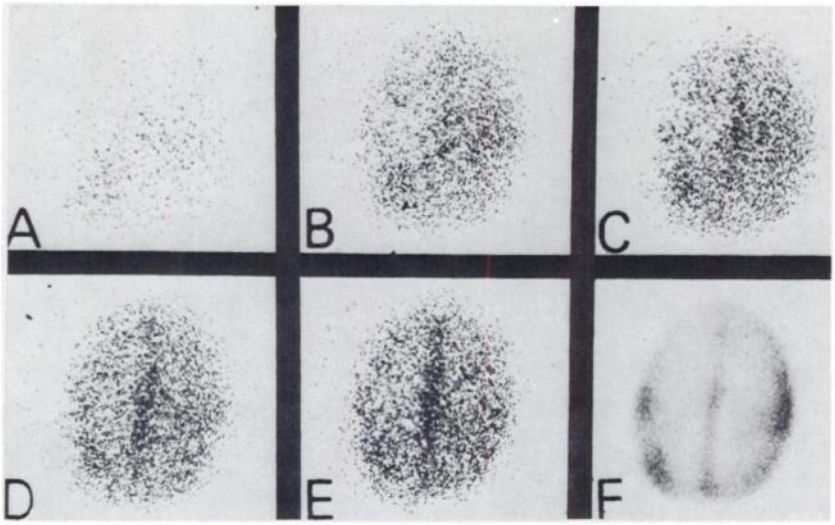

FIG. 4. Abnormal rCBFe in patient with left middle cerebral artery occlusion. Note sustained decrease in activity on left in frames B–E.

patients with ischemic strokes involving the internal carotid artery system, and in 50% of all the patients with acute strokes (Table 2). A typical example is shown in Fig. 4. Two types of abnormality were observed in patients with cerebrovascular disease: sustained decrease in activity in one cerebral hemisphere; and transient decrease in activity in the affected hemisphere which subsequently had greater activity than the unaffected side ("flip"). The latter is the result of delayed transit through the involved region of the brain and was observed in 25% of the abnormal studies in patients with cerebrovascular disease (Fig. 5). Only one patient of 80 without cerebrovascular disease demonstrated one of the above abnormalities.

The conventional brain scan in the patients with acute ischemic stroke involving the internal carotid artery or its branches was abnormal in 15 of 47 patients. Either one of the tracer studies was abnormal in 31 of the 47 patients (66%).

The incidence of abnormal rCBFe increased to 92% in patients with angiographic demonstration of internal carotid artery stenosis greater than 90% or middle cerebral artery branch occlusions (Table 3).

In three patients with angiographically demonstrated bilateral cerebrovascular disease and in one patient who did not have a contrast study, the rCBFe abnormality appeared worse on the side not clinically affected. Six of the patients with acute ischemic strokes in the internal carotid artery distribution, who had normal rCBFe, had contrast angiograms: two were normal, one each showed bilaterally severe

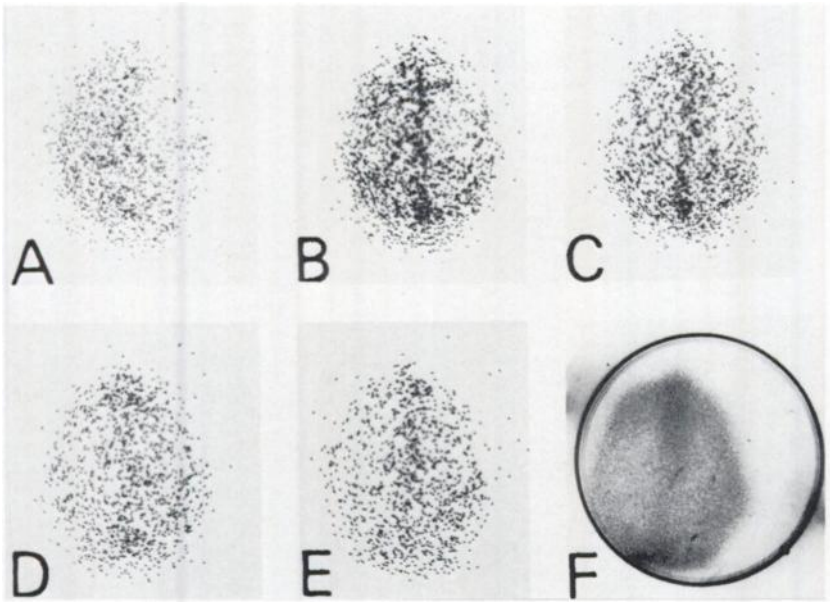

FIG. 5. Abnormal rCBFe in patient with left hemiparesis. Prolonged transit through right hemisphere is indicated by decreased activity in frames A and B, followed by increased activity in frames D and E ("flip").

internal carotid artery stenosis, severe unilateral internal carotid artery stenosis with good collateral, unilateral anterior cerebral artery occlusion, and a large plaque in an internal carotid artery.

Chronic cerebrovascular disease. Four patients out of 19 with focal neurological signs from 3 months to 10 years in duration had abnormal rCBFe, and two of these had contrast angiographic confirmation of cerebrovascular disease. A smaller fraction of the patients without focal signs had abnormal studies (Table 4).

Transient ischemic attack. Only two patients with transient ischemic attacks had abnormal rCBFe, and one correlated with the side clinically affected (Table 5). Ten patients underwent contrast angiography with the following results: two studies were normal, one each showed no filling of an anterior cerebral artery, severe stenosis of an internal carotid artery, and occlusion of one branch of a middle cerebral artery.

Neoplasm and arteriovenous malformation. In contrast to the findings in cerebrovascular disease, patients with very vascular neoplasia or arteriovenous malformations (Table 6) had focal increases in tracer activity corresponding in location to abnormalities on the brain scan. Very rapid transit was indicated by an early blush of intense activity followed by a rapid waning of the activity (Fig. 6). No patient with a primary intracerebral neoplasm had a unilateral decrease in activity.

Patients without cerebrovascular disease. One patient of the 40 with noncerebrovascular neurological diseases had abnormal rCBFe. This patient, who presented with marked hemiparesis, was diagnosed as progressive multifocal leukoencephalopathy. Re-

TALBE 3. ACUTE STROKE—CORRELATION WITH CONTRAST ANGIOGRAPHY

Contrast angiography findings	No. patients with abnormality	rCBFe* abnormal†	Brain scan abnormal
Unilateral internal carotid stenosis (>90%)	9	8	4
Bilateral internal carotid stenosis (>90%)	1	0	1
Moderate internal carotid stenosis (50–90%)	2	1	1
Middle cerebral artery branch occlusion	4	4	1
Anterior cerebral artery occlusion	3	1	1
Posterior cerebral artery occlusion	1	0	0
Basilar artery irregularity	1	0	1
Vessel displacement	2	1	2
Aneurysm	5	3	1
Other	3	1	0
Normal	7	3	1
Total	38	22	13

* Regional cerebral blood flow estimation.
† Unilateral decrease in activity.

TABLE 4. CHRONIC CEREBROVASCULAR DISEASE

				Contrast angiography	
Patient category	Number	rCBFe* abnormal†	Abnormal scan	Number	Number abnormal
With focal signs	19	4(21%)	1	3	3
Without focal signs	7	2(28%)	0	4	3
Total	26	6(23%)	1(4%)	7	6(85%)

* Regional cerebral blood flow estimation.
† Unilateral decrease in activity.

peat rCBFe 1 month later was normal. None of the 17 patients who had contrast angiography had significant abnormalities of the cerebral vasculature.

All of the 40 survey patients without symptoms of cerebrovascular disease had normal rCBFe.

DISCUSSION

A major problem in the diagnosis of intracranial tumors is that the symptoms may be attributed to cerebrovascular disease, especially in the elderly. Although the abrupt onset of symptoms is characteristic of cerebrovascular accidents, symptoms may appear with great suddenness in patients with tumors, especially glioblastomas (*9*). The conventional brain scan is helpful in decreasing the probability that the patient has a mass lesion since about 85–90% of patients with cerebral neoplasia have abnormal scans (*10,11*). However, if the brain scan is abnormal and if the abnormal activity is located in the distribution of a single cerebral artery, cerebral infarction is more likely than tumor. The shape of an abnormality may also help differentiate tumor from infarction (*12*).

Despite these guidelines, however, diagnostic problems still arise. In such cases regional cerebral blood flow estimation (rCBFe) can aid in the interpretation of both normal and abnormal brain scans. The finding of *decreased* blood flow in the distribution of a cerebral artery coupled with a normal brain scan greatly increases the probability of cerebral ischemic disease. Decreased rCBFe in the region of a lesion seen in the brain scan reduces the likelihood of tumor (Fig. 7) since all the patients with tumors in our series had normal or *increased* flow in the region of the lesions.

In ischemic disease involving the internal carotid artery or its branches, we found rCBFe twice as likely to be abnormal as the brain scan at the time the patient was first examined (*13*). Twenty seven of 47 patients had abnormal rCBFe, and another four had normal rCBFe but abnormal brain scans; thus the overall sensitivity of the tracer studies was 66% in patients with disease of the internal carotid or middle cerebral artery. In a similar group of 86 stroke patients, Rosenthall and Martin, employing the anterior view, found abnormal rCBFe 45% of the time while either of the tracer studies was abnormal in 57% of the patients (*5*). Other investigators have reported not strictly comparable series of stroke

TABLE 5. TRANSIENT ISCHEMIC ATTACKS

Patient category	Number	rCBFe* abnormal†	Brain scan No. abnormal	Contrast angiography Number	Contrast angiography Number abnormal
Carotid	11	2(18%)	0	8	3
Vertebrobasilar	3	0	0	2	0
Total	14	2(14%)	0	10	3(30%)

* Regional cerebral blood flow estimation.
† Unilateral decrease in activity.

TABLE 6. CEREBRAL NEOPLASIA AND ARTERIOVENOUS MALFORMATION

Diagnosis	Number	rCBFe* Normal	rCBFe* Increased activity
Arteriovenous malformation	3	0	3
Meningioma	7	0	7
Glioblastoma	4	0	4
Astrocytoma grade III	4	2	2
Astrocytoma grade II	2	2	0
Chromophobe adenoma	1	1	0
Craniopharyngioma	1	1	0
Total	22	6(27%)	16(73%)

* Regional cerebral blood flow estimation.

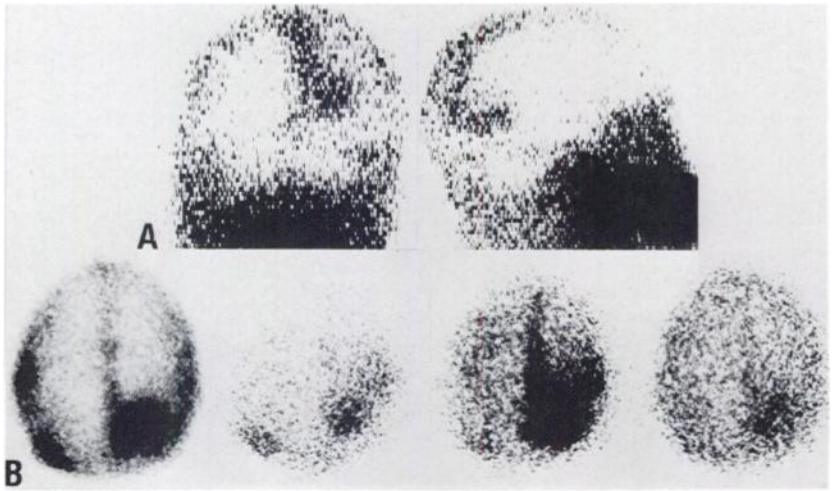

FIG. 6. Patient with left-sided focal seizures. A shows posterior and right lateral views from conventional brain scan with focus of abnormal activity in right occipital region. B shows rCBFe in same patient. First frame is equilibration image. Next frames recorded at 10, 12, and 30 sec after injection. Note early blush in right occipital region with subsequent waning of activity. Contrast angiogram confirmed presence of arteriovenous malformation.

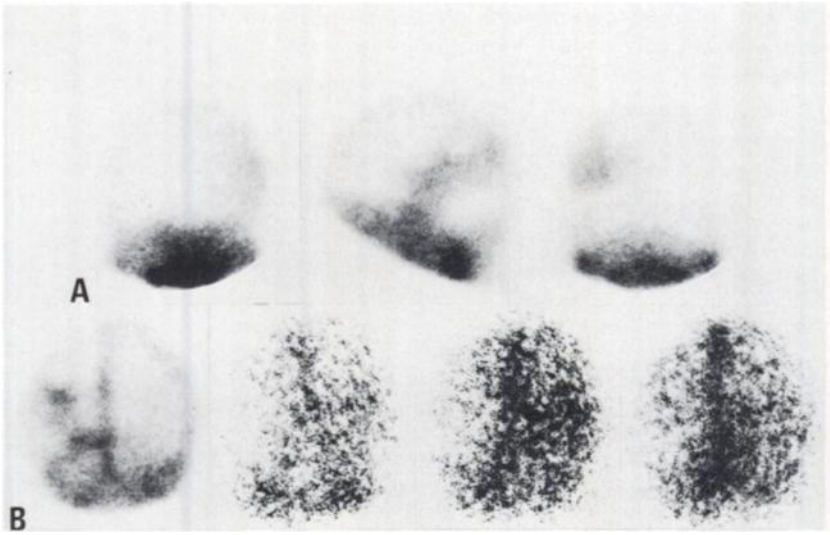

FIG. 7. Patient with left internal carotid artery occlusion. A shows anterior, left lateral, and posterior views from conventional brain scan with large area of increased uptake of tracer in left parietal region. B, same patient—rCBFe. There is sustained decrease in activity in left hemisphere.

patients where the incidence of abnormal rCBFe was 75–83% (*14,15*).

In cerebral neoplasia rCBFe is helpful in evaluating the vascularity of the lesions. The greatly increased blood flow through an arteriovenous malformation was easily identified (Fig. 6). Increased activity in the lesion soon after administration of the tracer with progressive increase in contrast between the lesion and surrounding tissues was characteristic of meningioma and glioblastoma. A normal pattern was found with low-grade gliomas.

How does the method described in this report compare with the ^{133}Xe techniques (*16,17*)? One advantage of ^{133}Xe is that the gas is eliminated rapidly by the lungs, and the procedure can be repeated frequently. However, for this procedure an intracarotid injection is usually required, and the technique is therefore not applicable to large numbers of patients.

There are two major advantages to the intravenous ^{99m}Tc-pertechnetate method of rCBFe. One is that it requires only an intravenous injection and is therefore suitable for examining large groups of patients. Repeat studies can be performed to assess the efficacy of various modes of therapy in cerebrovascular disease. A second advantage is that imaging devices such as the Anger camera can be employed to obtain an image with a high degree of spatial resolution. The observer can then ask specific questions about regional function and with the assistance of a small, general-purpose computer obtain numerical answers (*18,19*). This system may enhance the sensitivity of rCBFe.

A potential source of error inherent in the intravenous methods is the contribution of activity in the extracerebral tissues. Although the magnitude of this error in man is not known, there is reason to believe that it is small during the initial transit of the tracer (*20*).

Since as many as 84% of stroke patients have clinical involvement in the area of brain supplied by the middle cerebral arteries (*21*), we think it important to visualize as much of that vessel's distribution as possible. Thus we prefer the vertex view for rCBFe since this view includes parts of the territories of the anterior and posterior cerebral arteries as well as the middle cerebral artery. Although we have not detected isolated occlusions of the anterior or posterior cerebral arteries, we have visualized decreased flow to the posterior branches of the middle cerebral artery. With the vertex view we cannot detect lesions in the vertebrobasilar system, but these can usually be distinguished from disease of the middle cerebral artery on the basis of clinical evidence.

CONCLUSIONS

Regional cerebral blood flow estimation using intravenous ^{99m}Tc-pertechnetate has been found to be a simple and useful technique in the differential diagnosis of brain tumors and cerebrovascular disease. Characteristic abnormal findings were observed in 57% of the patients presenting with acute ischemic stroke involving the internal carotid artery or its branches. Regional cerebral blood flow estimation gives information about vascularity of cerebral neoplasia and helps distinguish these lesions from cerebral infarction.

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