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Cerebral Blood Flow Measurement in Cerebrovascular Oclusive Diseases

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SUMMARY In order to evaluate cerebral blood flow (CBF) patterns among individual patients with increased statistical confidence, CBF measurements were carried out using the 133Xe-inhalation method and external head detectors. F(1) values representing gray matter flow from 3 to 6 head detectors were averaged to form 16 different regions for each cerebral hemisphere. Normative values were obtained from 46 healthy volunteers, and data from individual regions were analyzed for absolute blood flow rates (ml/100g/min), for concordance between right and left hemispheres and as percent of mean hemispheric flow. CBF measurements were then carried out among 37 patients with cerebrovascular occlusive diseases, and results were compared with normative values. A high incidence of abnormal flows were detected among symptomatic patients with intracranial arterial stenosis or occlusion and those with extracranial internal carotid artery occlusion. By using the above method for data analysis, it was possible to delineate hypoperfused areas among these patients. Even though the 133Xe-inhalation method has inherent limitations, this is a practical and safe method for measurement of CBF which can provide reliable information useful for management of patients with cerebrovascular occlusive diseases, particularly when the results are presented with statistical confidence.

SINCE THE DEVELOPMENT of a method for measurement of cerebral blood flow (CBF) in 1948 by Kety and Schmidt,1 CBF measurement by intra-arterial and intravenous administration and inhalation of gamma-emitting radioisotopes have been used successfully for patients with various neurologic and psychiatric disorders. More recently three-dimensional measurements

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of regional CBF (rCBF) with gamma-emitting2 or positron-emitting3 radioisotopes have become available. The concept of measuring CBF by inhalation of 133Xe gas was developed by Mallett and Veall4 and has been modified for practical use by Obrist et al,5 Risberg et al,6 and Meyer et al.7 With the currently utilized method, it has been possible to evaluate CBF in patients with cerebrovascular diseases.8-12 Although these studies clearly demonstrated the feasibility of this method for quantitation of rCBF, it is still difficult to express the results from individual patients with statistical confidence. Yet, there is a clinical need of CBF measurements for identification of patients with cerebrovascular occlusive diseases who are amenable to surgical
intervention and for evaluation of therapeutic efficacy. This report deals with an approach to data interpretation which permits evaluation of the results for individual patients with increased statistical confidence. The method of analysis, data from normal volunteers and results from patients with cerebrovascular occlusive diseases are presented.

Methods

rCBF was measured by the $^{133}$Xe inhalation method using a Novo Cerebrograph 32B (Novo Laboratories, Wilton, Conn.). The instrument was equipped with 16 collimated scintillation head detectors containing NaI crystals ($\frac{4}{4}$" diameter $\times$ $\frac{3}{4}$" long) for each side of the head. The location of each detector is shown in figure 1. For placement of detectors, the method described by Prohovnik et al.\(^{13}\) was followed. The resting state was induced by instructing each patient to close both eyes, dimming the room light and reducing the background noise level.\(^{13}\) $^{133}$Xe gas mixed with room air (5 to 7 mCi/L) was delivered for 1 minute through a close-fitting facemask or mouthpiece. A clearance curve was recorded from each detector (placed in skin contact to the head) and from the end-tidal air for 10 minutes. The energy discriminator window for each detector was set between 60 and 90 KeV. The expiratory CO$_2$ was analyzed by the two-compartment method of analysis, data from normal volunteers and results from patients with cerebrovascular occlusive diseases. This investigation was carried out both for establishment of normative values and for evaluation of patients with cerebrovascular occlusive diseases. This investigation because of frequent artifact in detector 1, 6 and 8 (fig. 1). Leakage of $^{133}$Xe gas occasionally contaminated the counts in the detectors in the frontal region. Artifact from radioactivity in the air passages was markedly reduced or eliminated by the use of a mouthpiece instead of a face mask. Leakage of $^{133}$Xe gas was infrequent by the use of a mouthpiece.

In order to evaluate various regions of the cerebral hemisphere, the $F_i$ values from 3 to 6 detectors were combined and averaged, rather than considered individually as has been customary. The arrangement of major regions are shown in figure 1. The frontal, frontoparietal, parietal and posterior parietal regions were further divided into the superior and inferior subregions with a combination of 3 or 4 detectors, and the temporoparietal region was further divided into anterior and posterior subregions with 3 detectors each. The rCBF in the temporal region was also measured by averaging the $F_i$ values from detectors 8 and 12. Altogether rCBF for 16 different regions can be measured with this method, whenever necessary. The inferior frontal region (detectors 1, 3 and 4) was excluded from the present investigation because of frequent artifact in detectors 1 and 3 from radioactivities in air passages. The mean value and the standard deviation were calculated for $F_i$ values from normal volunteers for the entire brain (an average of the hemispheric flow from each side), each cerebral hemisphere (an average of the $F_i$ values from all detectors on each side) and for each region. The $F_i$ value of each region was further expressed as percent of the $F_i$ value of the corresponding region on the opposite side, or as percent of the ipsilateral or contralateral hemispheric $F_i$ value. If any artifact was detected by visual inspection of the clearance curves in any detector during data processing or if there was an insufficient peak count rate or an inadequate curve fit standard deviation in any detector,\(^{14}\) the input from this detector and the corresponding detector on the opposite side were deleted. This elimination procedure was carried out both for establishment of normative values and for evaluation of patients with cerebrovascular occlusive diseases. This investigation was approved by the institutional Radiation Control and Human studies Committee, and informed consent was obtained.

Results

1) Normal Subjects

The relationship of CBF (average flow of two hemispheres) and age based on 46 normal volunteers with age between 25 and 87 years is shown in figure 2.
Correction for $P_{CO_2}$ at the rate of 2.0%/mmHg for the deviation from 37.5 ± 3.2 (S.D.) mmHg was used. The correction factor of 2.0%/mmHg was chosen because the correction of 1.2 ml/mmHg reported by Lennox et al\textsuperscript{15} corresponded to approximately 2.0%/mmHg for most CBF measurements. Also the correction based on a percentage value seems better suited for an adjustment of low CBF. As seen in figure 2, CBF was relatively high between 25 and 29 years and low between 60 and 87 years, while CBF values from normal volunteers between 30 and 59 years were scattered. This resulted in a shallow regression line of $y = -0.25x + 80$ with the correlation coefficient of 0.39. The mean CBF for the age between 25 and 29 years was 75.1 ± 12.1 (S.D.) ml/100 g/min, for the age between 30 and 59 years was 69.3 ± 9.3 (S.D.) ml/100 g/min and for the age over 60 years was 57.5 ± 8.1 (S.D.) ml/100 g/min.

The mean, standard deviation, 95% normal interval, and the 99% normal limit for individual regions are shown in table 2. The rCBF from the side with the lower value was expressed as a percent of the corresponding side with the higher value. This was preferred to the custom of using a comparison of the dominant and nondominant side, since cerebrovascular pathology can occur on either side. The concordance for the hemispheric flow was 97.8 ± 1.6 (S.D.)% with the coefficient of variation of less than 0.02. This resulted in the 99% normal limit (mean -3 S.D.) of 93.0%, thus making the difference between two sides of over 7% as outside the 99% normal limit. Concordances for individual regions were slightly less, but were still within 95% with the coefficient of variation ranging from 0.03 to 0.04. Thus, the difference of approximately 15% between two sides was necessary to call the value outside the 99% normal limit for individual regions. Comparison of rCBF in individual regions with hemispheric blood flow is shown in table 3. The gradient from the frontal to occipital region was clearly seen. The coefficient of variation was below 0.03 for the frontoparietal, parietal and posterior parietal regions but was over 0.05 for the occipital region.

2) Cerebrovascular Occlusive Disease

CBF of 37 patients with cerebrovascular occlusive diseases was evaluated. The abnormal rCBF was defined as (1) the value outside the 95% normal interval for the actual hemispheric or regional blood flow (ml/100 g/min) and/or (2) outside the 95% normal limit for the concordance of hemispheric or regional blood flow. Although the 99% normal limit has been used in our laboratory for evaluation of the concordance of

### Table 1: Regional Cerebral Blood Flow in Normal Volunteers

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean (ml/100 g/min)</th>
<th>SD</th>
<th>95% Normal Interval</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemisphere</td>
<td>69.3</td>
<td>9.3</td>
<td>87.9–50.7</td>
<td>88.4–51.5</td>
</tr>
<tr>
<td>Frontal</td>
<td>74.3</td>
<td>10.5</td>
<td>95.3–53.3</td>
<td>96.8–53.2</td>
</tr>
<tr>
<td>Frontoparietal</td>
<td>71.5</td>
<td>9.8</td>
<td>91.1–51.9</td>
<td>89.7–50.8</td>
</tr>
<tr>
<td>Parietal</td>
<td>69.0</td>
<td>9.6</td>
<td>88.2–49.8</td>
<td>86.8–51.2</td>
</tr>
<tr>
<td>Posterior parietal</td>
<td>67.2</td>
<td>9.3</td>
<td>85.8–48.6</td>
<td>89.6–52.0</td>
</tr>
<tr>
<td>Occipital</td>
<td>66.8</td>
<td>9.0</td>
<td>84.8–48.8</td>
<td>87.5–50.1</td>
</tr>
<tr>
<td>Temporoparietal</td>
<td>66.1</td>
<td>8.6</td>
<td>83.3–48.9</td>
<td>80.7–48.7</td>
</tr>
</tbody>
</table>

The value for each region was an average of the right and left side. The data are based on 27 control subjects aged between 30 and 59 years. The blood flow values were corrected for deviation of $P_{CO_2}$ from 37.5 mm Hg (± 3.2 SD).

### Table 2: Right-Left Concordance of Regional Cerebral Blood Flow in Normal Volunteers

<table>
<thead>
<tr>
<th>Region</th>
<th>Percent</th>
<th>95% Normal Limit</th>
<th>99% Normal Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemisphere</td>
<td>97.8</td>
<td>94.6</td>
<td>93.0</td>
</tr>
<tr>
<td>Frontal</td>
<td>95.3</td>
<td>87.9</td>
<td>84.2</td>
</tr>
<tr>
<td>Frontoparietal</td>
<td>96.0</td>
<td>89.2</td>
<td>85.8</td>
</tr>
<tr>
<td>Parietal</td>
<td>96.1</td>
<td>90.7</td>
<td>88.0</td>
</tr>
<tr>
<td>Posterior parietal</td>
<td>95.8</td>
<td>89.0</td>
<td>85.6</td>
</tr>
<tr>
<td>Occipital</td>
<td>95.1</td>
<td>87.7</td>
<td>84.0</td>
</tr>
<tr>
<td>Temporoparietal</td>
<td>95.9</td>
<td>89.9</td>
<td>86.9</td>
</tr>
</tbody>
</table>

The results are expressed as percent of the rCBF from the side with lower value as compared to the side with higher value. The data are based on 46 control subjects aged between 25 and 87 years.
Table 3

Comparison of Regional Cerebral Blood Flow to Hemispheric Blood Flow in Normal Volunteers

<table>
<thead>
<tr>
<th>Region</th>
<th>Percent Mean</th>
<th>SD</th>
<th>95% normal interval</th>
<th>99% normal interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>107.5</td>
<td>3.8</td>
<td>99.9-115.1</td>
<td>96.1-118.9</td>
</tr>
<tr>
<td>Frontoparietal</td>
<td>102.9</td>
<td>2.4</td>
<td>98.1-110.7</td>
<td>95.9-111.7</td>
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<tr>
<td>Parietal</td>
<td>98.8</td>
<td>2.7</td>
<td>93.4-104.2</td>
<td>90.7-106.9</td>
</tr>
<tr>
<td>Posterior parietal</td>
<td>96.3</td>
<td>2.7</td>
<td>90.9-101.7</td>
<td>88.3-104.4</td>
</tr>
<tr>
<td>Occipital</td>
<td>95.9</td>
<td>5.3</td>
<td>85.3-106.2</td>
<td>80.0-111.5</td>
</tr>
<tr>
<td>Temporoparietal</td>
<td>95.0</td>
<td>3.1</td>
<td>88.5-101.9</td>
<td>85.7-104.3</td>
</tr>
</tbody>
</table>

The results are expressed as percent of the hemispheric blood flow. The data are based on 46 control subjects aged between 25 and 87 years.

Table 4

Cerebral Blood Flow in the Cerebrovascular Occlusive Diseases

<table>
<thead>
<tr>
<th>Abnormal CBF</th>
<th>Total Number</th>
<th>Normal CBF</th>
<th>Combined*</th>
<th>Reduced F, Asymmetry</th>
<th>Combined*</th>
<th>Reduced F, Asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Intracranial stenosis or occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B. Extracranial carotid stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. Extracranial carotid occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic</td>
<td>14</td>
<td>1</td>
<td>13</td>
<td>10</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>uncertain</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>11</td>
<td>26</td>
<td>18</td>
<td>24</td>
<td>22</td>
</tr>
</tbody>
</table>

*Combined indicates the presence of one or both abnormalities (reduced F, asymmetry).
sations were moderately impaired. CT scan of the head revealed a small area of slightly decreased attenuation in the subcortical white matter in the left posterior frontal region which was enhanced by radiocontrast material. Transfemoral cerebral angiography revealed 2 areas of moderate and severe stenosis in the supraclinoid segment of the left internal carotid artery.

The result of the CBF study is shown in figure 3. The hemispheric flow was within normal limits on each side. However, the flow on the left side was significantly reduced as compared to the flow on the right side. The rCBF of 40.6 ml/100g/min in the left superior parietal region was lower than expected for his age. A wider area of reduced flow of 44.0 ml/100g/min was detected in the left frontoparietal to parietal region superiorly when the rCBF in this area was compared to the rCBF value on the right side or compared to the ipsilateral or contralateral hemispheric flow.

Among 6 patients with symptomatic extracranial unilateral or bilateral internal carotid stenosis, 3 patients had abnormal CBF studies and 3 others had normal CBF studies. While the hemispheric F1 value was abnormal in only one patient, asymmetry of the hemispheric flow existed in all 3 patients with abnormal CBF studies. For rCBF, 2 patients had abnormal F1 values and all 3 had asymmetry in the clinically relevant areas. The degree of stenosis did not explain the outcome of the CBF studies. Symptomatic patients with normal CBF studies may have had embolic events. Carotid stenosis was coincidental finding in 2 asymptomatic patients.

Twenty patients with extracranial internal carotid occlusion were studied. Of 14 symptomatic patients, 13 had an abnormal CBF. One patient with normal CBF had amaurosis fugax and ipsilateral venous stasis retinopathy. The hemispheric F1 value was abnormal in 6 patients while asymmetry of the hemispheric flow was observed in 10 patients. In 2 patients with bilateral abnormalities, the hemispheric F1 values were abnormal but there was no asymmetry. When two modalities were combined, 11 symptomatic patients showed abnormalities. On the other hand, asymmetry of rCBF existed in 13 symptomatic patients and the F1 value was abnormal in 10 of them. Of 4 asymptomatic patients, the CBF study was abnormal in 2 patients. In one patient, the hemispheric F1 value was reduced bilaterally but the concordance was within the 95% normal limit. rCBF was reduced bilaterally in the frontal to parietal region but more on the right side. However, the difference was again within the 95% normal limit. Another asymptomatic patient was found to have bilateral occlusion of the internal carotid arteries by cerebral angiography elsewhere. The hemispheric F1 value was normal but there was asymmetry with reduction on the right side. The regional F1 value was abnormal in the right frontal to parietal region with significant asymmetry. In 2 patients, it was difficult to determine whether the occluded carotid artery was responsible for any neurologic signs and symptoms. The CBF study was abnormal in both cases, but the hemispheric and regional F1 values were within the 95% normal interval in one of them. The following case illustrates the clinical history and the CBF study of one symptomatic patient with extracranial occlusion of an internal carotid artery.

Case 2:

This 58-year-old right-handed male began to experience transient numbness of the right upper and lower extremities in January, 1982. In July, 1982, he underwent thoracotomy elsewhere for traumatic hemothorax. Post-operatively, he was found to have right hemiparesis and expressive aphasia. However, these neurological dysfunctions gradually resolved with mild residual signs. In October, 1982, he was found to have marked stenosis of the left internal carotid artery in the neck on intravenous digital subtraction angiogram and underwent left carotid endarterectomy elsewhere. In February, 1983, he began to experience transient weakness and numbness in the right upper and lower extremities, and these spells occurred 1 to 3 a day at the time of our evaluation in March, 1983. Neurological examination revealed anaomia and mild right hemiparesis. CT scan of the head revealed an area of low attenuation primarily involving the white matter in the left frontoparietal region. Cerebral angiogram done elsewhere just prior to his referral to us showed a complete occlusion of the left internal carotid artery above the bifurcation, but there was filling of the left anterior and middle cerebral artery branches from the right side via the anterior communicating artery.

The result of the CBF study is shown in figure 4. The hemispheric flow was within normal limits on each side. However, the flow on the left side was significantly reduced as compared to the flow on the right side. The rCBF in the left frontal region of 50.4 ml/100g/min was lower than expected for his age. There was a wider area of reduced flow of 51.3 ml/100g/min in the left frontoparietal region when rCBF in this area was compared to the ipsilateral hemispheric flow. An even wider area of reduced flow of 51.6 ml/100g/min existed in the left frontoparietal region when the rCBF in this area was compared to...
the value in the corresponding area on the right side. The flow in the right frontoparietal to parietal region of 67.8 ml/100g/min was higher than expected when it was compared to the ipsilateral hemispheric flow.

Discussion

The method for rCBF measurement using inhalation of 133Xe gas, which was developed by Mallett and Veal and modified by Obrist et al.9 and Risberg et al.,10 is a noninvasive technique which can be safely administered to patients with cerebral pathophysiological conditions. Obviously, this method lacks the ability for three-dimensional presentation of rCBF as shown by single photon emission tomography11 or positron emission tomography12,13 and lacks high resolution achieved by CT scanning during inhalation of stable xenon.14 Other methodological shortcomings include scattered radiation, nonrecognition of the regions with very low flow and uncertainty of the partition coefficient for diseased tissues.15 The problem of scattered radiation can be reduced by setting the energy threshold discrimination to the 81 KeV peak. Nonrecognition of a nonperfused region is theoretically possible, but this is unlikely a practical problem when the rCBF study is combined with CT scan or other noninvasive procedures. The problem of defining the partition coefficient is difficult to solve, but this is also a problem with other radioisotope methods for measurement of rCBF at the present time.

The method of interpretation used in the present investigation may appear to defeat the purpose of utilizing multiple small detectors. However, the ischemic areas in symptomatic cerebrovascular occlusive diseases appear to be larger than the area viewed by a single detector, and CT scan is likely to detect a small embolic infarction. Therefore, the present approach of combining together a few detectors is justifiable. The advantage of the present method of interpretation is (1) that averaging of the values from 3 to 6 detectors reduces variation as compared to the values from individual detectors, (2) that a slight shift in the location of a detector can be compensated and (3) that elimination of the value from one detector due to artifact or insufficient counting can still provide valid data. Above all, the presentation of rCBF values with the added degree of statistical significance would help clinicians when they use the data for management of individual patients.

Among 3 different methods for analysis, the F1 value (ml/100g/min) gives the absolute value. However, this modality was relatively insensitive for detection of the hypoperfused area because of the wide variation of the hemispheric and regional blood flow among normal volunteers. Out of 26 patients whose CBF studies were abnormal, the hemispheric F1 value was abnormal only in 10 patients or 38% and the regional F1 value was abnormal in 18 patients or 69% (table 4). In the present study, we chose the classic expression of CBF (ml/100g/min), but other methods such as the initial slope index may be more sensitive for detection of hypoperfused areas. The hemispheric flow from our normal population did show the gradual decline with advanced age (fig. 2) similar to the decline observed by others,15,16,21 and appears to be appropriate to be used as the control group. Because of the good concordance of the hemispheric and regional flows between right and left side, comparison between two sides proved to be very sensitive for detection of hypoperfused areas. Out of 26 patients with abnormal CBF studies, 24 patients or 92% had asymmetry of rCBF and 20 patients or 77% had asymmetry of the hemispheric flow (table 4). With the combination of the F1 value and concordance, the evaluation of rCBF detected 26 patients with abnormal CBF. On the other hand, the combination of those 2 modalities for the hemispheric flow detected 22 out of 26 patients with abnormal CBF. This indicates the necessity of rCBF for adequate evaluation of CBF studies for patients with cerebrovascular occlusive diseases.

Comparison of rCBF with the ipsilateral or contra-lateral hemispheric flow was the least reliable method among the 3 modalities because the flow value for a given area was influenced by flow values in other areas. However, this modality became more important in pathophysiological conditions involving cerebral hemispheres bilaterally. From time to time, this modality detected collateral flow in the ipsilateral frontal region from the ophthalmic artery, in the ipsilateral parieto-occipital region from the basilar circulation, and in the contralateral frontoparietal region via the anterior communicating artery. The analysis of bilateral pathophysiological conditions involving the cerebral hemispheres was complicated, but a combination of those 3 analytical methods could delineate abnormal rCBF patterns. The presence of cerebral infarction on CT scan requires cautious interpretation of rCBF, since the decreased rCBF could be due to the presence of infarcted tissue. The present method could detect an area of hypoperfusion beyond the infarcted area seen with CT scan of the head, as shown in Case 2.

There was a good agreement between the results of CBF studies and symptomatic patients with intracranial arterial stenosis or occlusion, or extracranial carotid occlusion (table 4). This is partly because many of
them were selected to test the validity of this procedure. Even so, the CBF study can provide useful information for medical or surgical management of individual patients. A combination of the CBF study with intravenous digital subtraction angiography or with noninvasive studies such as CT scan, oculoplethysmography, doppler study and ultrasound scan may reduce the need for intra-arterial angiography for high risk patients or elucidate intracranial pathophysiological conditions in patients who cannot have radiocontrast materials.

An important question which was not addressed in this investigation was the usefulness of the CBF study in the followup evaluation of patients undergoing surgical anastomosis of the superficial temporal artery to the middle cerebral artery. The information is still limited in the literature, and this question needs to be addressed in the future.

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