Limitations of circulation time in the diagnosis of intracranial disease¹

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SUMMARY The mode circulation time was measured using intravenously injected technetium 99m and a collimation system devised to discriminate between the right and left sides of the head. The results in 21 normal men were used as a basis of assessing the findings in 205 patients, made up of five diagnostic groups (ischaemia, haematoma, subarachnoid haemorrhage, intracranial tumour, and head injury). The average mode circulation time in the affected hemisphere for the three groups with vascular disease was increased, but even in these groups half the patients had a mode circulation time within 1 SD of normal mean; similar results were found for asymmetry between the hemispheres. In serial measurements in 45 patients no correlation was found between change in mode circulation time and the clinical state. That so many results are within the normal range limits the value of this method.

The regional cerebral blood flow (rCBF) can be measured quantitatively by the inert gas clearance method but this necessitates intracarotid injection and fairly elaborate data processing. Oldendorf has proposed the measurement of the cerebral circulation time of a non-diffusible isotope as a simpler alternative, and has published the results in a series of patients with various intracranial disorders. (Oldendorf, 1962; Oldendorf and Kitano, 1967). Subsequently Taylor applied the method to patients with head injuries, with subarachnoid haemorrhage, and with senile dementia and claimed to find a significant variation from normal in certain groups of patients with these conditions (Taylor and Bell, 1966; Kak and Taylor, 1967; Ball and Taylor, 1967).

The relative simplicity of this method makes it attractive to clinicians, but the deductions which can validly be drawn about the cerebral circulation from measurements of the circulation time have been challenged by Lassen (1967) and by James (1967). As a result of this controversy two questions about this method now demand an answer. Are the results in normal individuals sufficiently consistent to make identification of the abnormal reliable enough to be useful? And is the velocity of the circulation, which this method measures, a reliable index of cerebral

blood flow (or perfusion), the parameter of the circulation which is believed to be of most biological importance? This paper explores the first question by seeking to establish the range of normal values and by comparing these with measurements in 205 patients with intracranial disease. The findings are discussed in the light of animal experiments which were designed to answer the second question (Rowan, Harper, Miller, Tedeschi, and Jennett, 1970).

METHOD

A non-diffusible isotope is injected intravenously, and its passage through the brain is monitored by recording the gamma activity through the intact skull. The primary curve obtained gives the relationship of activity against time; this is then differentiated to obtain a secondary curve of rate of change of activity against time. The time interval between the maximum and minimum points of this bipolar curve denotes the difference in time between the arrival and disappearance of maximum radioactivity in the field of view of the detector and this gives the mode circulation time (MCT) (Fig. 1).

THE ISOTOPE AND ITS INJECTION Both Oldendorf and Taylor used iodinated hippuran labelled with ¹³¹I, which has a half life of eight days, in dosages of 0.05 to 0.5 mCi. In the present studies technetium^{99m} has been used; its half life is only six hours and it can therefore be given in increased dosage—to provide larger count rates—without at the same time increasing the radiation hazard to the patient. Because this is the isotope most commonly

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FIG. 1. Primary and secondary curves. Calculation of MCT is from secondary curve, as indicated.

used for brain scanning, the opportunity can be taken to record the MCT on any patient having a scan by the simple expedient of setting up the detecting system over the head when the intravenous injection for scanning is being given. Indeed, this is the way in which we have gathered much of the information reported here. For scanning we normally use 5 mCi of ^{99m}Tc , but many centres use 10 mCi; for circulation time studies alone only 1.3 mCi is required, and serial measurements involving repeated injections can therefore be made over a period of days or weeks, without risk to the patient.

THE DETECTING SYSTEM Both Oldendorf and Taylor employed a sodium iodide scintillation counter collimated to view the whole head and centred over the inion. But

many of the clinical conditions under study affect one side of the brain only, or the two hemispheres unequally. We have therefore devised a system for detecting the circulation time on each side of the head separately, which enables asymmetry in the circulation time to be recognized. Two scintillation crystals 1 in. in diameter and 1 in. deep were collimated with lead such that when placed over the forehead 90% of the activity recorded by the detector on one side is derived from the ipsilateral hemisphere (Fig. 2). Pulses from each detector were fed via an amplifier, pulse height analyser, and digital tape recorder to a ratemeter the output of which was filtered and electronically differentiated to provide a graph of rate of change of activity against time. The graphs from each detector channel were written out simultaneously on a

FIG. 2a Area of overlap 1 in. crystal collimated with lead.

FIG. 2b Only 10% of activity recorded by left sided detector originates from right hemisphere.

FIG. 2. Detectors for discriminating hemispheres.

two-channel chart recorder and the intervals between the maximum and minimum points on each curve were measured to provide the MCT for each hemisphere.

ANALYSIS OF CURVES In our studies only the mode circulation was measured. Other workers have attached significance to the slope of the line drawn on the primary activity/time curve from the point of appearance of the isotope in the head to the point of maximum activity, and to the slope of the line drawn from this peak value to the point of clearance of the activity to the recirculation level: furthermore, significance has been attached also to the 'appearance-to-peak' and the 'peak-to-clearance' time intervals. These parameters depend on so many variables—for example, injection time lag, fraction of

total blood volume supplied to the brain, distribution of activity within the injection bolus—that their measurement could give rise to quite erroneous conclusions concerning the cerebral circulation. We have concentrated on the differentiated curve and measured only the time interval between the maximum and minimum points on this curve, which has been termed the mode circulation time.

SUBJECTS STUDIED

NORMAL ADULTS The subjects were 21 members of the medical and scientific staff who agreed to the investigation. The results from these normal men showed a mean MCT of 9.5 secs (1.8 SD) for each hemisphere; the mean

right-left difference was 1 sec (0.6 SD). On this basis we categorized the results from the patients as within 1 SD of normal mean, between 1 and 2, or more than 2 SD from normal mean.

PATIENTS This report is based on the first 205 patients studied, divided into five diagnostic groups. In some analyses the correlation with various grades of severity of hemiparesis or impairment of consciousness was studied. Serial measurements were made in a certain number of patients. Most patients were studied incidentally in association with brain scanning but others had specific injections of isotope for the purpose of making circulation measurements.

RESULTS IN PATIENTS

ABSOLUTE MCT MEASUREMENTS IN AFFECTED HEMISPHERES The difference from the normal mean was most significant for groups of patients with ischaemia and haematoma ($P < 0.01$) (Table 1a). The difference was less significant for patients with subarachnoid haemorrhage ($P < 0.05$), but there was also a significant difference between the means for subarachnoid haemorrhage patients with spasm and those without (Table 1b). There was no significant difference from normal in the case of the means for patients in the head injury and tumour groups.

When clinical state and diagnosis were taken together the numbers in each group were small. There were significant differences between the means in the various grades of hemiparesis and conscious state only in the case of ischaemia and hemiparesis (Table 1c), and in the case of subarachnoid haemorrhage associated with spasm, when a significant difference was found between the means for grades 1 and 2 of conscious state (Table 1d).

When patients are considered as individuals rather than as groups it transpires that 60% of all patients had MCT values within 1 SD of the normal mean. In the diagnostic groups the numbers in this category varied from 78% for patients with tumours to 40% for patients with ischaemia (Table 2a). Many of these patients with normal values had well-marked signs of hemisphere dysfunction. Indeed when those with varying degrees of hemiparesis are compared (regardless of diagnosis) there is no marked difference in the percentage of patients with MCT values within 1 SD of the normal mean, the figure varying from 50% to 60%. When impaired consciousness was considered, the percentage of patients with MCT values within 1 SD of the normal mean fell below 50% only in the group with marked impairment (Table 2b).

ASYMMETRY BETWEEN HEMISPHERES The difference from normal asymmetry was most significant for the group of patients with haematoma ($P < 0.01$), and not so significant for patients with ischaemia and subarachnoid haemorrhage ($P < 0.05$). There was no significant difference from normal asymmetry for patients in the head injury and tumour groups (Table 3).

There was no statistically significant difference in asymmetry between subarachnoid haemorrhage patients with and without spasm. When clinical state and diagnosis were taken together there was no significant difference in asymmetry between the three categories of hemiparesis and conscious state.

When patients are considered as individuals, we find that 64% of all patients had asymmetry values within 1 SD of the normal mean. In the diagnostic

TABLE 1

ABSOLUTE MCT (SECONDS) IN AFFECTED HEMISPHERES (MEAN FOR ALL PATIENTS IN GROUPS INDICATED)

Diagnostic group	N	Mean	SD	SE	Difference from normal mean	Difference in means	t	P
1a. Total patient series								
Cerebral ischaemia	40	11.8	2.6	0.41	2.3	—	4.60	< 0.01
Intracranial haematoma	38	11.0	2.3	0.37	1.5	—	3.26	< 0.01
Subarachnoid haemorrhage	47	10.3	1.5	0.22	0.8	—	2.42	< 0.05
Intracranial tumour	36	10.2	1.4	0.22	0.7	—	1.94	ns
Head injury	29	10.1	2.2	0.41	0.6	—	1.36	ns
1b. Patients with subarachnoid haemorrhage								
With spasm	16	11.2	2.1	0.52	—	1.3	2.45	< 0.05
Without spasm	31	9.9	1.5	0.26	—	1.3	2.45	< 0.05
1c. Patients with ischaemia								
Hemiparesis grade 1	5	11.2	1.6	0.71	—	2.4	2.4	< 0.05
Hemiparesis grade 2	9	13.6	3.0	1.00	—	2.4	2.4	< 0.05
1d. Patients with subarachnoid haemorrhage and radiological spasm								
Conscious state grade 1	7	9.9	1.6	0.60	—	3.2	2.67	< 0.05
Conscious state grade 2	6	13.1	2.4	0.87	—	3.2	2.67	< 0.05
1e. Patients with subarachnoid haemorrhage, without spasm								
Conscious state grade 1	13	9.7	1.6	0.44	—	0.8	0.94	ns
Conscious state grade 2	6	10.5	1.6	0.65	—	0.8	0.94	ns

TABLE 2
PERCENTAGE OF PATIENTS WITH MCT WITHIN VARIOUS RANGES OF NORMAL

	N	Within 1 SD [9.5 ± (<1.8)] (%)	Between 1 and 2 SD [9.5 ± (1.8 - 3.6)] (%)	> 2 SD [9.5 ± (>3.6)] (%)
2a. Total patient series by diagnostic groups				
Ischaemia	40	40	35	25
Haematoma	38	55	26	19
Subarachnoid haemorrhage	47	68	21	11
Tumour	36	78	19	3
Head injury	29	58	28	14
2b. Total patient series by clinical states				
Hemiparesis:				
Grade 1	42	60	26	14
Grade 2	62	50	26	24
Grade 3	22	59	23	18
Conscious state:				
Grade 1	83	55	17	11
Grade 2	52	50	27	23
Grade 3	22	32	50	18

TABLE 3
ASYMMETRY OF MCT (IN SECONDS) BETWEEN HEMISPHERES

Diagnostic group	N	Mean	SD	SE	Difference from normal mean	t	P
Ischaemia	46	1.6	1.5	0.22	0.6	2.31	< 0.05
Haematoma	38	2.0	1.8	0.30	1.0	3.03	< 0.01
Subarachnoid haemorrhage	52	1.5	1.3	0.17	0.5	2.27	< 0.05
Tumour	37	1.2	1.2	0.20	0.2	0.83	ns
Head injury	32	1.3	1.4	0.24	0.3	1.07	ns

groups the figure for this category varied from 78% for patients with tumours to 53% for patients with haematoma (Table 4a). Again among these patients were many with well-marked signs of hemisphere dysfunction. Consideration of hemiparesis and conscious state, regardless of diagnosis, produced no marked difference in the percentage of patients within 1 SD of the normal mean, the figure varying from 45% to 58% for hemiparesis and 49% to 70% for conscious state (Table 4b).

SERIAL INVESTIGATIONS In 45 patients MCT measurement was repeated and, in a few, three tests were done; in the 51 pairs of measurements there were 11 which differed by less than one second, and should therefore be regarded as being essentially unchanged; in four of these the clinical condition was also the same on the two occasions, but in seven the patient had improved.

In the 40 pairs of measurements which differed by more than one second no correlation could be discovered between the direction or degree of the change in MCT and the clinical state (Table 5). Not only did improving patients as often have a slower MCT on the second occasion but deteriorating patients more often showed a faster circulation when they were worse.

TABLE 4
PERCENTAGE OF PATIENTS WITH ASYMMETRY WITHIN VARIOUS RANGES OF NORMAL

	N	Within 1 SD 1 ± (<0.6) (%)	Between 1 and 2 SD 1 ± (0.6 - 1.2) (%)	> 2 SD 1 ± (>1.2) (%)
4a. Total patient series by diagnostic groups				
Ischaemia	46	59	17	24
Haematoma	38	53	18	29
Subarachnoid haemorrhage	52	64	17	19
Tumour	37	78	11	11
Head injury	32	72	9	19
4b. Total patient series by clinical states				
Hemiparesis:				
Grade 1	43	58	19	23
Grade 2	57	56	16	28
Grade 3	22	45	23	32
Conscious state:				
Grade 1	84	70	13	17
Grade 2	51	49	27	24
Grade 3	24	58	4	38

DISCUSSION

The results show that the average MCT is increased for a group of patients with ischaemia or haematoma or subarachnoid haemorrhage (and in the last group it is greater when there is spasm). However, this

TABLE 5

DIRECTION OF CHANGE OF MCT IN SERIAL MEASUREMENTS

Change in circulation time		Clinical condition		
		Same	Worse	Better
>1 sec	Faster	8	6	9
	Slower	6	2	9
>2 sec	Faster	3	3	6
	Slower	2	0	5

information is of very limited value to the clinician because if he is confronted with a MCT result on an individual patient it is very likely that this will lie within the range expected from normal patients—that is, normal mean $\pm$ 2 SD. In fact, 60% of our results lie within one standard deviation of the normal mean. Due to the relatively large standard deviation found for asymmetry of MCT between the two hemispheres in normal patients, this measurement has not increased the sensitivity of the method.

Even so, it is of interest that these results suggest that in patients with ischaemia the degree of hemiparesis is an important indication of reduced circulation, while in subarachnoid haemorrhage with spasm conscious state is a better guide; this accords with the experience of clinicians making bedside judgements.

Disturbances of the cerebral circulation in and around various intracranial lesions are very complex and care is needed in interpreting data about such situations. An area of infarction due to vessel occlusion may not affect the flow in a sufficiently large area of surrounding brain to affect measurements of rCBF or of MCT, both of which may therefore remain quite normal. However, rCBF studies in patients with strokes, tumours, and head injuries have shown that focal area of hyperaemia may occur adjacent to pathological zones, but that

these may not be detected by methods which 'look at' large areas of brain, in which the average flow may be normal (Brock, Fieschi, Ingvar, Lassen, and Schürmann, 1969). Even when flow is altered in the brain as a whole, the MCT may not alter in a commensurate fashion. This we have shown in experiments on baboons involving simultaneous measurement of circulation and rCBF (Rowan *et al.*, 1970). It is no surprise, therefore, to discover that circulation times should remain within normal limits in such a high proportion of patients with intracranial lesions. This, together with the rather wide range of the MCT in normal subjects, considerably restricts the value of this method of investigating the cerebral circulation, both as a screening test and in the recording of changes in individual patients.

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