Resting and Hypercapnic rCBF in Patients with Unilateral Occlusive Disease of the Internal Carotid Artery

André Keyeux, Christian Laterre, and Christian Beckers

Centre de Médecine Nucléaire, Service de Neurologie, University of Louvain Medical School, Brussels, Belgium

Regional cerebral blood flow was measured by the $^{133}$Xe inhalation technique in 15 patients with severe unilateral internal carotid artery stenosis (75%) or occlusion, and in the absence of evidence of any sign of occlusive disease in other main afferent cerebral arteries. A comparison with normal subjects showed that lowered resting flow in both hemispheres was a common finding in all patients. Interhemispheric asymmetry was present only in patients with occlusion and the precentral, posterior temporal, and occipital regions were the most seriously affected. The CO$_2$ reactivity was substantially reduced in both hemispheres of all stenotic and occluded patients, but occluded patients showed an increased reduction of CO$_2$ reactivity only in the ipsilateral hemisphere. In addition to an hypothetical age effect, the atherosclerotic involvement of the cerebral vascular system leads to a reduction of flow and loss of CO$_2$ reactivity in both hemispheres. In this context, the collateral supply capacity is not overloaded in case of a unilateral severe stenosis but fails in case of a unilateral occlusion of the internal carotid artery. A suitable estimate of the blood flow reduction as a result of occlusion is made by the hemispheric and regional laterality indices applied in resting and hypercapnia conditions. These indices could be used as indicators for endarterectomy or bypass surgery as well as a sensitive means for appreciating cerebral blood flow response to treatment.


In the management of cerebrovascular atherosclerosis, the evaluation of the hemodynamic consequences of the disease is of particular interest in all cases of stenosis and/or occlusion of the internal carotid arteries because it can help the clinical decision to perform surgery. The xenon-133 ($^{133}$Xe) inhalation method of regional cerebral blood flow (rCBF) measurement and cerebrovascular reactivity assessment has been used as a safe and practical means for testing blood flow and vascular reserve changes in both hemispheres (1–5). Provided the evaluation is to be restricted to the effects of a localized occlusion, however, it should be stressed that the relevance of regional cerebral blood flow (rCBF) measurement depends on the capacity of the available parameters to demonstrate the resulting vascular impairment as well as the influence of interfering factors, such as extension of the atherosclerosis process to the whole-brain microvasculature or the presence of multiple sites of occlusion and/or stenosis in arteries of both hemispheres.

Because an estimation of the potential benefit on cerebral blood flow of bypass surgery or endarterectomy in the case of total or partial unilateral internal carotid occlusion needs an accurate evaluation of the subsequent rCBF disturbance, it is essential to assess the factors which may interfere with the measurements. This paper attempts to illustrate such control by comparing rCBF and cerebrovascular reactivities between rigorously selected normal subjects and patients with a unilateral severe stenosis or occlusion strictly limited to the internal carotid. In this context, the reliability of conventional rCBF parameters as well as the sensitivity and the usefulness of a laterality index are examined.

Received Dec. 29, 1986; revision accepted Sept. 14, 1987.

For reprints contact: Dr. A. Keyeux, Centre de Médecine Nucléaire, UCL 54.30, University of Louvain Medical School, avenue Hippocrate 54, B-1200 Bruxelles (Belgium).
MATERIAL AND METHODS

Instrumentation and Data Processing

The $^{133}$Xe inhalation method as described by Obrist et al. (6) was used to measure rCBF. The cerebrograph (TASC-5 System, Harshaw Chemical Company, Solon, OH) was equipped with 16 collimated scintillation detectors distributed over both hemispheres by means of a transparent helmet. The converging arrangement of the detectors minimizes as much as possible the cross-talk phenomenon. Xenon-133 gas mixed with room air (200 to 250 MBq/l) was delivered through a tight-fitting face mask and a rebreathing spirometer for 1 min followed by 10 min of rebreathing room air. In such a way, a 10-min clearance curve was recorded from each head detector and from a separate detector monitoring radioactivity in a sample of expired air (end-tidal air curve). The discriminators of the pulse-height analyzers were adjusted to accept pulses between 65 and 95 keV. A count rate between 20,000 and 30,000 cpm was obtained at the peak of all head curve. The data from the 17 detectors were stored in a computer where each head curve was analyzed according to a two-compartment model and using a computer program previously developed by Obrist et al. (6) and extended by Risberg et al. (7).

Data Acquisition

The arterial PCO$_2$ (P$\text{$_a$CO}_2$) was estimated from the end-tidal concentration of CO$_2$ expressed as a percentage of CO$_2$ in expired air by a capnograph (Capnograph Mark II, Gould Godart, Bilthoven, The Netherlands). The blood pressure was measured by auscultation before and after each session of rCBF measurement and expressed as mean arterial blood pressure: MABP = (SP + 2DP)/3.

Each subject was submitted to two consecutive measurements. Before the first measurement, information about the procedure was given in detail to the patient in order to limit the influence of any unavoidable anxiety. The first measurement (A) was started when breathing parameters (respiratory rate and maximum percentage of CO$_2$ in expiratory air) had become stable. The background activity was recorded for 5 min preceding the second measurement (B), which started 10 min after the end of the first measurement. A gas mixture with 5% CO$_2$ and 95% dry air was administered for 1 min prior to the $^{133}$Xe inhalation, discontinued during the 1-min $^{133}$Xe intake, and then started again until the end of the measurement.

Parameters

Because only the fast compartment is exclusively relevant to the nutritional blood circulation in the brain matter (7,8), rCBF measurements were restricted to those derived from the fast compartment characteristics, namely $F_1$, $FF_1$, and ISI. $F_1$ is derived from the fast clearance rate (k$_f$) of the first compartment and conventionally estimates the blood flow in gray matter as ml.min$^{-1}$.100 g$^{-1}$. $FF_1$ is defined as the fractional flow for the gray matter and is expressed as a percentage of the total blood flow. ISI (initial slope index) is an index of the blood flow in all tissues recorded but is highly dominated by the gray matter blood flow. It is the most reliable variable in conditions with low flow and unstable compartments and is expressed in "ISI units" (ISIU) (7).

The hemispheric and the regional symmetries of the cerebral blood flow were evaluated for $F_1$ and ISI by a laterality index (9) calculated as follows:

$$L.I. = 100 \left( \frac{\text{right flow} - \text{left flow}}{\text{right flow} + \text{left flow}} \right)$$

The CBF reactivity to P$\text{$_a$CO}_2$ change between first (A) and second (B) measurements was evaluated for $F_1$ and ISI as follows:

$$\Delta \text{CBF} = \frac{\text{CBF(B)} - \text{CBF(A)}}{\text{P$_a$CO}_2(B) - \text{P$_a$CO}_2(A)} \times 100 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}.$$ 

This latter evaluation was complemented by that of the associated cerebrovascular resistance changes. The cerebral vascular resistance (CVR) was calculated from the mean arterial blood pressure (MABP) divided by CBF ($F_1$ and ISI) values (10) and the cerebrovascular resistance changes between first (A) and second (B) measurements by CVRI = (CVR(B)/CVR(A)) × 100.

Study Groups

Healthy subjects (Group 1). Measurement of rCBF under normocapnia and hypercapnia was performed in 18 normal subjects, selected on the basis of absence of any subjective or objective symptomatology as well as any hypertension (MABP < or = 110 mmHg) and any other risk factors (diabetes, signs of atherosclerotic disease, and hyperlipemia). The ages of the normal subjects ranged from 23 to 52 yr (mean ± s.d. 32 ± 8 yr). No subject over 60 yr old fulfilling the totality of the above criteria was available. Under normocapnia, P$\text{$_a$CO}_2$ was 36.2 mmHg ± 2.7 (s.d.) and MABP was 95 mmHg ± 10 (s.d.), while under hypercapnia, P$\text{$_a$CO}_2$ was 43.1 mmHg ± 2.8 (s.d.) and MABP was 100 mmHg ± 11 (s.d.).

Patients (Groups 2 and 3). The 15 patients were divided into two groups depending on the severity of unilateral stenosis of the internal carotid artery. In both groups, the loss of arterial patency was identified and evaluated by velocity measurements using Doppler ultrasound (n = 15), aortic arch angiography (n = 15), or selective bilateral angiography of the carotids (n = 3).

Group 2 consisted of five patients with normal vertebral arteries and unilateral stenosis (higher than 75%) of the internal carotid artery. Age ranged from 55 to 67 yr (mean ± s.d. 61 ± 5 yr). Under normocapnia, P$\text{$_a$CO}_2$ was 35.6 mmHg ± 2.5 (s.d.) and MABP was 115 mmHg ± 14 (s.d.), while under hypercapnia, P$\text{$_a$CO}_2$ was 46 mmHg ± 3.8 (s.d.) and MABP was 126 mmHg ± 9 (s.d.). Three patients had TIA only with normal x-ray computed tomographic (CT) scan and two patients had small infarction with early recovery and only mild residual symptoms. CT scan revealed a small lacunar infarct in only one of these two patients.

Group 3 consisted of ten patients with normal vertebral arteries and unilateral internal carotid artery occlusion. Age ranged from 41 to 73 yr old (mean ± s.d. 57 ± 9 yr). Under normocapnia, P$\text{$_a$CO}_2$ was 35.2 mmHg ± 3.4 (s.d.) and MABP was 108 mmHg ± 14 (s.d.), while under hypercapnia, P$\text{$_a$CO}_2$ was 46 mmHg ± 3.8 (s.d.) and MABP was 124 mmHg ± 16 (s.d.). Eight patients had had a stroke with mild or no residual
symptoms but small low density lesions at CT scanning. Two patients had TIA symptomatology with normal CT scans. Blood flow in the ophthalmic artery was reversed in six patients and absent in one patient.

Statistical Analysis
The statistical significance of the data related to the CO₂ effect inside each group was tested by a paired t-test. The differences between controls and patients were examined by an unpaired t-test.

RESULTS
The hemispheric mean values of ISI, F₁, and FF₁ for Groups 1, 2, and 3 are listed in Table 1.
As far as healthy normocapnic subjects (Table 1, Group 1) were concerned, the results and their standard deviations for the three parameters agreed with those found in an extensive study on their reproducibility (16). As already underlined in that study (16), the mean values of ISI, F₁, and FF₁ were systematically higher in the right hemisphere than in the left, and the difference was statistically significant for ISI and FF₁. All parameters of mean hemispheric CBF were strongly reduced in both hemispheres of patients suffering from unilateral stenosis (Group 2) or occlusion (Group 3) of the internal carotid. Insofar as CBF on the stenosed side is concerned, the lowering was significant and dependent on the severity of the arterial stenosis for ISI and F₁. On the contralateral side, the reduction of CBF was similar to that of the stenosed side in Group 2 and was not significantly enhanced by occlusion in Group 3. The fractional flow FF₁ was similarly reduced on both sides and in both groups (2 and 3).
The modifications of the distribution of rCBF throughout the hemispheres were evaluated by the variations of the laterality index (LI). The values of LI more and less than 100 denote the dominancies of the right and left hemispheres (Group 1) or undiseased and diseased hemispheres (Group 2 and 3), respectively. With this in mind, the results collected in Table 2 (Group 1) confirm the dominance of all the regions of the right hemisphere.
Unexpectedly, most of the values of LI-ISI and LI-F₁ shown in Table 2 disclosed a blood flow dominance on the stenosed side (Group 2), but not to a statistically significant degree. In the case of occlusion (Group 3), LI calculated from the noncompartmental parameter ISI, is the preferred method for showing a change in blood flow between asymmetrical regions. Both hemispheric values of LI-ISI and of LI-F₁ indicate the high significance of the blood flow dominance on the non-occluded side. However this dominance was strongly supported by 6/8 LI-ISI regional values and by only 4/8 LI-F₁ regional values. For both parameters, the regional distribution indicates a maximum disruption in laterality in precentral and temporo-occipital regions.

Excepting some opposite modifications in the frontal and parietal regions, the regional as well as the hemispheric values of LI-FF₁ were about the same and were close to neutral value (≈ 100). For both compartmental parameters, the distribution of regional values showed a predominant sensitivity of LI-F₁ in posterior regions of the brain while the sensitivity of LI-FF₁ was predominant in the anterior regions of the brain.

CO₂ Effect
In normal subjects breathing air with 5% CO₂, both hemispheric blood flows increased very significantly and similarly irrespective of the parameter (Table 1, Group 1). As shown in Table 2 (Group 1), the right hemisphere dominance, as observed during normocapnia, disappeared and a limited left anterior dominance became evident.
Unilateral severe stenosis of the internal carotid artery did not prevent a similar increase of blood flow in both hemispheres of the brain as a consequence of hypercapnia (Table 1, Group 2). However, the degree of significance of such an increase was different depending on the parameter; it was high for ISI, moderate for F₁, and low for FF₁. On the other hand, the regional distribution of flow through the hemispheres was not substantially modified by hypercapnia. In these conditions, it is not surprising to find in Table 2 (Group 2) very stable values of all of the laterality indices.
In patients suffering from unilateral occlusion of the internal carotid artery, the increase of CBF hemispheric values as a result of hypercapnia was restricted to ISI and F₁ (Table 1, Group 3), with degrees of significance identical to those quoted for Group 2. The regional distribution of flow through the hemispheres was strongly disturbed as evaluated by both compartmental parameters (Table 2, Group 3). LI-F₁ was significantly increased in prefrontal, precentral and sylvian regions, indicating an enhancement of dominance of the non-occluded side compared to the occluded side during hypercapnia. A similar observation can be made for LI-FF₁ in precentral region. This shows the particular high suitability of LI-F₁ and LI-FF₁ to detect loss of vascular reactivity.
Results concerning the evaluation of the CBF reactivity to arterial PCO₂ changes are collected in Table 3. As far as ISI is concerned, there was no statistical difference between the reactivity values of either different hemispheres or different groups. The mean hemispheric increment was ≈2% or 0.9 ISIU, with a cerebral vascular resistance index (CVRI-ISI) of ≈90–95% of resting values. The corresponding changes for F₁ were different since the values of CO₂ reactivity fell significantly from a mean value of ≈3.5% (or 2.7 ml) in normals to ≈2–2.5% (or 1–1.5 ml) in patients. Indices of cerebral vascular resistance for F₁ were largely depressed in normals and significantly less depressed in one group of patients at least.
TABLE 1
Mean Hemispheric Values (±s.d.) of the CBF Parameters in Three Different Groups of Subjects*

<table>
<thead>
<tr>
<th></th>
<th>ISI (ISIU)</th>
<th>F1 (ml·100g⁻¹·min⁻¹)</th>
<th>FF1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>Normocapnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>54.4 ± 5.9</td>
<td>41.5 ± 5.4***</td>
<td>40.5 ± 3.9***</td>
</tr>
<tr>
<td>b</td>
<td>55.0 ± 6.1</td>
<td>42.0 ± 4.5***</td>
<td>37.3 ± 4.3***</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>61.9 ± 7.0***</td>
<td>49.2 ± 4.9***</td>
<td>49.0 ± 5.4***</td>
</tr>
<tr>
<td>b</td>
<td>62.1 ± 7.5***</td>
<td>49.7 ± 4.5***</td>
<td>44.4 ± 4.7***</td>
</tr>
</tbody>
</table>

* The figures quoted in the upper line (a) concern the left side (Group 1) and the nonstenosed side (Groups 2 and 3), while those quoted in the lower line (b) refer to the right side (Group 1) and to the side with stenosis (Groups 2 and 3).

Significance of the difference between Groups 1 and 2, and Groups 1 and 3 were evaluated by unpaired "t" test and quoted by : *p < 0.05; **p < 0.01; ***p < 0.001.

Significance of the differences between "a" and "b" (interhemispheric differences) and between normo and hypercapnia in comparable hemispheres were evaluated by paired t-test and quoted respectively by : , p < 0.05; , , , p < 0.001 and , , , p < 0.01; , , , p < 0.001.
### TABLE 2
Mean Values (±s.d.) of Laterality Indices (LI) Derived From ISI, F1, and FF, for Eight Cerebral Regions and the Hemispheres in Three Different Groups of Subjects

<table>
<thead>
<tr>
<th>Normocapnia</th>
<th>LI-ISI</th>
<th>LI-F1</th>
<th>LI-FF1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>Sup. frontal</td>
<td>100.9 ± 1.9</td>
<td>99.6 ± 3.1</td>
<td>102.4 ± 4.8</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>100.9 ± 2.1</td>
<td>99.4 ± 2.9</td>
<td>103.6 ± 4.3*</td>
</tr>
<tr>
<td>Precentral</td>
<td>100.8 ± 2.4</td>
<td>99.2 ± 4.6</td>
<td>106.7 ± 5.3***</td>
</tr>
<tr>
<td>Sylvian</td>
<td>100.2 ± 2.3</td>
<td>99.8 ± 2.9</td>
<td>103.6 ± 3.1**</td>
</tr>
<tr>
<td>Temporal</td>
<td>100.8 ± 3.1</td>
<td>98.8 ± 8.6</td>
<td>101.8 ± 3.8</td>
</tr>
<tr>
<td>Parietal</td>
<td>101.2 ± 3.0</td>
<td>100.7 ± 2.0</td>
<td>105.7 ± 8.0*</td>
</tr>
<tr>
<td>Post temporal</td>
<td>99.9 ± 2.0</td>
<td>99.4 ± 5.3</td>
<td>105.2 ± 4.7***</td>
</tr>
<tr>
<td>Occipital</td>
<td>100.1 ± 2.7</td>
<td>96.7 ± 3.2</td>
<td>105.4 ± 5.4***</td>
</tr>
<tr>
<td>Hemispheric</td>
<td>100.6 ± 1.1</td>
<td>99.2 ± 1.3</td>
<td>104.3 ± 3.2***</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypercapnia</th>
<th>LI-ISI</th>
<th>LI-F1</th>
<th>LI-FF1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>Sup. frontal</td>
<td>99.6 ± 1.6e</td>
<td>99.6 ± 2.2</td>
<td>104.5 ± 3.6</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>99.4 ± 1.8e</td>
<td>98.9 ± 2.2</td>
<td>105.8 ± 5.3</td>
</tr>
<tr>
<td>Precentral</td>
<td>99.9 ± 1.7</td>
<td>99.3 ± 2.2</td>
<td>105.6 ± 3.4</td>
</tr>
<tr>
<td>Sylvian</td>
<td>99.2 ± 2.0</td>
<td>99.8 ± 2.9</td>
<td>105.7 ± 5.0</td>
</tr>
<tr>
<td>Temporal</td>
<td>101.1 ± 2.3</td>
<td>100.3 ± 2.2</td>
<td>103.2 ± 3.4</td>
</tr>
<tr>
<td>Parietal</td>
<td>100.7 ± 2.0</td>
<td>99.0 ± 2.7</td>
<td>105.7 ± 5.7</td>
</tr>
<tr>
<td>Post temporal</td>
<td>100.0 ± 1.2</td>
<td>100.0 ± 2.6</td>
<td>106.6 ± 5.0</td>
</tr>
<tr>
<td>Occipital</td>
<td>100.0 ± 1.6</td>
<td>99.3 ± 2.1</td>
<td>103.3 ± 3.8</td>
</tr>
<tr>
<td>Hemispheric</td>
<td>100.0 ± 0.8e</td>
<td>99.5 ± 1.5</td>
<td>105.1 ± 3.7</td>
</tr>
</tbody>
</table>

LI (Group 1) = 100 \left(1 + \frac{\text{right} - \text{left}}{\text{right} + \text{left}}\right)

LI (Groups 2 and 3) = 100 \left(1 + \frac{\text{undiseased} - \text{diseased}}{\text{undiseased} + \text{diseased}}\right)

Significance of the differences between Group 1 and Group 2, and Group 1 and Group 3 was evaluated by unpaired t-test and quoted by: *, p < 0.05; **, p < 0.01; ***, p < 0.001.

Significance of the differences between normo and hypercapnia in comparable regions was evaluated by paired t-test and quoted by: @, p < 0.05.
TABLE 3
Cerebral Blood Flow (ΔCBF) and Cerebrovascular Resistance (CVRI) Reactivity to CO₂ Evaluated from Hemispheric Values of ISI and F₁ for the Three Groups of Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>STEN(%)</th>
<th>ΔISI [ISIU/mmHgP₅CO₂]</th>
<th>ΔF₁ [ml·100g⁻¹·min⁻¹/ mmHgP₅CO₂]</th>
<th>CVRI(ISI) %</th>
<th>CVRI(F₁) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>0.75±0.43</td>
<td>0.97±0.39</td>
<td>2.86±0.94</td>
<td>2.68±0.93</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.79±0.24</td>
<td>0.77±0.14</td>
<td>1.06±0.98</td>
<td>1.13±0.78</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.89±0.34</td>
<td>0.75±0.30</td>
<td>1.47±1.05</td>
<td>1.20±0.79</td>
</tr>
</tbody>
</table>

Each group is characterized by the degree (%) of stenosis (STEN) of the two internal carotid arteries.
In each group, the hemispheric values of the four parameters are related to the degree of stenosis of the corresponding internal carotid artery.

"n" is the number of patients.
Significance of the differences between group 1 and 2, and group 1 and 3 was evaluated by unpaired "t" test and quoted by : *, p < 0.05; **, p < 0.01; ***, p < 0.001.

DISCUSSION

Reliability of Parameters
According to the literature (16,17), the parameters and indices available for rCBF measurement by use of the ⁱ³³Xe inhalation method are numerous and sometimes show little consistency. Among the two categories of rCBF numerical expressions, the noncompartmental ISI and the compartmental F₁ and FF₁ are the less speculative. Although they are assumed to measure the fast nutritional blood flow in the cellular compartment of the brain, both types of parameter were claimed not to be equivalent for demonstrating any blood flow changes in situations other than normal (7). In the presentation of our results, ISI was compared to F₁,FF₁, in order to evaluate their respective behavior in normal subjects and in patients suffering from unilateral stenotic or occlusive disease of the internal carotid artery.

In normocapnia, both types of parameters provide largely similar results. Under hypercapnia, a discrepancy arises between the data from ISI and F₁. The CO₂ reactivity in both hemispheres was either unmodified or altered by disease according as ISI or F₁ is concerned. This finding corroborates the opinion of Risberg and Prohovnik (21) who consider that F₁ is more sensitive than ISI to activation procedures because at high flow rate the relative influence on the ISI slope of slowly perfused tissue is increased and thus its sensitivity to flow increase in rapidly perfused tissues is decreased. This approach is strongly supported by the results collected in Table 3 which show underestimated values of ISI in Group 1 (normal subjects). On the other hand, in both groups of patients where the flow rate is lowered, the differences between ISI and F₁ disappear or are not significant. These considerations render ISI unreliable as a means to evaluate the CO₂ reactivity and the cerebrovascular reserve in occlusive disease (1). However, the interdependence between F₁ and FF₁, implies that the variations of the former cannot be used for any accurate measurement of blood flow changes when the influence of the latter is not understood or at least controlled. Unfortunately, the physiologic meaning of the fast flow fraction (FF₁) distribution and its changes remain unclear (16).

The sensitivity of the laterality index (LI) for the detection of hypoperfused areas is supported by the good agreement between the hemispheric and regional blood flow in the right and left sides in normals. The corresponding results (Table 2, Group 1) compare favorably with those reported elsewhere (9). As far as unilateral cerebrovascular occlusive disease is concerned, a 75% stenosis of the internal carotid artery does not reduce the flow in any region of the ipsilateral hemisphere if compared with the contralateral hemisphere while an occlusion generates an important relative hyperperfusion in a territory corresponding closely to the distribution of the middle cerebral artery. The perfusion of the frontal superior region which depends mainly on the cerebral anterior artery is not significantly different from side to side. The effect of internal carotid occlusion on the temporal region is most likely masked by the vicinity of the superficial temporal artery. In high flow rate conditions due to hypercapnia, the higher sensitivity of compartmental parameter (F₁,
and FF) is once more emphasized (Table 2, Group 3) by an ipsilateral regional (prefrontal, precentral, and sylvian) depression of blood flow only demonstrated by LI (F) and LI (FF).

It must also be emphasized that the low variability of LI (FF) infers that an individual hemispheric value falling outside the very small range of normal values (99–101) is a very sensitive indicator of pathologic blood flow.

Symmetry of rCBF

The significant, although small, right hemisphere dominance for ISI and FF (Table 1, Group 1) was firstly observed by Blauenstein and co-workers (16) and more recently in a PET study of the normal human brain (31). Furthermore, the hemispheric and regional values of LI (Table 2, Group 1) which are close to those of Matsuda and co-workers (9), also confirm the dominance of almost all the regions of the right hemisphere. However, the vasodilatation due to hypercapnia modifies the interhemispheric distribution to make hemispheric blood flows symmetrically. This fact suggests that the loss of symmetry, as observed in normocapnia, is more due to a functional vascular response of the normal brain than due to differences in the vascularity of the hemispheres.

Aging Effect

The aging effect on cerebral blood flow is variously appreciated according to the type of investigation (14, 22), the type of analysis (4,9–12,23) and, above all, the selection of the subjects (9–14,22,23). Taking into account that only ~50% of brains are free of atherosclerosis after 50 yr, it is possible that reduced cerebral blood flow in the elderly is not a necessary consequence of old age but rather of asymptomatic cerebrovascular disease (15). In this study, particular attention has been paid to “health-exclusionary” criteria with the consequence that the mean age of the normal subjects does not match that of both diseased populations. rCBF values of our healthy population compare favorably with those reported elsewhere for people <50 yrs old (10,16,17). If health status is the major factor that accounts for differences reported in age studies of cerebral blood flow, the rCBF values collected in Table 1 (Group 1) could be considered to be age invariable and could thus be reliable normal control values. In such instances, the comparison between normal subjects and patients leads to the conclusion that patients suffering from occlusive disease of the cerebral artery (even if demonstrated on one side only) have a depressed blood flow in both hemispheres.

According to the literature describing a progressive decline of CBF with age, losses varying from 9 to 19% for F, and from 9 to 16% for ISI could be expected between 32 yr of age (mean age of our controls) and 57–61 yr of age (mean ages of both groups of our patients) (9–14). In comparison, the losses of blood flow between our controls and the undiseased hemisphere of stenosed and occluded patients are, respectively, 24% and 28% for F, and 24% and 26% for ISI. These percentages are thus largely higher than those expected from any reported age-effect relationship (9–14). Furthermore, CBF contralateral depression is higher in patients with occlusion despite the fact that they are a little younger than patients with stenosis. These arguments support the opinion that even if the effectiveness of age decline is considered, the unilateral occlusive disease of the internal carotid is characterized by a bilateral loss of blood flow and not just on the occluded side alone as found by others (1).

CO2 Reactivity

Normal hemispheric CO2 reactivity was determined to be ~3.6%/mmHg or 2.8 ml/mmHg for F, and 1.8%/mmHg or 1 ISIU/mmHg for ISI (Table 3). These values are in full agreement with those reported with the use of the similar inhalation technique (12,18,19,21). In the steady state, the vascular responses to hypercapnia with advancing age tends to parallel flow values (12). Assuming that CBF is not influenced by an aging effect, CO2 reactivity occurs as a constant factor independent of the age of subjects (12,23). Contrarily to ISI, F, indicates a loss of reactivity in both groups of patients, which is particularly significant on the occluded side. In agreement with Kety’s finding (20), the cerebrovascular indices (CVRI < 100) indicate that the cerebral blood flow increase as a result of CO2 is the consequence of a loss of vascular resistance. In addition, CO2 administration exerts only vascular effects and thus provides a valuable means for evaluating the brain vascular reserve.

Effect of Occlusion

It was suggested that the subnormal CBF measured in both hemispheres of patients suffering from a unilateral occlusion process could be due to an evenly reduced demand in tissues of both hemispheres (1). Since determined by the metabolic rate, such a reduction of blood flow should be present without a significant reduction of the vascular reserve. In this study, patients suffering from a hemodynamically significant stenosis (>75%) of only one of the four afferent main vessels have an identical lowering of the resting blood flow with an identical reduction of the vascular reserve in both hemispheres. The uniform reduction of the vascular reserve in the whole brain invalidates the hypothesis of a reduction of blood flow in response to a low metabolic rate and suggests a generalized disability for vasodilatation. This could be due to a functional mechanism such as vasodilatation of intracerebral arterioles (on a regulatory basis) already present at resting flow (1) or to a widespread impairment of the whole brain vasculature due to atherosclerosis. Of these hypotheses, the
latter is the more likely because the former is not consistent with reduced resting blood flow. The reduction of CO₂ responsiveness confirms the failure of all afferent blood vessels together to provide an adequate blood supply to the brain, even at rest. From these facts we may infer that, besides the unilateral stenosis and despite the absence of evidence of a lesion on the contralateral carotid and vertebral arteries, the capacity of the cerebral arterial pathways is also limited by disease. Nevertheless, in agreement with recent findings (4,5), our results show that even a severe unilateral stenosis of the internal carotid is compensated by the most efficient collateral pathway which is the circle of Willis (1), since a good concordance between both hemispheric and symmetrical regional blood flows is maintained without reversed flow in the ophthalmic artery.

In patients with a unilateral occlusion of the internal carotid, an additional reduction of flow of ~25% in only one afferent vessel yields an overloading of the collateral capacity via the circle of Willis and is responsible for a greater reduction of flow in the ipsilateral hemisphere. As frequently observed (1–5), an asymmetrical brain blood flow appears despite reversed flow in the ipsilateral ophthalmic artery (as found in a majority of patients). Because an inter-hemispheric asymmetry is a common fact even with “ophthalmic supply,” the detection of a retrograde ophthalmic flow appears to be more useful as a marker of the failure of the collateral flow via the circle of Willis. The inadequacy of the perfusion level in the precentral, posterior temporal and occipital regions is shown in the case of occlusion by the most significant losses of symmetry. These regions correspond, respectively, to the vertical and the horizontal branches of the median cerebral artery distribution area and have the highest risk of stroke (24,25).

According to our data, the loss of CO₂ responsiveness reflects an impairment of the cerebral vascular reserve generalized to both hemispheres and already present in patients with a unilateral severe stenosis efficiently supplied in blood by way of the circle of Willis. However, in patients with carotid occlusion the vascular reserve is more depressed in the territory of the median cerebral artery on the side of occlusion. As suggested by Norrving et al. (1) and in agreement with the demonstration of a lower collateral vascular resistance (26), the more pronounced loss of CO₂ responsiveness localized in the hemisphere on the occluded side could be interpreted on an autoregulatory basis, by a preexistent vasodilatation as a response to hypotension in the corresponding territory. This attractive hypothesis of an additional localized functional reduction of the cerebral vascular reserve is supported by the enhancement of the CO₂ reactivity observed on the occluded side after bypass surgery (2).

From these considerations, a number of conclusions may be drawn: First, compartmental analysis possesses greater sensitivity than noncompartmental analysis of cerebral blood flow data for the evaluation of cerebrovascular reactivity changes. Second, the finding of an impaired CO₂ response extended to the whole brain does not provide information about the adequacy of the collateral circulation to the occluded hemisphere but rather seems to be indicative of the severity of the cerebral atherosclerosis which is a common feature in all patients of this study. Third, in this context, an additional restriction in the cerebral perfusion, like that resulting from the occlusion of only one afferent large vessel, provides an overloading of the most efficient supply by way of the circle of Willis. Finally, the local hypotension, associated with the unilateral deficit of blood supply, induces a vasodilatation which enhances the reduction of the vascular reserve in the most ischemic areas.

With respect to these conclusions, an endarterectomy or bypass surgery will be expected to be of great benefit in at least the diseased hemisphere, not only by preventing future emboli (27,28) but by improving hemodynamics. However, whether an improvement of cerebral hemodynamics is observed or not after surgery is a matter of divergent opinions that requires further clarification (1–4,29,30).

ACKNOWLEDGMENTS

The authors thank Miss H. Heule and Mr. A. Ries for their technical assistance, and Mrs D. Vangebergen for her secretarial assistance.

This work was supported in part by grant from the “Fonds de la Recherche Scientifique Médicale” nr 3-4535-83.

REFERENCES


