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Radioisotope Measurement of Brain Blood Turnover Time as a Clinical Index of Brain Circulation[1]

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INTRODUCTION

A number of workers have applied radioisotopes as an indicator for the assessment of human brain blood flow. Seeking safety and simplicity, individuals in several laboratories have used intravenous injection to radiolabel the blood allowing simple external measurements of various parameters related to blood flow (1-8). Described here are clinical studies conducted utilizing a tracer technique that defines the most common or mode transit time of the tracer through the brain blood pool by means of externally monitoring the cranial passage of a bolus of gamma-labeled hippurate injected intravenously. The mode of the transit times of the brain passage of tracer is considered the brain blood pool transit time (BTT) and is applied here as a clinical index of the rapidity of brain blood pool turnover.

MATERIALS AND METHODS

The basic technique and its theoretical basis have been described (9-11). The present technique differs from its earlier form (9) primarily in the utilization of detection equipment of much higher quantum efficiency, thus allowing more accurate measurements with a smaller administered isotope dosage. Although large, specially shaped sodium iodide crystals are used in the present studies, smaller, suitably shielded, standard crystals would be practical, provided an increased dosage of radioactivity was injected. A pair of 2×2 inch crystals would require three to four times the dosage used here.

Fifty microcuries of ^{131}I iodo-hippurate are deposited as abruptly as possible into the right heart by an atraumatic method of venous distention which includes subsequent occlusion by an arm cuff followed by an injection of isotope and abrupt removal of the cuff. This method has been compared with simple rapid intravenous injection and found to result in a more abrupt deposition into the right

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heart (12). After cardiopulmonary passage, the bolus of tracer leaves the left heart and ten to twenty per cent is distributed to the brain. It is assumed here that the indicator is non-diffusible and remains in the blood during the first brain passage. Nearly total renal clearance of the hippurate (13) minimizes the early recirculation artifact produced by isotope reappearing in the arterial supply of brain after the first passage through peripheral organs, since the very early return will be largely renal.

A crystal photomultiplier gamma-radiation detection system is positioned bilaterally adjacent to the head and shielded to allow only radiation from the cranial portion of the head to be detected. The amount of tracer rostral to the floor of the cranial cavity is continuously monitored and plotted as a function of time. This count rate is represented by the uninterrupted curve of Figure 1.

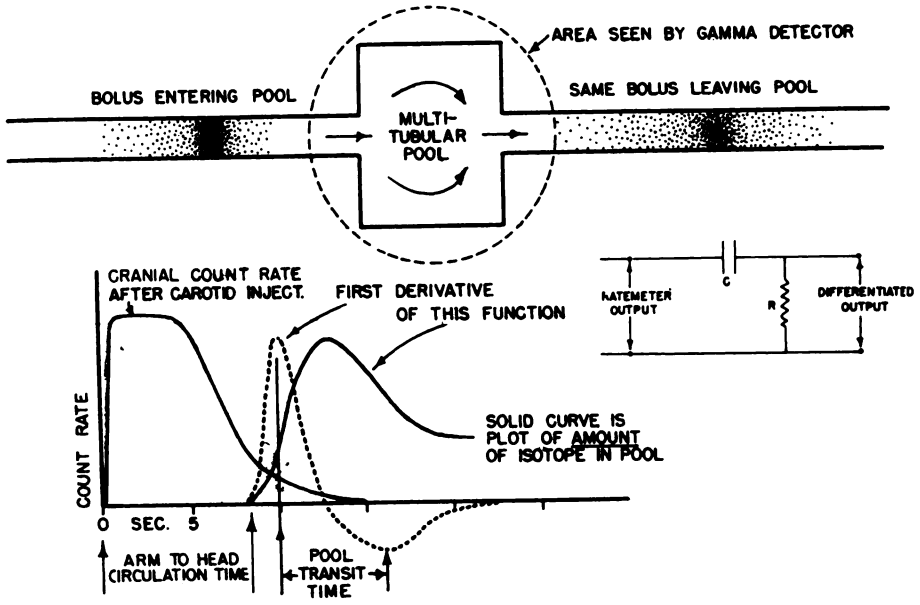

Fig. 1. A diagram showing the somewhat dispersed bolus of radioactive tracer approaching the cranial blood pool and the same, more dispersed bolus as it would appear leaving this pool and the field seen by the detection system. The times of maximum rate of increase and decrease mark the entrance and exit of the most concentrated part of the bolus from the cranial blood pool. This differentiation is easily achieved by a simple circuit which will provide a useful output voltage which closely defines the rate of change or first derivative of the count rate meter output voltage. A capacitor C is placed in series with the rate meter output voltage and the right plate of the capacitor is shunted to ground by resistance R. Current flow through C and R will closely approximate the rate of change of the rate meter output provided the time constant C and R is short relative to rates of change in rate meter output voltage. For a varying signal such as found in the present work, a differentiating time constant of about 0.1 second is adequate. This might be obtained with a value for C of 1 mfd and R of 0.1 megohms. Ideally, the output impedance of the rate meter will be substantially lower than the value of resistance R. A reserve of display sensitivity must be available since this additional circuitry results in a considerable attenuation of the input voltage. Because of an enhancement of noise inherent in the differentiation process, additional high frequency filtering may be required.

As the bolus of radioactivity begins to arrive in the head, usually 7 to 10 seconds after release of the venous obstruction, the count rate curve begins to increase as the leading edge of the bolus arrives in the cranial portion of the head. The initial interval between release of the bolus from the arm to its appearance in the detector field, defines the arm-to-head circulation time (AHCT). The tissues seen will be predominantly brain, with a minor contribution from scalp circulation (14). The count-rate curve subsequently reaches a maximum and then falls as the bolus of tracer passes on through and out of the cranial blood pool (uninterrupted curve in Figure 1).

The most concentrated portion of the bolus is used as a reference point for defining the transit time of the bolus. The entrance into and exit from the detector field of the densest segment of the bolus are defined by noting the time of occurrence of the maximum rate of rise of the cranial count-rate (entrance into pool) and its subsequent exit at the time of the maximum rate of fall (interrupted curve in Figure 1).

Capacitance differentiation of the rate meter output voltage (Figure 1) conveniently defines these two times, producing a diphasic curve with a positive peak (entrance time of the densest part of the bolus) and a subsequent negative peak (exit time). The interval between these two peaks is the most common or mode time of the tracer bolus through the cranial portion of the head and is here considered to be the brain blood pool transit time (BTT) which is seen as the interrupted curve in Figure 1.

In this presentation, the BTT will be used as a clinical index of the rapidity of the brain blood pool turnover. The clinical validity of such an indication of the adequacy of brain blood flow is examined in the discussion. Measurements of BTT and arm-to-head circulation times (AHCT) were performed in about 534 subjects at Wadsworth General Hospital. These included normal subjects and subjects with primary neurological, cerebrovascular and other diseases. All are final diagnoses. "Hypertensive" here refers to subjects with brachial systolic pressures over 160 mm Hg or diastolic pressures over 90 mm Hg at the time of the study.

RESULTS

BTT in Normals

Sixty-five normal subjects have been studied. Nearly all were male patients on the surgical and medical wards and all were free from systemic disease. During the course of the studies, several artificial conditions were imposed, i.e. hyperventilation, Valsalva maneuver and neck compression and effects on BTT were observed.

When BTT in the group of 65 normals is plotted versus age, there is a general trend of increasing BTT with increasing age (Fig. 2). The range seen is from about six seconds in young adults to 10-11 seconds in healthy old age. Of the 65 subjects in this group, 22 were less than 40 years of age.

In 10 of 12 normal subjects studied before and after three minutes hyperventilation, the BTT was lengthened one to six seconds. In two, there was no measurable change in BTT. There was a corresponding change of AHCT in all

twelve. Using a non-diffusible tracer (RIHSA), the brain blood pool volume was found reduced by hyperventilation by an average of 6%, suggesting a reciprocal relationship between BTT and pool volume.

In fifteen normal subjects subjected to 30 mm Hg pressure applied by means of a sphygmamometer cuff placed around the neck, there was a demonstrable lengthening of BTT time relative to the uncompressed condition. The brain blood pool volume using a non-diffusible tracer was also increased by approximately ten per cent (15).

Elevation of intrathoracic and abdominal pressure by the Valsalva maneuver resulted in a prolongation of BTT in all of the eight normal subjects studied in this way. During the performance of individual tests, alterations of intrathoracic pressure (initiation of swallowing, phonation and sometimes with regular respiration) affected the display of the count-rate curves, particularly in the later segments of the curve when the bolus was largely in the venous portion of the pool. These effects on count-rate apparently reflect changes in the volume of the venous pool in response to outflow jugular pressure (15).

BTT in Neurological Disease

Results in a number of disease states are summarized in figures three to five. Alterations in BTT are broadly grouped here as: shortened; within normal limits; slight, moderate, or marked prolongation. These changes in BTT show the following correlations with the disease groups classified here (Fig. 3).

Shortening of BTT is evident in: arteriovenous malformation and the "headache" group. Within normal limits BTT is seen in: idiopathic epilepsy, alcoholic epilepsy, non-cerebral neurological disease and hypertensive extracranial major arterial disease. Slight prolongation in BTT is shown in: post-traumatic seizures, transient cerebral ischemic disease and hypertensive cerebral infarction. Moderate prolongation of BTT is evident in: alcoholic encephalopathy, extracranial major arterial disease and brain tumor. Marked prolongation in BTT is seen in: post-traumatic encephalopathy, degenerative neurological disease and normotensive cerebral infarction.

Case 1

One subject (no. 357) with extreme prolongation of BTT is of particular interest. This 40-year-old negro male was hospitalized with a diagnosis of chronic atrial fibrillation, idiopathic myocarditis and hypertrophy, and peripheral vascular insufficiency. B.P. was 120/70; pulse rate, 44. The BTT was 35 seconds shortly after admission. The AHCT was 29 seconds. Two weeks later, the BTT was 30 seconds and the AHCT was 21 seconds. This is the longest BTT we have encountered. It is significant that he was able to stand and walk but, although conscious and cooperative, was severely intellectually impaired.

BTT in Cerebrovascular Disease

In this group of patients, all experienced sudden onset of neurological deficit due to infarction (Fig. 4). Our preliminary findings in occlusive disease have

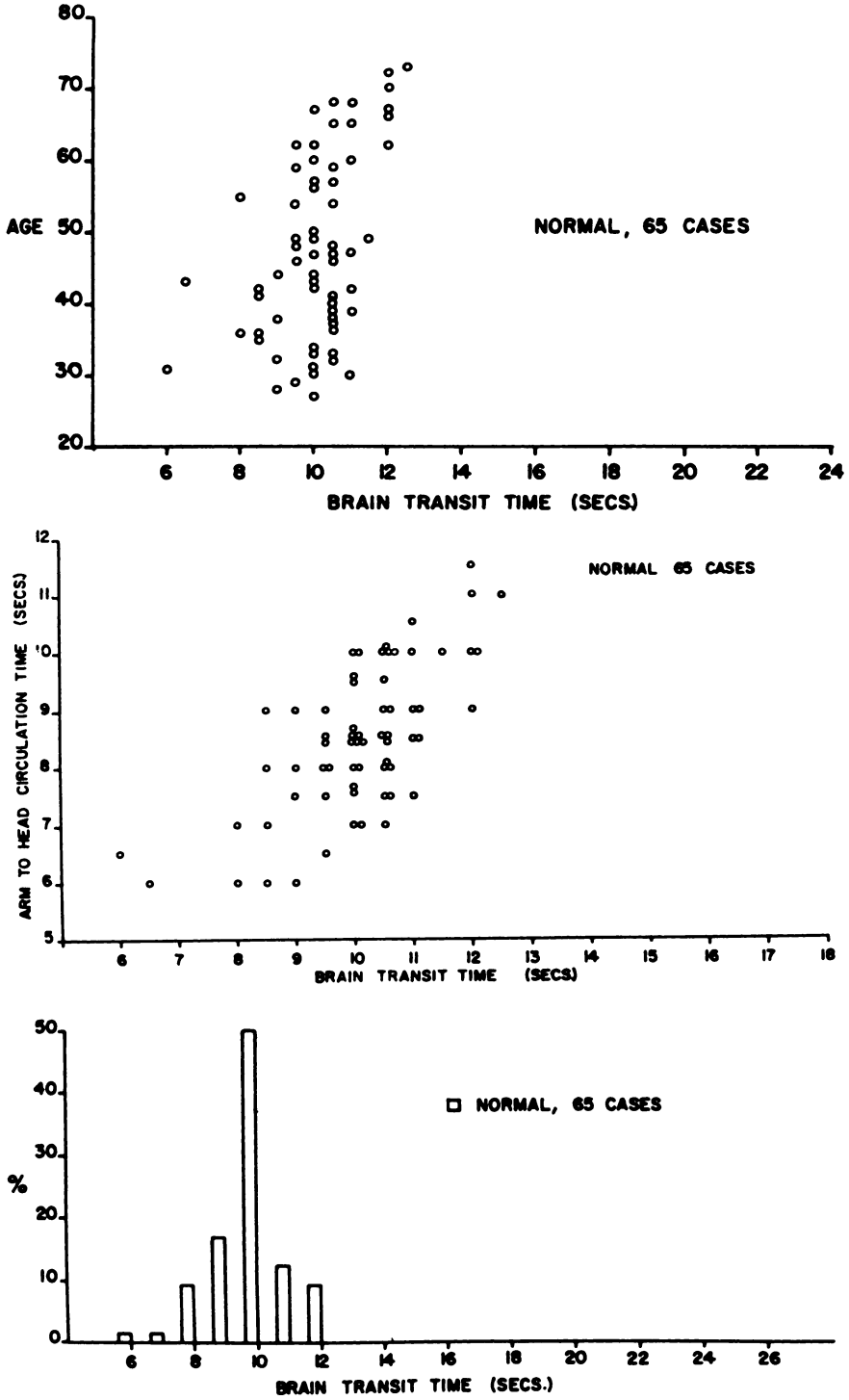

Figure 2

(see legend at bottom of following page.)

been reported previously (11). This category has been further sub-divided into 101 normotensive, 30 hypertensive and two with known systemic arteritis (three Buerger's disease, one lupus erythematosis, one Takayasu's disease).

In the group of cases with cerebral infarction, the turnover time was more prolonged in the older age groups. In the group of cases with hypertension, no marked prolongation in BTT was seen. This phenomenon is in contrast to the prolongation in BTT seen in those cases without hypertension.

Averaged characteristics of bolus passage through the brain blood pool are indicated in figure four for the group of normal subjects relative to the group with cerebrovascular disease.

In the cerebrovascular disease group, there was no evident relationship between BTT and severity of symptoms. However, in several individual cases studied serially, a parallel was seen between the general clinical state and BTT.

Case 2

This is a serial study of L. Gt. (no. 172), a 66-year-old white male. Seven years ago, the patient suffered a "stroke" at which time he had a left hemiparesis which subsequently completely resolved. At that time he was discovered to have diabetes, and had been treated by an oral antidiabetic agent. Five years prior to admission he had a coronary thrombosis.

Three days prior to the first of the present studies he became somnolent, was dysarthric, hiccoughing, vomiting, and showed a fluctuating state of conciousness. There was no evidence of specific neurological deficit except a general weakness.

Case 3

This is a serial study of a case showing improvement. W.N. (no. 346) is a 74-year-old white male. The patient was well until one month prior to admission, when he began to complain of fatigue. Two days before admission, his gait became "rubbery" and ataxic and he was mildly confused, delusional, and hallucinating. Past history revealed chronic atrial fibrillation.

On admission pulse rate was 120 with multiple PVCs. B.P. was 220/110. He was disoriented and aphasic. Peripheral pulses were normal. Hospital course showed a gradual recovery of all function. There were essentially no residual neurological signs. Diagnosis was cerebrovascular infarction, possibly embolic and arteriosclerotic and hypertensive heart disease with chronic atrial fibrillation.

AHCT and BTT

In the test performed in this study, the time of release of the bolus from the arm vein and the time of its subsequent arrival in the head are quite well-defined,

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Fig. 2. Mode brain blood pool turnover times determined in 65 normal hospitalized adults. The top figure displays brain turnover (transit) times as a function of age. The middle figure plots this variable as a function of arm-to-head circulation time and the bottom figure displays the distribution of turnover times within this group. Included here are 22 adults below, and 43 over, the age of 40.

allowing easy measurement of AHCT (Fig. 1). The AHCT has been compared, in all subjects studied, with the BTT. In Table III the relationship between these two measurements in the various disease categories is expressed more precisely by calculation of the slope (m) of the regression line of y on x where x is the BTT; y is the AHCT.

TABLE I

SERIAL CIRCULATION TESTS—CASE 2

Days after stroke	*3 days*	*5 days*	*7 days*	*10 days*
Consciousness	responded	responded	semicomatose	expired
Blood Pressure	160/90	130/80	140/80	
Respiration	regular	regular	Cheyne-Stokes	
AHCT (secs)	15.5	18.0	27.0	
BTT (secs)	17.0	19.5	27.0	

TABLE II

SERIAL CIRCULATION TESTS—CASE 3

Days after admission	*12 days*	*15 days*	*22 days*	*30 days*
Blood Pressure	170/80	152/80	150/80	discharged
AHCT (secs)	15.5	15.0	16.0	
BTT (secs)	20.0	18.5	16.0	

Several observations are of interest. In the normotensive cerebral infarction group, the BTT was more affected than the AHCT (Fig. 5a). In the post-traumatic encephalopathy group (without seizure) and the alcoholic encephalopathy group, the AHCT is not prolonged, despite prolongation of the BTT (Fig. 5b). It is also of interest to note that in the disease categories of brain tumor and degenerative neurological disease, in which isolated abnormalities of the nervous system would be anticipated, the AHCT is prolonged approximately in proportion to the BTT (Fig. 5c). The same relationship was seen in subjects with brain arteriovenous malformations (Fig. 5a) and in the "headache" group (Fig. 5b). In general, the AHCT is of the order of ¾ of the BTT.

DISCUSSION

The requirement of an absolute continuity of an adequate blood flow to nervous tissue has generated considerable interest in quantifying this flow. Because of the delicacy of human brain function, radioisotope techniques have been

widely applied as non-destructive means to this end. Radioactive tracers have been introduced into the blood perfusing brain by arterial (16-22), pulmonary (14, 23, 24), and venous routes (1-8, 25). Utilizing external monitoring devices, the subsequent amount of isotope in brain as a function of time can be defined. To be clinically applicable to a large number of cases any such technique should not only be safe, but simple to administer and interpret. To fulfill these criteria we have pursued an intravenous method in which an essentially non-diffusible, rapidly excreted, gamma-emitting label is deposited abruptly into the venous return to the heart and its subsequent passage into and out of the brain blood pool defined by external gamma radiation detectors.

This intravenous method has the advantage of safety and simplicity and produces an index of brain blood flow in terms of the time of passage of the indicator through brain. Since there is a range of circulation times through brain, the most useful parameter of such a frequency distribution of transit times through brain would be the mean transit time. If the pool volume is known and the mean transit time (or mean pool turnover time) can be determined, the absolute pool flow rate becomes:

$$\frac{\text{pool volume in cc.}}{\text{turnover time in min.}} = \text{brain blood flow in cc/min.}$$

From the theoretical point of view, the method under discussion here, like all methods depending on the time of passage of the peak-concentration of a bolus of indicator past two points in a stream, provides the mode transit time rather than the mean. Since the frequency distribution of transit times through brain is somewhat skewed (11), the mode differs from the mean in brain; and appears to be of the order of 10% shorter. Nevertheless, it bears some reasonably constant relationship to the mean time and should be an index of circulatory adequacy nearly as useful as the mean time.

The validity of circulation time or turnover time as an index of brain blood flow has been disputed (26) although a number of authors have attached significance to this index (1, 2, 7, 11, 16-17, 27).

Transit Times of the Brain

In the adult human brain there is, in the arteries, capillaries, and veins, a volume of blood of the order of 150 cc (25) referred to here collectively as the "brain blood pool". Well-established techniques, such as the Kety Schmidt nitrous oxide method (28), indicate there is a volume of blood of 800-1000 cc per minute passing through this pool. There is, therefore, a mean turnover (or replacement) time of the order of eight seconds.

When labeled blood is injected abruptly into the carotid system and the jugular outflow of this labeled blood serially sampled, as has been described for red cells by Nylin *et al* (25), the initially compact bolus becomes quite dispersed in a single brain pool passage. This phenomenon indicates a range of circulation times. Such a study further provides directly, in the shape of the jugular concentration curve, the frequency distribution of circulation times through the pool. If all of the indicator traversed the pool in the same interval,

the bolus would leave as abruptly as it entered and the time-concentration curve in the jugular blood would represent the rate of arterial injection. The curve of jugular concentration following carotid injection indicates the shortest transit times (for red cells) to be about four seconds and the longest to about 15-17 seconds, with the most common (mode) time of seven to nine seconds and a mean transit time of nine to eleven seconds (25). Variations of transit time of fractions of the bolus will be due to several factors, such as laminar flow in vessels, multiple path lengths, arteriovenous shunting, and with separate labelling of red cells and plasma compartments, to differential flow rates of red cells and plasma in the brain microcirculation (29, 30).

The transit time presumably bears an inverse relationship to flow rate, being shorter in the presence of high flow rates. This relationship is valid, however, only in the presence of a fixed blood pool volume. Since little is known about the volume stability of the human brain blood pool, precise quantification of flow measurements of transit times is limited. We have attempted to measure the absolute volume of the cranial blood pool by external measurement of a nondiffusible gamma emitter but, because of Compton scatter and use of a plasma label, arrived at unrealistically large volumes (10, 15).

It is to be expected that the frequency distribution of brain blood pool transit times will be a valuable index of organ hemodynamics, since it contains a great deal of information related not only to overall tissue perfusion rate, but to other local abnormalities of flow such as devious collateral paths and perhaps to hydrodynamic shear abnormalities of blood flowing in the microcirculation. It is our impression that there is less distortion of the bolus in transit through young healthy subjects than in the presence of cerebrovascular disease (Fig. 4). Although the intravenous technique most commonly used by us provides only the mode time with useful dependability, it is clear that in obvious abnormalities of local flow, such as found in large arteriovenous malformations, there is a dis-

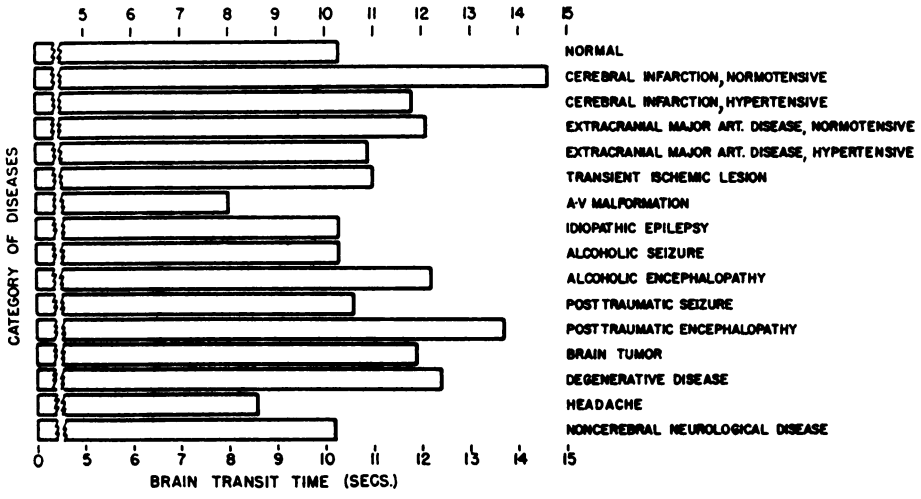

Fig. 3. Averaged turnover times in various disease categories in about 517 subjects.

tinct portion of the bolus which has a shorter transit time than that through the remainder of the brain. To plot a frequency distribution curve with sufficient definition to see small regional abnormalities of transit times in tumors and infarcts

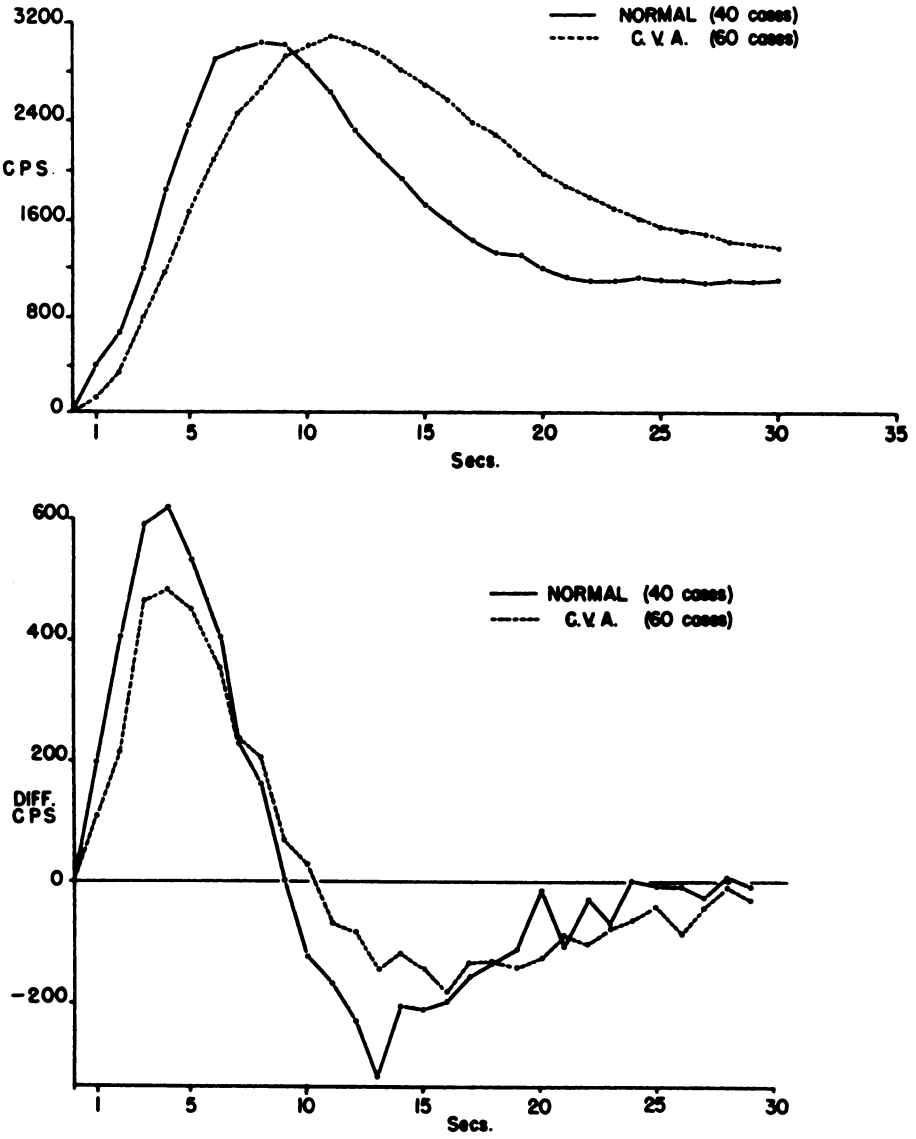

Fig. 4. Curves synthesized by averaging count rates from 40 normal subjects and 60 with cerebrovascular disease. Time zero is the first appearance of the bolus of isotope in the field of the detectors. The top figure is the direct display of count rate as a function of time and therefore is representative of the amount of radioactive tracer present in the brain blood pool. The lower curve is the first derivative of the top figure and represents the rate of change of the isotope content of the pool. Not only is the mode transit time prolonged in the disease group but the streaming out of the bolus is more pronounced in the disease group as indicated by the blunting of the negative first derivative peak defining the bolus leaving the pool.

requires a very abrupt input of tracer into the brain, which can be achieved only by carotid injection. This procedure has not been practised routinely in this laboratory because of the slight, but real, hazard to the subject. It could, however, ethically be included as part of the angiographic procedure.

Other radioisotope methods for determining brain transit times have used either rapid serial sampling of carotid and jugular blood after intravenous injection of radio-tracer (25) or external monitoring of gamma emitters. These tracers have been injected either intravenously and passage of the bolus to and from the brain timed by monitoring the great vessels in the neck (2, 7) or torcular herophili (1), or injected intracarotid with monitoring of the torcular herophili or jugular veins (17-18), or the cerebral vessels directly (16, 21).

Those intravenous methods using focal collimation to monitor the neck vessels show ill-defined peaks representing bolus passage (2, 7) despite rather large doses of isotope, probably because of the relatively large volume of adjacent tissue inevitably included in the detection field and the small volume of blood contained in the great vessels within the detection field. In these studies the blood from the brain circulation is also mixed with a considerable flow draining tissues in the external carotid distribution.

Usefulness of Various Indices of Flow

Various indices of expression of brain blood flow have been applied clinically. These have given results in terms of absolute volume of total organ flow (31), cc per unit weight of brain tissue (19, 28), and transit time (2, 7, 11, 16-18, 27). Each of these indices has obvious limitations in special clinical circumstances. In the presence of arteriovenous shunting, none will adequately express the hemodynamics of both the shunt and the rest of the brain. Only the cortical washout of gases will accurately define the most desired flow characteristic, effective tissue perfusion of the brain microcirculation. In the partial absence of functioning brain tissue, the remainder of normally functioning brain would presumably provide a normal flow rate in any techniques based upon the rate of tissue uptake or washout of indicator.

The validity of pool turnover time as an index of total organ blood flow requires that the blood pool volume be known in absolute terms or known to be constant from patient to patient. If a flow index in terms of volume of flow per unit time is desired, the turnover time can be expressed as a number of cc of flow per minute per 100 cc of pool volume by the simple expression: $\frac{60}{MTT} \times 100$ where MTT is the mean turnover time of the pool.

In general, definition of a parameter (such as brain blood flow) in terms of time of occurrence of reference points in a bolus enjoys an advantage of insensitivity to the absolute magnitude of the bolus concentration, greatly simplifying the measurement.

It may well be shown that the attachment of a simple number to the total brain blood flow is of limited clinical applicability and some other expression of organ flow in which either the time distribution of pool transit times or regional

distribution of blood flow rates as defined would be more clinically useful. This latter approach has been pursued using multiple focal detectors (32) or a gamma camera to define the distribution in the human brain of ^{133}Xe injected into the carotid artery (33). The pattern of initial tissue distribution and subsequent washout probably will be found to be of clinical interest.

Magnitude of Turnover Time

Judging from the rate of passage of angiographic contrast media (16, 27) and the transit time of labeled red cells (25), the transit times obtained using the present technique seemed to us slightly prolonged. However, several factors may, in part, explain this prolongation.

The blood compartment labeled in the technique described here is plasma. Since plasma brain transit time is, in brain (29, 30), as in most organs, substantially slower than red cells, it is to be expected that the transit time using a plasma label would be longer than when using a red cell label. The transit times found using the present method seem then, in good agreement with those of Nylin (25). A lower effective viscosity of angiographic contrast media in the brain microcirculation may explain their rapid passage relative to plasma. In the

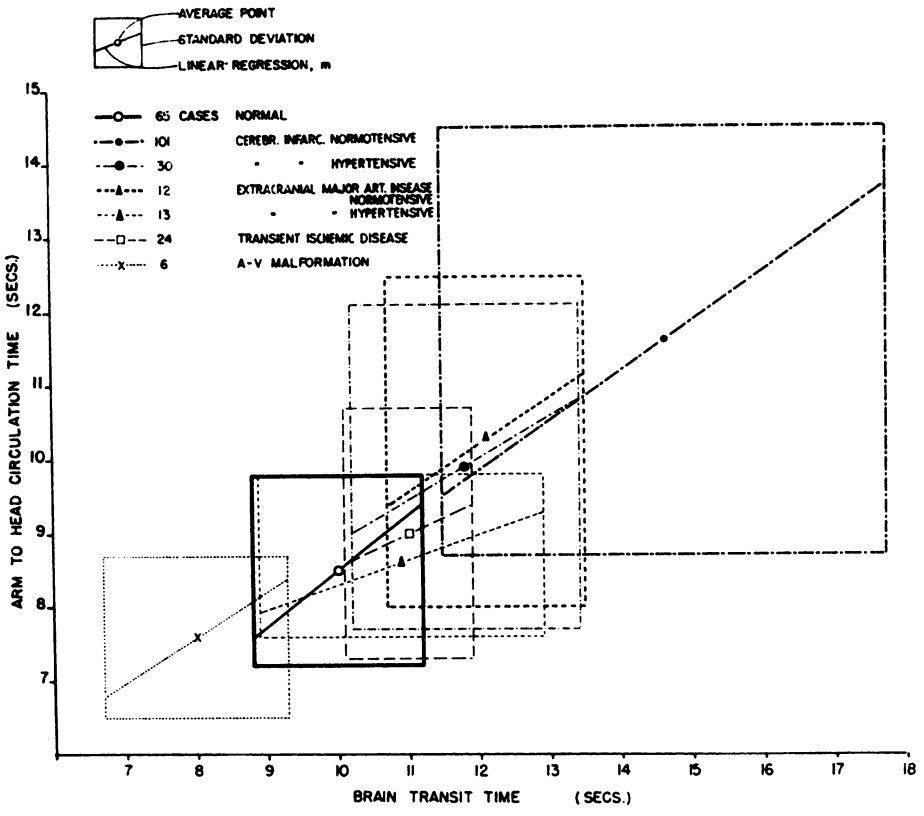

Fig. 5a.

angiographic transit time studies of Greitz (16), the time of passage of the peak concentration of contrast medium from the carotid siphon to parietal veins was measured. This would be shorter than our time measured to the exit from the cranial cavity. In several cases in the present series in which careful comparisons were carried out, there was excellent correlation between angiographic circulation time and the BTT. The times found upon intravenous injection also were found to correlate well when the label was injected intracarotid in the same patient. The positive and negative first derivative peaks were more precisely definable following arterial injection.

The present technique, being virtually atraumatic and painless, studies the patient in a normal state of respiration and is unattended by any great anxiety, despite the absence of premedication. This might be expected to bring about changes in hemodynamics relative to other more complex techniques.

The demonstration of an increasing turnover time with increasing age presumably reflects a gradually diminishing organ flow and is in keeping with established findings using the nitrous oxide technique (34). The prolonged time in cerebrovascular occlusive disease is in keeping with a general reduction in brain

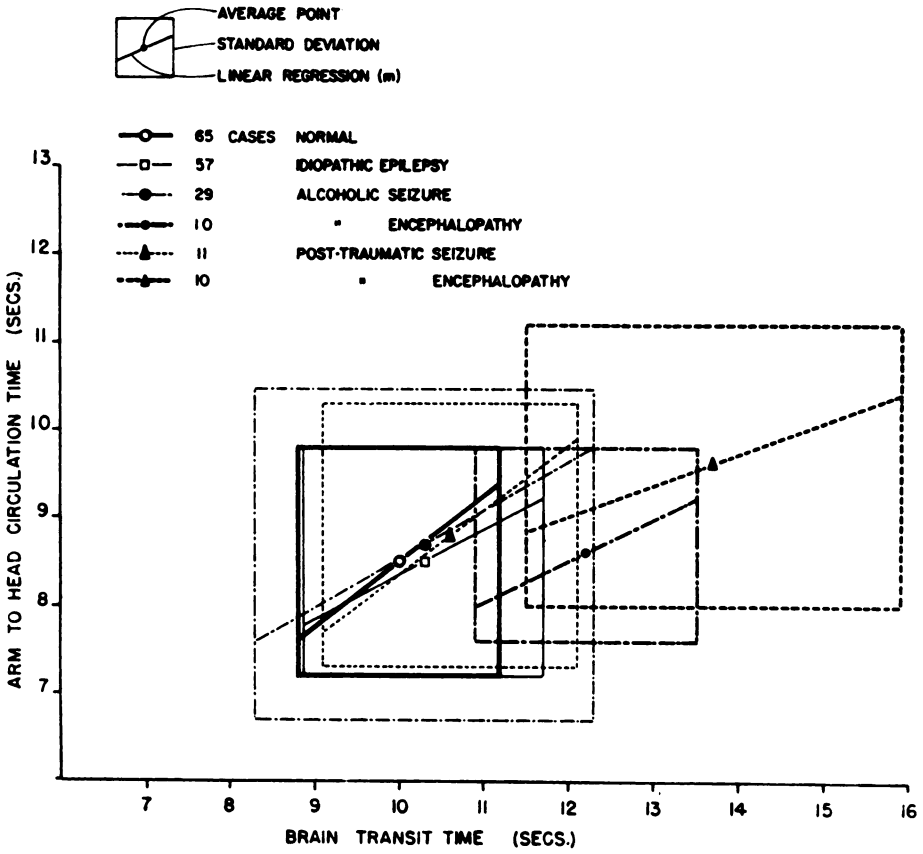

Fig. 5b.

blood flow found in this disease using the nitrous oxide technique (35, 36) and xenon washout (37, 38). This finding, with different methods, of a general reduction of brain blood flow in the presence of clinically focal disease, suggests a general brain blood flow abnormality of which the apparently focal clinical findings are simply isolated manifestations representing regional infarction in the distribution of the arterial tree rendered generally prone to thrombosis by sluggish flow.

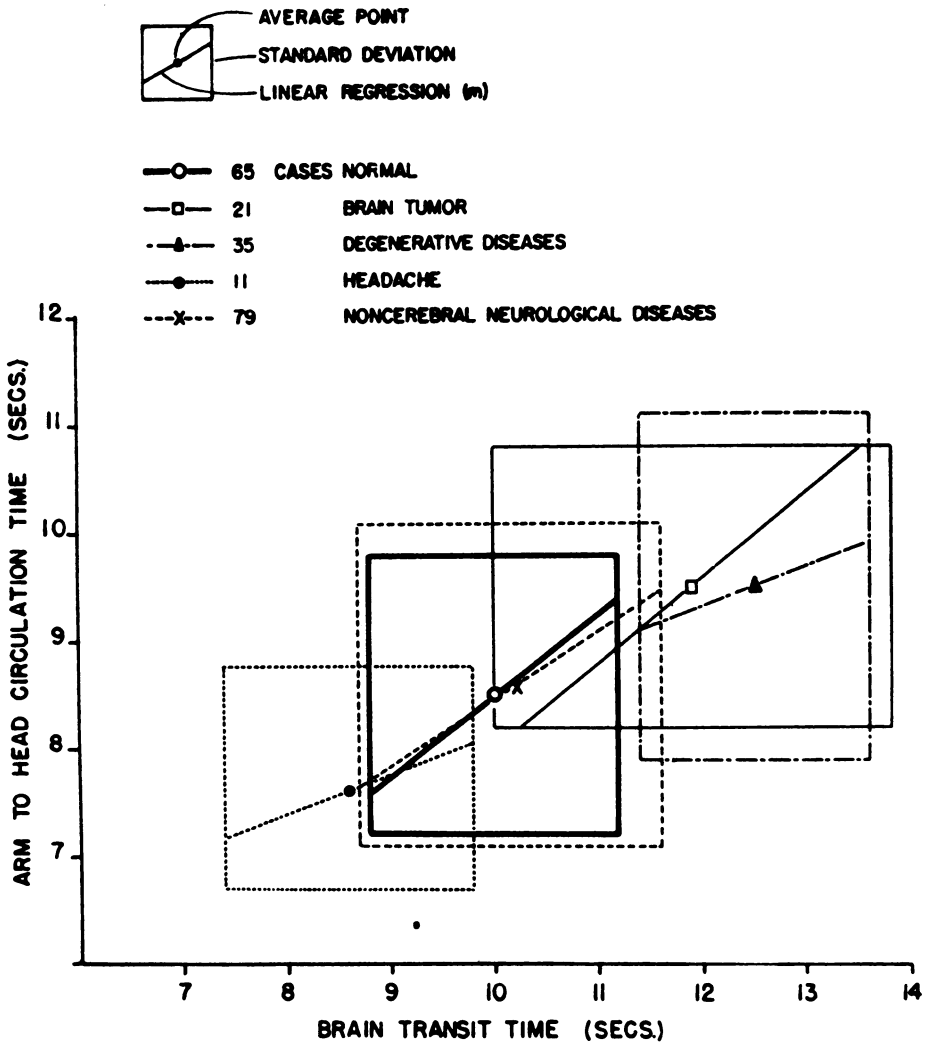

Fig. 5c.

Figs. 5a, 5b, 5c. Figure 5a, b, and c indicate the relationship between arm-to-head circulation time and the mode transit time of the brain blood pool in various disease categories. The rectangular box indicates the standard deviation of pool transit times and arm-to-head circulation times within each disease group. The slope m of the regression line of y on x is defined for each category of diseases classified in Figure 3, and Table III.

TABLE III

Categories of Disease	*No. of Cases*	*Average Age*	*Brain Transit Time (Seconds)*			*Arm-to-Head Circulation Time (Seconds)*			*Linear Regression m*
			S.D. of Population	*Average*	*S.D. of Average*	*S.D. of Population*	*Average*	*S.D. of Average*	
Normal	65	48	1.2	10.0	0.2	1.3	8.5	0.2	0.75
Below 40 years old	22	34	1.1	9.6	0.2	1.1	8.1	0.2	0.57
Over 40 years old	43	55	1.4	10.3	0.2	1.4	8.7	0.2	0.85
Cerebrovascular occlusive disease	134	62	3.0	14.0	0.3	2.8	11.2	0.2	0.67
Cerebral infarction, normotensive	101	62	3.0	14.6	0.3	2.9	11.6	0.3	0.72
Cerebral infarction, hypertensive	30	63	2.2	11.8	0.4	2.2	9.9	0.4	0.57
Diffuse arteritis	3								
Extracranial major arterial disease	25	53	1.7	11.5	0.2	2.0	9.4	0.4	0.64
Normotensive	12	50	1.4	12.1	0.4	2.3	10.3	0.7	0.77
Hypertensive	11	59	2.0	10.9	0.6	1.1	8.7	0.3	0.43
Ligated	2								
Transient ischemic brain disease	24	54	0.9	11.0	0.2	1.7	9.0	0.4	0.34
A-V malformation	6	44	1.3	8.0	0.5	1.1	7.6	0.5	0.65
Idiopathic epilepsy	57	45	1.4	10.3	0.2	1.3	8.5	0.2	0.43
Alcoholic brain disease	39	44	1.9	10.8	0.3	2.0	8.7	0.3	0.62
Seizure	29	43	2.0	10.3	0.4	2.1	8.7	0.4	0.62
Encephalopathy	10	47	1.3	12.2	0.4	1.1	8.7	0.3	0.55
Post-traumatic brain disease	21	40	2.4	12.1	0.5	1.6	9.2	0.3	0.40
Seizure	11	40	1.5	10.6	0.5	1.5	8.8	0.5	0.76
Encephalopathy	10	40	2.2	13.7	0.7	1.6	9.6	0.5	0.36
Brain tumor	21	50	1.9	11.9	0.4	1.3	9.5	0.4	0.83
Degenerative Neurological Disease	35	44	1.1	12.9	0.2	1.6	9.5	0.3	0.33
Headaches	11	46	1.2	8.6	0.5	1.0	7.7	0.3	0.33
Noncerebral Neurological Disease	79	48	1.5	10.2	0.2	1.5	8.6	0.2	0.62
Peripheral neuropathy	54	48	1.4	10.2	0.2	1.3	8.4	0.2	0.64
Myelopathy	18	50	1.0	10.7	0.3	1.5	9.6	0.4	0.60
Myopathy	7	40	1.7	9.3	0.7	0.8	7.5	0.3	

The prolongations of BTT in post-traumatic encephalopathy and degenerative neurological disease suggest a reduction in overall brain metabolism with a consequent reduction in organ blood flow. The shortening of BTT in arteriovenous malformations can be attributed to the arteriovenous shunting in these lesions.

The direct relation of brain transit time to the arm-to-head circulation time indicates a systemic circulatory inadequacy usually exists when brain circulation is slowed. These coincident inadequacies in brain and in the remainder of the subject probably reflect some general circulatory abnormality of which brain circulation is but a part. A possibly more specific relationship might be established by noting that the general behavioral patterns of the individual are usually more sedentary and slowed when the brain transit time is prolonged. This condition could lead to a reduced cardiac output based solely on a general reduction of skeletal muscular activity. This phenomenon may result in some long-term thixotropic rheological abnormality in blood subsequent to prolonged low shear rates in the microcirculation. The shortened AHCT time in our "headache" cases may represent a generally increased level of anxiety and consequent increased cardiac output in these subjects. Further interpretation of this relationship seems unwarranted to us at this time.

SUMMARY

Brain blood pool transit times were studied in 534 subjects by an intravenous radioisotope technique utilizing external monitoring of brain passage of a bolus of non-diffusible radioactive indicator. This transit time (or pool turnover time) was used as an index of brain blood flow.

Brain blood pool transit times ranged between six and eleven seconds in healthy subjects with a general increase toward the long end of this range in advanced age.

Findings in hospitalized patients in a variety of disease categories are reported. Marked prolongation of transit times is seen in normotensive cerebrovascular disease, post-traumatic encephalopathy, and degenerative neurological disease. Moderate prolongation of brain transit time is seen in alcoholic encephalopathy, extracranial major arterial disease and brain tumor.

Slight prolongation of brain transit time is seen in post-traumatic seizures, transient cerebral ischemic disease and hypertensive cerebral infarction. A normal transit time is seen in idiopathic epilepsy, alcoholic epilepsy, non-cerebral neurological disease and hypertensive extracranial major arterial disease. Shortening of brain transit time is seen in arteriovenous malformation and the headache group.

There is generally a positive relationship between brain transit time and the arm-to-head circulation time. The significance of these data is discussed.

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