Regional Arm-Brain Mean Transit Time
In the Diagnostic Evaluation of Patients
With Cerebral Vascular Disease

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SUMMARY By analyzing time-activity curves over selected brain regions, following intravenous administration of a non-diffusible radionuclide, it is possible to assess regional arm-brain mean transit time (rABmtT).

By evaluating this parameter in normal subjects a relatively small range of differences between symmetrical regions can be found (0.30 ± 0.14 sec, mean ± sd). An increase of this difference above statistical limits was found in 82 % of patients with acute complete stroke, in 56 % of patients with chronic complete stroke and in 21 % of patients with transient ischemic attacks.

INTRAVENOUS radionuclide angiography with non-diffusible tracers permits improved brain scan detection of cerebral vascular lesions and permits discrimination between these lesions and tumors, thus providing a qualitative index of cerebral perfusion. The subjective nature of the visual record of asymmetrically distributed activity in sequential scintiphotos limits our ability to detect minor perfusion defects, thereby making a quantitative approach preferable.

By recording regional time-activity curves a quantitative evaluation may be attempted, although it will be biased by bolus dispersal prior to entrance into the regional vascular volume, which could affect estimation of parameters related to cerebral perfusion.

Attempts to evaluate particular aspects of the curves related to cerebral perfusion have been made: analysis of the interval peak to peak or origin to first peak of the derivative of the monitored functions; estimation of the area under the upslope of the curves; and assessment of the first derivative of the monitored functions.

The normal first mathematical moment of monitored activity, calculated about the time of the injection, may correspond to a whole path transit time beginning in the injected vein and ending in regional cerebral outflow surfaces.

In a previous report it has been shown that, by calculating regional arm-brain mean transit time (rABmtT), it was possible to obtain a small range of interregional transit time differences in normal region pairs, which significantly increased in patients with angiographically proven carotid thrombosis.

This report describes further experience with this method in normal subjects and in patients with cerebral vascular disease or tumors.

Subjects and Method

One hundred ninety-four subjects were considered: 70 who had cerebral scintigraphy as a screening procedure for minor symptoms and had a normal brain scan were considered as controls; the other were 102 patients with an acute neurological deficit and 22 patients with an intracerebral tumor.

Ninety-two patients with an acute neurological deficit had a final diagnosis of cerebral ischemia while another 10 had intracerebral hemorrhage. Among the patients with cerebral ischemia, 39 were examined within 10 days from the onset of symptoms (acute complete stroke), and 34 from 10 days to 2 months from the onset (chronic complete stroke). The 19 who had a transient ischemic attack, were examined at various intervals after the episode.

Tumors were diagnosed as meningiomas in 10 patients, lung metastasis in 10 and glioblastomas in 2.

The diagnoses were based upon accepted clinical criteria including the results of cerebral spinal fluid examination in 72 patients. Computed tomography was used for 54 patients and cerebral angiography was done in 27 patients with cerebral vascular disease and in all except 2 patients with brain tumor.

Method

Before cerebral scintigraphy, patients had radionuclide cerebral angiography with the same tracer used for brain scanning (99mTc pertechnetate). The examinations were made with the patient in the usual supine anteroposterior projection. Following injection of the tracer (about 15 mCi) in a brachial vein, a sequence of the scintiphotos was initiated at 2 second intervals for approximately 40 seconds after the injection. Detection equipment was a gamma camera (Pho gamma H.P., Nuclear Chicago); sequential scintiphotos were taken with a 35 mm time lapse motor driven Nikon camera attached to the oscilloscope of the scintillation camera. The selection and quantitative reading of the areas of interest was made by photodensitometer as described elsewhere. Six symmetrical areas on each hemisphere, along with 3 on the midline, were selected (fig 1).

Data Analysis

An example of a typical regional time-activity curve is shown in figure 2. Following injection of the tracer in a brachial vein at time t=0, there is a time interval...
before the tracer bolus reaches the detector field. After onset of detected activity, the curve rises rapidly to a maximum, the activity then slowly decreases, reaches a minimum and then is followed by a slow rise due to recirculation.

Following intravenous administration at \( t=0 \), regional cerebral monitored activity results from the convolution of an input function, \( I(t) \), with the response of the system to the unit impulse, \( R(t) \):

\[
Q(t) = \int_{0}^{t} I(\tau) R(t-\tau) \, d\tau \quad (1)
\]

\( Q(t) \) is monitored activity, \( t=0 \) is injection time.

The input function \( I(t) \) describes the rate at which the tracer is introduced into the regional volume inflow and reflects the motion of the tracer in portions of the circulatory bed traversed before actual entrance.\(^{18}\) The function \( R(t) \) is, by definition, the time-activity curve which would have been recorded for a unitary impulse administration of the tracer at the inflow of the system and corresponds to the residue function of this same system.\(^{14}\)

Using a Laplace transform, the first mathematical moment about the time of injection of the monitored activity, normalized by the whole area under the curve, is:

\[
\frac{\int_{0}^{\infty} tQ(t) \, dt}{\int_{0}^{\infty} Q(t) \, dt} = \frac{\int_{0}^{\infty} tI(t) \, dt}{\int_{0}^{\infty} I(t) \, dt} + \frac{\int_{0}^{\infty} tR(t) \, dt}{\int_{0}^{\infty} R(t) \, dt} \quad (2)
\]

The term \( \int_{0}^{\infty} tI(t) \, dt / \int_{0}^{\infty} I(t) \, dt \) is the actual mean transit time of the tracer from the injected vein to the regional cerebral inflow surface.\(^{14-18}\) The term \( \int_{0}^{\infty} tR(t) \, dt / \int_{0}^{\infty} R(t) \, dt \) is the centroid of the time-activity plot per unit impulse administration at the regional cerebral inflow, and corresponds to regional cerebral mean transit time.\(^{14-17}\) The moment of the monitored activity, therefore, corresponds to a mean transit time of the entire path from the injected vein to the regional cerebral outflow surface (\( rABmT \)).

Owing to recirculation of the tracer that masks the final part of the downslope of the monitored activity, equation 2, as such, cannot be utilized. As an approximation, moments were calculated by limiting the integration to a time \( t_r \), indicating initiation of recirculation.

As discussed elsewhere,\(^{14}\) this operation results in an underestimation of the moments and may be correct only if one restricts his interest to interregional differences. It is believed that a) the curves in the terminal part tend to decrease in a similar fashion, b) the neglected time may, therefore, be roughly similar for two symmetrical regions, and c) while the moments are underestimated, the difference between moments of 2 symmetrical regions may correspond to the real difference of transit times.

Results

Normal Subjects (table 1)

In this group the mean value of \( rABmT \), assessed by the truncation method, was 19.07 ± 3.4 seconds (mean ± sd). The mean difference in \( rABmT \) between pairs of symmetrical regions was 0.30 ± 0.14 seconds (mean ± sd). A change of 0.58 seconds or more (mean + 2 sd) was selected as an index of abnormality.

In this group only 8 pairs of regions with a difference above this limit were found. No subject had
TABLE 1. Changes of rABmtT in Normal Subjects and in Patients with Cerebral Vascular Disease

<table>
<thead>
<tr>
<th>Patients with cerebral vascular disease</th>
<th>Normal subjects</th>
<th>Patients with cerebral vascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Subjects</td>
<td>70</td>
<td>102</td>
</tr>
<tr>
<td>No. Regions</td>
<td>420</td>
<td>612</td>
</tr>
<tr>
<td>Mean rABmtT</td>
<td>19.07 ± 3.4 sec</td>
<td>24.96 ± 5.78 sec</td>
</tr>
<tr>
<td>Subjects with asymmetrical rABmtT</td>
<td>8 (11%)</td>
<td>79 (77%)</td>
</tr>
<tr>
<td>Region pairs with asymmetrical rABmtT</td>
<td>8 (2%)</td>
<td>248 (40%)</td>
</tr>
<tr>
<td>Mean number of asymmetrical region pairs per subject</td>
<td>0.11</td>
<td>2.43</td>
</tr>
<tr>
<td>Subjects with more than 2 abnormal region pairs</td>
<td>0</td>
<td>62 (60%)</td>
</tr>
</tbody>
</table>

**a significant difference in more than one pair of regions.**

**Patients with Cerebral Vascular Disease**

The mean value of rABmtT was 24.96 ± 5.78 seconds (mean ± SD). A significant difference of rABmtT between symmetrical regions was found for 248 pairs of regions (40% of the total number) in 79 out of 102 patients (77%). The change was evident in at least 2 contiguous regions in 62 patients (60%). The increased mean transit time corresponded to the side of the lesion, as determined by clinical data, in 66 out of 102 patients (218 region pairs); however, in 13 patients (30 region pairs) a paradoxical decrease of mean transit time on the injured side was found.

**a) Patients with Acute Complete Stroke (table 2)**

Thirty-five out of 39 patients with acute complete stroke had a significant difference of rABmtT (89%); the change involved at least 2 contiguous region pairs in 32 patients (82%). An average of 4 out of 6 region pairs were involved in each patient. Thirty-two patients had an increased mean transit time on the side of the lesion, 2 patients had a paradoxical decrease and 1 patient had regions with both decreased and increased mean transit time.

The mean of the regional increases was 1.38 ± 0.68 seconds.

**b) Patients with Chronic Complete Stroke**

Twenty-five out of 34 patients with chronic complete stroke (73%) had a significant difference of rABmtT. The change involved 2 or more contiguous regions in 19 cases (56%). Sixty-five region pairs were involved with an average of 2 out of 6 pairs for each patient. Twenty-one patients exhibited an increased rABmtT on the side of the lesion and 4 had a paradoxical decrease.

The mean of the regional increases was 0.9 ± 0.35 seconds.

**c) Patients with Transient Ischemic Attacks**

A significant difference of rABmtT was found in 10 out of 19 patients; 5 patients exhibited an increased rABmtT on the affected side, while the remaining 5 had a paradoxical decrease. Only 4 patients had the same change involving two regions or more.

The mean of the regional increases was 0.95 ± 0.25 seconds.

TABLE 2. Changes of rABmtT in Patients with Cerebral Vascular Disease According to Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Complete stroke</th>
<th>Transient ischemic Attacks</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>No. Patients</td>
<td>39</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>No. Region pairs</td>
<td>234</td>
<td>204</td>
<td>115</td>
</tr>
<tr>
<td>Asymmetrical rABmtT increased on injured side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. Patients</td>
<td>32 (82 %)</td>
<td>21 (61 %)</td>
<td>5 (26 %)</td>
</tr>
<tr>
<td>No. Region pairs</td>
<td>135</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>Asymmetrical rABmtT decreased on injured side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. Patients</td>
<td>2 (5 %)</td>
<td>4 (11 %)</td>
<td>5 (26 %)</td>
</tr>
<tr>
<td>No. Region pairs</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Patients with two or more abnormal regions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. Abnormal regions per patient</td>
<td>3.6</td>
<td>1.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Mean increase on injured side</td>
<td>1.38 ± 0.68 sec</td>
<td>0.9 ± 0.35 sec</td>
<td>0.95 ± 0.24 sec</td>
</tr>
</tbody>
</table>
d) Patients with Intracerebral Hemorrhage

A significant difference of $r_{AB}mtT$ was found in all 10 patients examined. The change involved at least 2 contiguous regions in 7 and 8 patients had an increased $r_{AB}mtT$ on the side of the lesion. The remaining 2 had a decrease.

Patients with Intracerebral Tumors (table 3)

Changes were found in 11 out of 22 patients (50%); in 7 cases the change involved 2 contiguous regions (32%). The change corresponded to the site of the lesion in all except 2 patients where it involved the whole hemisphere; one had a parasagittal meningioma and the other a frontal meningioma. Changes were characterized by increased $r_{AB}mtT$ at the site of the lesion, excepting one patient with a glioblastoma in which a decrease was found.

Discussion

Analysis of time-activity curves may be a useful addition to intravenous radionuclide cerebral angiography as it provides a more objective criterion of the evaluation based on statistical data. Moreover, transit time measurements are independent of detection efficiency.

The method presented here permits evaluation of a mean transit time in the whole path from the injected vein to each regional outflow surface. This time reflects both the shape of the function describing tracer input into monitored vascular volume and the distribution frequency of the transit times within the same vascular volume. Changes in the regional tracer input may be due to cardiac factors (in this case, all regions will be affected in the same way), or to altered canalization of the carotid and vertebral arteries. Changes in the distribution of the transit times within the monitored segment may be due to altered canalization within the region itself. Interregional differences are determined only by events occurring in the segment of circulation usually affected in cerebral vascular disease, namely the carotid and vertebral arteries and the intracranial vessels.

Changes of perfusion assessed with this method are expressed as changes in tracer transit time. Usually, since flow corresponds to the ratio of vascular volume to transit time, a change of transit time results in an expected change of flow in the opposite direction. Possible changes of vascular volume, due either to variation in the number of patent vessels (faulty microcirculation, neovascularization) or to changes in vessel radius (autoregulation, response to $P_{CO_2}$ changes), make further considerations necessary.

In a branching network of vessels such as the cerebral vasculature, velocity of the blood stream in any region will be, for the most part, affected by the sum of cross surfaces of all cerebral vessels traversed at a given time. Provided that the flow is steady and that the radius of branches of the same order is the same, velocity will be the same in all regions; in particular, velocity will be independent of the cross surface of the vessels actually seen by the detector. However, when changes of regional vessel cross surfaces result from variation of vessel caliber due to vasodilatation or vasoconstriction, the above considerations cannot be applied, so that regional velocity will be affected by regional conditions and will differ from that of other regions traversed at the same time.

Asymmetries of transit time may be detected when mean velocity is different in 2 symmetrical regions, this may occur when there is: a) altered canalization with collateral circulation that entails both a longer path and different velocity and b) regional changes of the vessel caliber.

It is possible that an asymmetry of flow dependent upon a change in the number of patent vessels may be undetected by transit time estimation and, conversely, a transit time asymmetry may be detected in spite of symmetrical flow when the caliber of the vessels in the 2 regions is different.

Because the statistical criterion of asymmetry, based on normal controls, is $\pm 2 \times SD$ (0.05 level), a certain number of positive judgments of asymmetry can be expected purely on the basis of chance; i.e., due to measurement error or other random events.

On the basis of the above arguments, it is possible that the paradoxical decreases of $r_{AB}mtT$ found in these patients do not always represent luxury perfusion syndrome or "hot stroke" which is sometimes associated with a cerebral infarct.

Diagnostic Accuracy

Positivity must be evaluated by taking into account the number of true as well as false positive results.

Choosing as a limit of normality a deviation of $r_{AB}mtT$ between symmetrical regions corresponding to the mean $\pm 2 \times SD$ of the deviations found in normal subjects, abnormality was detected in 8 of 420 region pairs in normal subjects and 248 of 612 region pairs (40%) in patients with cerebral vascular disease.

Assuming as an index of positivity a change in the same direction of at least 2 contiguous region pairs, no false positives were found. Using this criterion the patients, as a whole, had a 57% incidence of true positives. The highest incidence of such true positives was 82% in patients with acute complete stroke, followed by 70% in patients with intracerebral hemorrhage and 56% in patients with chronic complete stroke. Patients with transient ischemic attacks had a

### Table 3. Changes of $r_{AB}mtT$ in Patients with Intracerebral Tumors

<table>
<thead>
<tr>
<th>No. Patients</th>
<th>Meningioma</th>
<th>Metastasis</th>
<th>Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetrical $r_{AB}mtT$ increased on injured site</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Asymmetrical $r_{AB}mtT$ decreased on injured site</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>
21% incidence of positivity and patients with tumor had a 32% incidence.

For cerebral vascular patients, these percentages compare favorably with brain scan results and are of the same order as those found with visual evaluation of the sequential scintiphotos.24

Usually estimation of rABmtT and visual evaluation gave the same results, but sometimes differing conclusions were reached. Nevertheless, this method may be more useful since it allows a quantitative determination of the extent and degree of a perfusion defect; in particular, it may be useful in follow-up examinations. Patients with acute complete stroke had a more extensive defect than patients with chronic complete stroke or transient ischemic attacks. When there was an increased rABmtT, the extent of the change was greater in patients with acute complete stroke than in patients with chronic complete stroke.

About one-third of the patients with tumor had a significant change of rABmtT. The defect was restricted to the site of the lesion. However, 2 tumors were misleading in this respect: a parasagittal meningioma, in which there was extensive involvement of the whole hemisphere, was probably due to encroachment upon the venous return, and a frontal tumor which occupied practically the whole projection of the hemisphere.

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References

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A Bartolini

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