Regional Cerebral Blood Flow in Acute Stroke: Preliminary Experience With the $^{133}$Xenon Inhalation Method

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Abstract:

The $^{133}$Xenon inhalation method of measuring regional cerebral blood flow was applied in serial studies comprising 100 measurements in 57 cases of acute hemiparesis and hemiplegia presumed due to arterial occlusion. Satisfactory data for analysis were obtained in over 95% of the cases studied. Significant flow reductions in the ischemic hemisphere were demonstrated in the cases with more severe clinical disability. This study demonstrates the feasibility of applying this method for serial regional cerebral blood flow measurements in most cases of acute stroke. The expected clinical usefulness and limitations of the method are discussed.

Additional Key Words: papaverine, arterial occlusion, hypertension, heparin, hemiparesis

If the treatment of acute stroke is to be given a rational basis, and achieve a success comparable with that of myocardial infarction, a system must be developed with the essential capability of continuously monitoring or frequently measuring regional cerebral blood flow over a period of three or more days.

The purpose of this paper is to report a preliminary experience with the $^{133}$Xenon inhalation method, and to report the results of a feasibility study of the applicability of this method in often uncooperative acutely ill patients. In undertaking this study, a quantitative evaluation of the method itself was not intended, and new information about the pathophysiology of cerebral infarction was not expected. It will be seen that though the method is logistically formidable, its essential safety can facilitate study of critically ill patients. Provided its quantitative accuracy is confirmed in ongoing studies, some progress in the rational management of acute stroke can be hoped for.

Methods

THE CEREBRAL BLOOD FLOW MEASUREMENT

This method has been described in detail by Obrist. In brief, the patients lay comfortably in bed wearing a close-fitting face mask with a one-way valve. $^{133}$Xenon was breathed in a concentration of 1.3 mc per liter for one minute. An exhaust tubing from the face mask to a powerful window fan directed the expired air out of doors without significant room contamination. The intake and exhaust tubing were made of plastic tubing 4 cm in diameter, covered with lead foil 3 mm in thickness. Expired air radioactivity was monitored in a five-turn glass helix, 2 mm internal diameter, resting on a scintillation detector. Air was drawn through the helix by a vacuum pump via an unshielded tubing from the face mask (4 mm internal diameter) and exhausted at the window fan. The fan, in addition, provided complete exchange of room air in about two minutes. Cranial radioactivity was monitored for ten minutes after the one-minute saturation by NaI scintillation detectors over the parietal and midfrontal regions of both hemispheres. The collimation was 18 mm in diameter and 18 mm in depth. No discrimination of radioactive energy was made. Arterial radioactivity was not monitored.

The cranial and expired air curves were analyzed by a computer program provided by Dr. Obrist, utilizing a two-compartment model. The rationale of this analysis is that the one-minute input time preferentially saturates the cerebral fast compartment and minimally the scalp and skull. Application of a two-compartment analysis of the ten-minute clearance yields a relatively pure cerebral fast compartment, and a slow compartment which includes both extracerebral and slow cerebral compartments. Only the fast compartment is of clinical significance. This represents gray matter flow in the intact brain, but compartmental integrity is uncertain in disease.

Blood pressure was measured by auscultation several times prior to and during the 11-minute study. Immediately after the study an arterial blood sample was drawn for the determination of $P_{O_2}$, $P_{CO_2}$, pH, and hemoglobin. Fast compartment flow in cubic centimeters per 100 gm brain per minute was calculated as the product:

$$F = k_1 A \times 100$$

where $k_1$ is 0.693 divided by the fast compartment half clearance time. The blood-brain partition coefficient $A$ was

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Supported in part by NINDS Grants NS 08802 and NS 11109.

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Stroke, Vol. 5, January-February 1974
corrected for hemoglobin according to the tables of Høedt-Rasmussen.2

Flow was not normalized for P_{CO_2} changes because of the certainty that CO_2 reactivity is altered in some acute stroke patients.4 Moreover, we have a conviction that the P_{CO_2} is affected in some cases by cerebral ischemia and is itself significant to the total description of the patients’ reaction to the disease.

THE PATIENTS
These were all cases of hemiparesis or hemiplegia under our care. Obvious cases of brain stem lesion were excluded, the intent being to limit this study to hemispheric lesions. When the clinical impression is supplemented with EEG, brain scan, and in some cases arteriography, we would expect about 5% of the remaining cases would be due to brain stem lesions.6 Arteriography was performed in two-thirds of the patients, usually between five and ten days after admission.

Spinal fluid was examined in all cases on admission, and was reexamined again in those patients suffering worsening of their disability after admission. In all cases there were less than 40 erythrocytes per cubic millimeter. We would expect about 5% of these cases to be due to cerebral hemorrhage. The total incidence of nonvascular disease, mainly undiscovered tumor or subdural hematoma, would be less than 1% in this series.

Most of the patients with mild or moderate disability were treated with parenteral heparin and papaverine. When hypertension was present, it was treated with an immediate objective of a systolic blood pressure reading of 160 mm Hg. Appropriate fluids, electrolytes, and antibiotic therapy were given when indicated.

Severe pulmonary disease, symptomatic heart failure and major respiratory pattern abnormalities were excluded from this study insofar as they could be identified by clinical examination, chest x-ray, and blood gas analysis.

Results
Satisfactorily expired air and cranial curves were obtained in 95% of the cases comprising the 100 studies summarized here. The crucial trick, which appears to be more art than science, is the proper fitting of the face mask without an air leak, and without discomfort to the patient. Particular problems were encountered in men with beards and old people without teeth. Except for dysphasic or dyspneic patients, enlisting their cooperation was not difficult. Peak cranial count rates in excess of 60,000 counts per minute were easily obtained, except in patients with Cheyne-Stokes respirations.

The patients are divided between those who made significant clinical improvement during the first two weeks after recurrence of maximum disability (improvement) and those who did not (no improvement). Clinical worsening occurred in the hospital after a blood flow measurement in one patient among the improvement group and in seven among the no improvement group. The initial disability was generally more severe in the no improvement group with the exception of the initial status of the seven who had a study prior to the occurrence of maximum disability.

Mean arterial blood pressure at various time intervals prior to and following the occurrence of maximal clinical disability. In this and all following figures the solid circle designates patients who did not improve and the open circles represent those who did improve. Mean and standard deviation are shown for each group. Only one patient, who subsequently improved, was studied prior to occurrence of maximal disability. The blood pressures were significantly different (p<.05) during the period 0 to 1 day after occurrence of maximal disability.

<p>| TABLE 1 |</p>
<table>
<thead>
<tr>
<th>Arteriographical Results</th>
<th>Improvement</th>
<th>No Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not done</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Carotid stenosis or occlusion</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Posterior cerebral</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>Mean age</td>
<td>63</td>
<td>66</td>
</tr>
</tbody>
</table>

<p>| TABLE 2 |
| Number of Patients Studied in Relation to Occurrence of Maximum Disability |</p>
<table>
<thead>
<tr>
<th>Days</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior</td>
<td>improvement</td>
</tr>
<tr>
<td>0-1</td>
<td>14</td>
</tr>
<tr>
<td>1-3</td>
<td>12</td>
</tr>
<tr>
<td>3-5</td>
<td>9</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
</tr>
</tbody>
</table>
to the development of maximal disability. Arteriographical findings are summarized in table 1. The number of studies performed in each time interval is shown in table 2.

The mean arterial blood pressure calculated as diastolic pressure plus one-third pulse pressure, arterial P<sub>CO</sub>, and hemoglobin are summarized for the two groups of patients in figures 1 to 3. There are no significant differences except that blood pressure was considerably higher in the immediate period following development of maximal disability in the no improvement group. The absence of blood flow studies in the no improvement group one to three days after the occurrence of a maximal disability is a combined artifact of our five-day work week, our 133Xenon procurement schedule, and the need to perform diagnostic brain scan which, in the absence of energy discrimination, interferes with the 133Xenon study for about 48 hours because of residual counts from the technetium.

The blood flow results are shown in figures 4 through 6, comparing the improvement and no improvement groups. The symptomatic hemisphere was the presumed location of the ischemic lesion, opposite the hemiparesis. The most ischemic region is the one with the slowest flow detected in the shortest time after the occurrence of the maximal disability. In patients with more than one study, the region initially designated the most ischemic retained this designation regardless of subsequent flow changes. For example, in patient B.H., on day one the anterior probe over the symptomatic hemisphere revealed a flow value of 45 cc/100 gm brain per minute while the posterior was

![Graph](image1)

Figure 1: Arterial P<sub>CO</sub>. Same symbols as in figure 1. The two groups did not differ significantly.

![Graph](image2)

Figure 2: Days after occurrence of maximum disability. No significant differences.

![Graph](image3)

Figure 3: Hemoglobin. Same symbols as in figure 1. There are no significant differences.

![Graph](image4)

Figure 4: Most ischemic region in symptomatic hemisphere. There are statistically significant differences between the two groups at all stages.

![Graph](image5)

Figure 5: Fast compartment regional cerebral blood flow in the most ischemic region in the symptomatic hemispheres. There are statistically significant differences between the two groups at all stages.

55. On day four, when the study was repeated, the anterior probe had increased to 58 while the posterior was 54. In this case the anterior probe was designated
The main observation here is the expected significantly slower flow in the most ischemic region of the no improvement group compared with the same region in the group which did improve. Note that the flow increased progressively with time in the improvement group but did not in the no improvement group.

The most relevant to our own interest in progressive stroke, though not statistically significant, is the decrease in flow in the no improvement group from prior to the occurrence of a maximal disability to the period 0 to 24 hours afterward. Another point of interest, though not statistically significant, is the persistently higher flow values in the asymptomatic hemisphere of the improvement group compared with the no improvement group.

**Discussion**

This report does not add to the understanding of the pathophysiology of stroke, nor was this the purpose of this study. All of the significant differences and suggestive trends have been demonstrated previously, with greater anatomical precision, in man and in animals with invasive techniques. The significant finding reported here is that regional abnormalities can be detected and serially followed with this noninvasive method in acutely ill patients in an intensive care setting without interfering with their necessary diagnostic study and medical management. This result encourages us to move forward with increasingly frequent serial measurements, utilizing deeper and narrower collimation with more detectors for better anatomical accuracy. This probably will require some increase in the isotope concentration, though we expect that safe limits will not be exceeded in this generally old patient group.

In undertaking this effort, certain limitations and reasonable expectations might be listed.

1. No information about flow abnormalities in the brain stem can be expected, except for occlusions of the main trunk of the basilar artery which may affect flow in the posterior cerebral arteries.

2. It is unlikely that occlusion of the lenticulostriate arteries, though capable of producing major clinical disability, will affect the predominantly
cortical measurements within the capability of this method.

3. As a corollary of 1 and 2, it is probable that the presence or absence of regional flow changes will be of diagnostic and prognostic importance in the presence of changing clinical disability.

4. Probably no significant improvement will result in the approach to the clinical problem of distinguishing among cerebral infarction, cerebral hemorrhage, tumor, and subdural hematoma in cases of acute hemiparesis and hemiplegia.

5. The flow measurements will probably not distinguish between a region supplied by a patent artery and one with an occluded artery with adequate collateral flow, except possibly in the context of serial measurements.

6. Extracranial and intracranial occlusive disease probably will not be distinguishable.

7. The most specific use of the serial regional flow measurements will be in determining when and whether to utilize hypertensive or hypotensive, vasodilator or vasoconstrictor drugs in the management of acute vascular occlusion, and vasospasm in subarachnoid hemorrhage. It may have adjunctive use in the management of head injury as a supplement to intracranial pressure monitoring.

Acknowledgment
We are very grateful to Dr. Walter Obrist, Duke University Medical Center, Durham, North Carolina, for his advice and help in developing this project.

References
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