Characterization of Malignant Gliomas and Cerebrovascular Disease by Cerebral Dynamic Studies

BY LYNN R. WITHERSPOON, M.D.,* R. S. PREISSIG, M.D., M. S. MAHALEY, JR., M.D., J. WENDELL TYSON, M.D.,† C. CRAIG HARRIS, JOHN R. LEONARD, M.D., AND JACK K. GOODRICH, M.D.

Abstract:
Characterization of Malignant Gliomas and Cerebrovascular Disease by Cerebral Dynamic Studies

A technique for analysis of dynamic radionuclide studies of the cerebral circulation is described. This technique permits objective classification of observed radionuclide distribution patterns. Variation in the time-to-peak activity, and in the maximum attained activity as determined by region-of-interest analysis of cerebral hemispheric activity, was defined for a normal population. Application of these normal values permits classification of observed hemispheric radionuclide distribution patterns in anaplastic gliomas and in occlusive cerebrovascular disease. Radionuclide activity in gliomas may be normal, decreased, or increased in the region of the tumor. In cerebrovascular occlusion, decreased activity, associated with a delay in time-to-peak activity, is frequently demonstrated in the affected hemisphere.

Additional Key Words: hemispheric activity, brain scanning, anaplastic glioma

Cerebral dynamic studies have been demonstrated to be diagnostically useful adjuncts to static brain imaging.1, 2 These studies rely for interpretation on subjective visual analysis of sequential scintiphotographs of the passage of a radioactive bolus through the neck and cranial vessels. Specific disease entities have been correlated with recognized patterns of abnormal tracer distribution.3, 4 Characterization of specific intracranial lesions has often been impossible because of the nonspecificity of recognized patterns. For example, either cerebrovascular occlusive disease or a mass lesion may result in scintiphotographic demonstration of diminished unilateral hemispheric activity.3, 4

To achieve satisfactory count densities on sequential scintiphotographs obtained after the injection of a bolus of radionuclide into a peripheral vein, two-second to three-second exposures are necessary. These relatively long time periods result in a time-smearing of data which may obscure transient asymmetries in hemispheric activity. Additionally, identification of diminished hemispheric activity as decreased, delayed, or both, often is not possible. It has been suggested that a numerical analysis of activity versus time relationships in the distribution of the carotid arteries, middle cerebral arteries, or cerebral hemispheres may provide a more sensitive and objective means of identifying abnormalities.6 Other studies have demonstrated that this numerical analysis permits definition of asymmetries in hemispheric tracer distribution in neoplasms and cerebrovascular occlusive disease.7-10

The purpose of this study was to develop a standard technique for analysis of activity versus time curves obtained from each cerebral hemisphere following the intravenous injection of a bolus of sodium pertechnetate (99m Tc). A group of normal patients, a group of patients with anaplastic intracranial gliomas, and a group of patients with cerebrovascular occlusive disease were studied. This technique has permitted a quantitative classification of abnormalities of intracranial tracer distribution not possible by examination of the sequential scintiphotographs alone.

Methods
The diagnosis of patients in each of three groups (normal, anaplastic gliomas, cerebrovascular disease) was established

From Duke University Medical Center and the Veterans Administration Hospital, Durham, North Carolina.

*Present address: Department of Nuclear Medicine, Ochsner Foundation Hospital, New Orleans, Louisiana 70121.
†Present address: Division of Nuclear Medicine, Louisville General Hospital, Louisville, Kentucky 40202.


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Reprint requests to Jack K. Goodrich, Division of Nuclear Medicine, Duke University Medical Center, Durham, North Carolina 27710.
at the completion of the patient's workup, and was correlated with the results of radionuclide study. Twenty-five patients, each studied once, comprised the normal population. In each patient intracranial vascular or neoplastic disease was excluded by further diagnostic studies. This group was used to establish criteria for normal hemispheric radionuclide distribution patterns.

One hundred twenty cerebral dynamic studies were obtained in 42 patients with anaplastic gliomas proved surgically (39) or angiographically (three). One hundred two of these 120 studies were postoperative. Fifty-one studies were obtained in 47 patients with cerebrovascular disease.

Dynamic studies of the cerebral circulation were performed on a Searle Pho/Gamma HP scintillation camera using the high resolution, low-energy (15,000 hole) collimator.

Patients with intracranial neoplasms were positioned in either the vertex, anterior, or posterior projection (whichever placed the lesion nearest the detector). All subsequent studies were performed in the same projection. All normal and cerebrovascular disease patients were studied in the anterior projection. Twenty to 30 mCi sodium pertechnetate (99mTc) were administered intravenously in an antecubital vein in a 0.5 to 1.0 ml bolus. The small volume and rapid injection minimized spread of the bolus as it arrived in the cerebral vessels, thus giving rapidly rising activity versus time curves with clearly defined peaks. All studies were recorded on videotape for later region-of-interest analysis of activity versus time in each cerebral hemisphere.

In all studies, region-of-interest "cursors" of equal size were selected to cover the diseased portion of the affected hemisphere and an identical area in the contralateral, presumed normal hemisphere. Variation in cursor size was controlled by first selecting the two regions-of-interest, generating activity versus time curves, then reversing the cursor positions and generating a second set of curves. Differences in these two apparent peak activities varied by 5% or less. Differences in time-to-peak activity were not measurable. It is unlikely that minor variation in cursor size or asymmetry of position produced artifactual differences in the parameter measured in excess of the allowed normal variation. In postoperative patients care was taken to avoid lateral superficial (postsurgical) activity.

Region-of-interest activity versus time curves from each cerebral hemisphere were generated on a dual ratemeter with an associated strip chart recorder (Nuclear Chicago 8732 ratemeter and Texas Instruments Servoriter II). The first 30 seconds of data were replayed at eight inches per minute chart speed with a 0.5-second ratemeter time constant.

Count rates in the regions-of-interest at peak activity and times from arrival of activity in the regions-of-interest to peak activities were chosen as parameters characterizing a particular study (fig. 1). Expected variations of these two parameters between the two hemispheric regions-of-interest were established for the normal group using the percentile method (fig. 2). On the basis of this analysis of the normal group, patient studies were classified as abnormal only if the time difference between peak hemispheric activities was greater than 1.5 seconds, or if activities at peak differed by greater than 10%. Variations between normal and abnormal hemispheres were classified as early or delayed peak activity or increased or decreased peak activity in the abnormal hemisphere (fig. 3). Combinations of these basic patterns also were observed. Beginning at the time of appearance of radioactivity in the base of the neck, sequential Polaroid and 35-mm scintiphotographs of the cranium were made every two to three seconds. These scintiphotographs were evaluated according to the criteria described by Fish et al. and were then compared with the region-of-interest findings.

Results

The hemispheric activity patterns for both groups of patients are shown in table 1. The correlation between

![Figure 1](https://example.com/figure1.png)

**FIGURE 1**

Parameters measured from each cerebral dynamic study. Differences in peak activity (Activity 1 minus Activity 2) and in time-to-peak activity (Time 2 minus Time 1) were chosen for study.

![Figure 2](https://example.com/figure2.png)

**FIGURE 2**

Distribution of cerebral hemispheric activity versus time region-of-interest findings in normal population (N = 25).
CHARACTERIZATION OF MALIGNANT GLIOMAS AND CVD

Patterns of observed cerebral hemispheric activity versus time: a = early time-to-peak activity, b = delayed time-to-peak activity, c = normal, d = increased peak activity, and e = decreased peak activity.

visually interpreted sequential scintiphotographs and hemispheric activity versus time curves for both groups is shown in table 2. Gliomas demonstrating delayed or decreased region-of-interest activity showed diminished arterial phase activity in the tumor-bearing hemisphere on scintiphotographs. Both early and increased region-of-interest activity was associated with increased arterial phase activity on scintiphotographs. Scintiphotographs and hemispheric region-of-interest activity versus time curves in an anaplastic glioma with diminished arterial phase activity are demonstrated in figures 4 and 5.

The group of cerebrovascular disease patients with delayed, delayed and increased, or delayed and decreased region-of-interest patterns demonstrated diminished arterial phase hemispheric tracer activity in 17 of 19 series of scintiphotographs. In eight of these 17 studies, late increase in tracer activity in the abnormal hemisphere was recognized on scintiphotographs as is demonstrated in figure 6. The region-of-interest hemispheric time versus activity curves generated from this study are shown in figure 7.

Discussion
Studies of the cerebral transit of nondiffusible tracers, such as is approximated by sodium pertechnetate (99m Tc), do not yield measurements of cerebral blood flow directly. Generation of activity versus time curves from the cerebral hemispheres permits an estimation of regional cerebral transit time, a value equal to the volume viewed divided by the rate of flow through that volume. The cumulative area under symmetrical hemispheric region-of-interest activity versus time curves to the initial time-of-peak activity has been shown to be a sensitive indicator of abnormal cerebral blood flow. Both methods provide some quantitative information regarding the intracranial abnormality being studied, probably related to altered cerebral blood flow.

Most commonly the transit of a nondiffusible tracer through the cerebral circulation is assessed by viewing sequential two-second or three-second exposure scintiphotographs. Among other parameters the scintiphotographs are evaluated for symmetry of arterial phase activity. An estimation is made of both relatively how much activity appeared in the hemispheres and the time this activity was maximal. The peak activity and time-to-peak activity defined by region-of-interest activity versus time curves obtained from both hemispheres provide essentially similar information. While these two parameters are empiric and not necessarily measures of altered cerebral blood flow, we undertook to examine them as indicators of brain disease.

TABLE 1

| Hemispheric Activity Patterns Defined by Region-of-Interest Analysis |
|-----------------------|----------------|------------|-----------|----------|----------|--------------------|----------------|----------------|
| Groups of patients    | Normal | Early   | Delayed  | Increased| Decreased| Delayed and increased| Decreased and decreased |
| Anaplastic gliomas (120 studies) |       |         |          |        |          |                      |                |
| Preoperative          | 10     | 0       | 0        | 4       | 4        | 0                  | 0                |
| Postoperative         | 25     | 1       | 1        | 14      | 57       | 4                  | 0                |
| Cerebrovascular occlusive disease (51 studies) | 17     | 0       | 8        | 4       | 11       | 1                  | 10               |

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Correlation Between Region-of-Interest and Scintiphotographic Findings

<table>
<thead>
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<th>Groups of patients</th>
<th>Region-of-Interest patterns</th>
<th>Scintiphotographs</th>
<th>No. studied</th>
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<td>Anaplastic gliomas</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>87</td>
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<tr>
<td>(120 studies)</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td></td>
<td>Abnormal</td>
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<td>(7 substantiated by other studies)</td>
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<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>27</td>
</tr>
<tr>
<td>(51 studies)</td>
<td>Normal</td>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Normal</td>
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<td>(7 substantiated by other studies)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(carotid disease)</td>
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</table>

A control group of patients in whom no evidence of organic intracranial disease existed was studied. Most normal patients had nearly identical region-of-interest curves in each hemisphere (fig. 2). Normal values for a population distribution may be established by the percentile method without assumptions concerning the distribution shape. For the purposes of this study it seemed preferable to assign limits that result in a low number of false-positive results. If limits are assigned which enclose 95% of values obtained in the “normal” group (N = 25), false-positive results may be anticipated in less than 15% of the tumor or cerebrovascular disease groups. Because of the precision of measurements possible from strip chart recordings and the use of a 0.5-second ratemeter time constant, a 1.5 seconds' difference in time-to-peak activity was chosen to be the upper limit of normal rather than a shorter time interval.

Postoperative studies in patients with anaplastic gliomas were reproducible on repeated studies and served to characterize a particular patient’s tumor. Postoperatively, the most commonly defined tracer distributions for these patients were normal or decreased tumor-bearing hemisphere activity (table 1). In this study combinations of altered time-to-peak activity together with abnormal peak activity were unusual tumor patterns. Increased activity in the tumor-bearing hemisphere postoperatively was usually observed in neoplasms presumed to be actively growing and was associated with clinical deterioration. Change from one pattern to another correlated with clinical evidence of tumor activity and is the subject of another communication.

This technique was not significantly more sensitive to abnormal tracer distribution in gliomas than visual inspection of scintiphotographs. While seven of the eight instances of abnormal region-of-interest curves with normal scintiphotographs were confirmed by subsequent dynamic study, brain scan, and clinical changes (table 2), there were five normal region-of-interest studies associated with abnormal scintiphotographs. Three of these five studies could be supported by the subsequent radionuclide studies and clinical changes.
About half of the postoperative region-of-interest studies in patients with anaplastic gliomas demonstrated decreased but not delayed tracer activity. Although there was no correlation between the extent of surgical resection, which varied from biopsy to frontal lobectomy, and tracer distribution, as defined by region-of-interest analysis, it is still probable that the region-of-interest patterns observed in this group were influenced by the previous surgical removal of brain and tumor tissue. It is of interest that brain resection and resultant arterial amputation did not produce delayed time-to-peak hemispheric activity as was seen in cerebrovascular disease. Peripheral activity in the surgical site did not appear to contribute to the arterial phase tracer distribution pattern.17

Observed activity in the tumor-bearing hemisphere in 18 studies performed on ten patients who had no cranial surgery showed four patients with increased activity (four studies), four patients with decreased activity (four studies), and four patients...
WITHERSPOON, PREISSIG, MAHALEY, TYSON, HARRIS, LEONARD, GOODRICH

RIGHT MIDDLE CEREBRAL ARTERY OCCLUSION - Anterior

Sequential scintiphotographs demonstrating decreased arterial phase activity in the right hemisphere followed by increased venous phase activity six days following onset of left hemiparesis.

With normal activity (ten studies). In this small series no instances of delayed peak activity were observed.

Characterization of cerebrovascular disease by region-of-interest analysis of cerebral dynamic studies permitted further definition of the usually described "diminished" tracer activity in the affected hemisphere as decreased or delayed, or both. The most frequently observed pattern was delayed time-to-peak activity; by contrast, in patients with anaplastic gliomas there was decreased peak activity but not delayed time-to-peak activity. These differences are demonstrated by comparing the decreased glioma activity in figure 5 with the delayed time-to-peak activity in cerebrovascular occlusion in figure 7. Because of data blending necessary for compilation of satisfactory scintiphotographs, delays in time-to-peak activity relative to the contralateral hemisphere of two to three seconds were in general appreciated only as reduced activity in the affected hemisphere. Longer delays were represented scintiphotographically by a decrease in arterial phase activity followed by a later increase in activity in the affected hemisphere (fig. 6).

Hemispheric tracer distribution was classified as normal by region-of-interest analysis in 17 patients in the cerebrovascular disease group. Fifteen of these 17 had normal scintiphotographs as well. The other two patients had abnormally decreased carotid activity seen on the scintiphotographs and carotid disease was also demonstrated in both patients by contrast angiography. In seven patients with normal scintiphotographs abnormal region-of-interest studies were correlated with proved cerebrovascular disease. In these seven of 51 studies, tracer distribution would have been believed normal if interpretation was based on visual inspection of scintiphotographs alone. Delayed time-to-peak activity defined by region-of-interest analysis in 19 patients was correctly characterized scintiphotographically in only eight of these 19 studies. These findings suggest that region-of-interest analysis of hemispheric activity is a more sensitive means of detecting abnormalities on cerebral dynamic studies in cerebrovascular disease than visual inspection of scintiphotographs.

An obvious limitation of this method is the assumption that one hemisphere is normal which may...
not always be the case. Coexistent cerebrovascular disease in patients with anaplastic intracerebral gliomas may influence the apparent tumor patterns defined by this technique. This technique is attractive, however, because it requires no more than usually available equipment and only a moderate extension of study time.

We have established that this region-of-interest technique permits objective classification of the distribution of radionuclide within the cerebral hemispheres. It is more sensitive to abnormal intracranial radionuclide distribution in cerebrovascular disease than scintiphotographs and it may be found useful in the differentiation of one intracranial abnormality from another. Examination of larger patient populations and extension to other intracranial disease, such as metastatic carcinoma, benign neoplasms, and inflammatory lesions, will be necessary to establish the true value of this technique.

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