rCBF in Patients with Carotid Occlusion

Resting and Hypercapnic Flow Related to Collateral Pattern

Bo Norrving, M.D., Bengt Nilsson, M.D., and Jarl Risberg Ph.D.

SUMMARY  rCBF was measured by 133Xenon inhalation technique in 39 patients with unilateral carotid artery occlusion in a subacute-chronic stage. Resting flow values (ISI) varied between 23.7 and 52.4 ml/100 g/min. An almost constant finding was interhemispheric asymmetry, the degree of which was correlated with the severity of the initial symptoms. An ischemic focus was an insignificant finding. The CO2 response was normal in patients with angiographic signs of circle of Willis collateral flow and without significant contralateral carotid stenosis, whereas it was impaired in patients with a retrograde ophthalmic flow or collateral flow via the circle of Willis and contralateral carotid stenosis ≥ 50%. It is concluded that the CO2 response is a useful rCBF variable and may be applied for analysis of collateral flow capacity in patients with carotid artery occlusion considered for bypass surgery.

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CAROTID OCCLUSION is the single most common arterial lesion considered for extra-intracranial bypass operation.1 Although this procedure is performed in numerous patients, its definitive therapeutic value remains unproven. In most centers, bypass surgery is confined to patients with TIA or only mild stroke at the time of the occlusion, and is attempted to reduce the incidence of future stroke. Recent studies suggest that the long term prognosis in carotid occlusion is favorable, with a stroke rate on the occluded side of only 1–2% per year.2,3 This would limit the value of bypass surgery as a general prophylactic measure in carotid occlusion. Because a bypass operation is a hemodynamically directed procedure, the identification of a subset of patients with impaired capacity of the collateral circulation would be of importance.

In this report we examine the usefulness of rCBF (regional cerebral blood flow) studies in evaluating hemodynamic features in carotid occlusion. rCBF was measured with the 133Xenon-inhalation technique during rest and induced hypercapnia and results were correlated with clinical symptoms and collateral flow pattern.

Patients and Methods

Thirty-nine patients with unilateral carotid occlusion were examined with rCBF by 133Xenon inhalation. The patients were collected in the following manner. Twenty-six patients were evaluated for bypass operation after angiographic identification of the occlusion at this or at an admitting hospital. The inter­val between the onset of the symptoms and the rCBF study was one to six months in these patients. From a recent study on the long-term prognosis in carotid occlusion,4 a further 13 patients with previous TIA or minor stroke were randomly selected for rCBF examination, performed one to nine years after the diagnosis of occlusion was established. The ratio male/female was 31/8 and the mean age of the patients was 60 years (range 34–77 years).

Angiograms were examined for the presence of lesions in extracranial arteries other than the occluded carotid as well as intracranially, and for the source of collateral supply to the occluded hemisphere. All patients underwent selective common carotid angiography on the occluded side. The contralateral carotid artery was studied with selective angiography in 33 patients and with aortic arch angiography in 6 patients. The vertebral arteries, examined in 30 patients, were

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studied selectively in 10 patients and with aortic arch angiography in 20 patients. The intracranial vessels distal to the internal carotid occlusion were clearly visualized in each patient. No patient had extension of the carotid thrombus beyond the circle of Willis nor major arterial lesions within the territory of the middle cerebral artery (MCA).

The source of collateral supply to the occluded hemisphere was designated as “ophthalmic” or “Willisi” type. These two pathways constitute the major collaterals in carotid occlusion. In patients with collateral flow of the “ophthalmic” type, the entire territory of the MCA on the occluded side was filled via this route with no or virtually no filling via the circle of Willis. In patients with the “Willisi” type, cross-filling via the anterior or posterior communicating arteries filled the entire MCA territory on the occluded side, but in some patients a slight retrograde ophthalmic flow was also present. However, via the latter route only the carotid siphon or a small part of the proximal MCA territory were visualized. In 22 out of 24 patients with collateral flow via the circle of Willis, the anterior communicating artery was the main supplying vessel.

CT-scan was performed in 27 patients, in 26 later than one week after the onset of the symptoms. Infarctions visualized were classified as lacunar (localized to the internal capsule, adjacent lentiform nucleus or corona radiata and less than 2 cm in diameter), small superficial (less than 3 cm in diameter) and large (major part of the MCA territory).

rCBF measurements were made by the $^{133}$Xenon-inhalation technique as described by Obrist et al. The present $^{133}$Xenon-inhalation system (Novo Diagnostic Systems, Inhalation Cerebrograph, Denmark) enables simultaneous measurement of cerebral blood flow in 16 homologous regions of both hemispheres by 32 scintillation detectors ($\frac{3}{4}" \times \frac{3}{4}"$ NaI (TI) crystals; lead collimators 20 mm deep and 22.5 mm wide) placed at right angle to the lateral surfaces of the head. $^{133}$Xenon mixed with air (9 mCi/l) was inhaled by the patients for one minute through a tight-fitting mask and a rebreathing spirometer system. This period was followed by 10 minutes of normal breathing. Arterial $pCO_2$ was estimated from recordings of end-tidal $CO_2$ concentrations (Beckman LB 2 $CO_2$ analyzer). Detailed technical descriptions of the present $^{133}$Xenon inhalation technique, have been given elsewhere.

Because the main region of interest in patients with carotid occlusion is the territory of the MCA, only the rCBF values from the seven detectors overlying the distribution of this vessel were used in this study. Detector localization is depicted in figure 1. Of the different rCBF variables obtained by computer analysis, the ISI (initial slope index) was utilized in this study because it is the most reliable variable in conditions with low flow and unstable compartments. The ISI is calculated from the slope of the head curve (corrected for recirculation) from 1 to 2 minutes following the end of the $^{133}$Xenon breathing.

The distribution of the rCBF values within the seven detectors over the MCA territory was evaluated for the presence of an ischemic focus. A focus was defined

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**Figure 1.** Assumed average location of the 7 detectors related to the cortex.
from the inter-regional distribution as a region with a rCBF value less than -2.0 S.D. of the distribution seen in normal subjects.  

Twenty patients had a consecutive rCBF measurement during inhalation of 4% (6 patients) or 6% (14 patients) of CO₂ mixed with air, causing a mean increase in arterial pCO₂ of 11.0 mmHg (range 6.8-15.7 mm Hg). The CO₂-air mixture was inhaled for 5 minutes prior to the ¹³³Xenon inhalation, discontinued for technical reasons during the one minute isotope intake and recommended for an additional 10 minutes.

There is no uniformity of opinion on the shape of the CBF/pₐCO₂ relationship within the physiological range (25-60 mm Hg). An exponential relationship has been found by some authors while others have reported a linear response. For the results in this study, calculation of the CO₂ response as Δ ml CBF/Δ mm Hg pₐCO₂ or logΔml CBF/Δ mm Hg pₐCO₂ yielded the same separation into normal and impaired responses. Therefore, CO₂ is expressed only as Δ ml CBF/Δ mm Hg pₐCO₂ in the text. During CO₂ administration, a slight increase in blood pressure (less than 10 mm Hg) was recorded in most patients.

Results

We divided the 39 patients into three groups according to the initial clinical symptoms. In Group I (N = 14) 10 patients had TIA only, 1 patient had a retinal stroke on the occluded side, 3 patients had an asymptomatic occlusion. Group II (N = 18) consisted of patients with a cerebral infarction with no or only mild residual symptoms, whereas Group III (N = 7) included patients with cerebral infarction and moderate or severe residua. Cerebral infarctions in Group II and III were restricted only to the distribution of the occluded carotid artery in all patients but one. This patient had a RIND (reversible ischemic neurological deficit) from the contralateral carotid territory one year prior to a severe ipsilateral stroke.

Table 1 details the angiographic findings. A stenosis > 50% in the contralateral carotid artery was seen in nine patients and in one or both vertebral arteries in five patients. In Group I collateral flow was mainly of the "Willisi" type, whereas in Group III the "ophthalmic" type prevailed. In Group II, the two patterns were more evenly distributed. Of the nine patients with a contralateral carotid stenosis ≥ 50%, four had collateral flow of the "Willisi" and five of the "ophthalmic" type.

CT was performed in seven patients in Group I; it was normal in five and revealed a small lacunar infarct in two patients, one of whom had an asymptomatic occlusion and one had TIA clinically. In Group II, CT-scan, performed in 14 out of the 18 patients, showed: small superficial infarction in 6, lacunar infarction in 5 and a normal finding in 3 patients. In Group III CT-scan visualized a large infarction in all seven patients.

The rCBF results (mean of seven detectors) during rest are given in figure 2 (individual data) and table 2 (mean values). Mean rCBF values on the occluded side were slightly lower in Group II than in Group I (n.s.), whereas patients in Group III had markedly reduced rCBF values on both the occluded and the non-occluded side (table 2). All but two patients had lower rCBF values on the side of the occlusion (fig. 2). The inter-hemispheric rCBF asymmetries were more pronounced in Group II than in Group I, and still greater in Group III, intergroup differences being highly significant (p < 0.01, Wilcoxon's test). The rCBF values or side asymmetries did not correlate with the time interval between the initial symptoms and the rCBF examination, nor was there any association with the collateral pattern seen in Group I or II.

rCBF examination was repeated in five patients in Group I and II after an interval of 6-12 months from the first study, which had been performed within 6 months after the onset of the symptoms. In three patients a slight decrease in rCBF was found (1-3 ml/100 g/min). However, two patients (both in Group II) had markedly higher rCBF on the second study without concomitant change in pₐCO₂. rCBF values had increased from 30.9 and 36.6 to 44.7 and 41.3 ml/100 g/min respectively. Both patients had been treated conservatively.

An ischemic focus within the seven detectors was found in 11 patients. Two patients had two regions with focally decreased flow whereas nine patients had only one detected focus. The appearance of a focus did not correlate with the time interval between the initial symptoms and the rCBF study or with the collateral pattern, nor with the CT finding of an infarct.

The CO₂ response was determined in 20 patients in Group I and II (fig. 3). The CO₂ reactivity was expressed as the change in ml CBF per mm Hg change in pₐCO₂. The normal value of 0.75 ml/mm Hg pₐCO₂ found in normal subjects is indicated in the figure. A clear relationship between the type of collateral pattern and the CO₂ reactivity on the occluded side is seen (p < 0.001, chi-square). Five out of six patients with collateral flow of the "ophthalmic" type had impaired CO₂ response on the occluded side, in addition to the inter-regional distribution as a region with a rCBF value less than -2.0 S.D. of the distribution seen in normal subjects.

Table 1. Mean Age, Angiographic Findings and Type of Collateral Flow in the Different Groups of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Mean Age</th>
<th>Contralateral carotid artery</th>
<th>Vertebral arteries</th>
<th>Type of collateral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal/</td>
<td>Stenosis</td>
<td>Normal/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 50%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td>63.1</td>
<td>12</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>II</td>
<td>18</td>
<td>57.9</td>
<td>13</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>56.6</td>
<td>5</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>
to three patients with the "Willisi" type of collateral flow and concomitant significant stenosis in the contralateral carotid artery. Conversely, all 11 patients with collateral flow via the circle of Willis, not associated with significant stenosis in the contralateral carotid artery, had a normal CO\(_2\) response. The time interval from the initial symptoms to the rCBF study did not seem to correlate with the CO\(_2\) response. Nine patients were examined later than one year after the diagnosis of occlusion had been established, four of whom had decreased CO\(_2\) reactivity. Also, no association between the resting rCBF values and the CO\(_2\) response was found.

The CO\(_2\) response was largely homogenous within the seven detectors studied, including the five patients with an ischemic focus and seven patients in Group II with an infarct visualized by CT-scan. A CO\(_2\) response deviating > 20% from the mean reactivity was seen only in five patients in one, or at most two, of the detectors. No region with non-reactivity or paradoxical response was seen.

**Discussion**

Cerebral blood flow studies have previously been performed to determine the value of this technique in selecting patients for bypass surgery. Using the intracarotid technique, Schmiedek et al.\(^{14}\) stated that patients with an ischemic focus in association with no or only moderate general rCBF reduction were the most suitable candidates for surgery. Similar conclusions were reached by Heilbrun et al.\(^{16}\) However, the intracarotid technique encounters specific problems in patients with obstructive lesions, which must be considered in the interpretation of data.\(^{18}\) The contribution of different vessels, chosen for isotope injection, to the blood flow of the occluded hemisphere is variable. If collateral flow is poor, an adequate delivery of isotope to the occluded hemisphere may be critical. Also, if isotope is injected in the contralateral carotid artery, radiation from the non-occluded hemisphere will contaminate the recording on the occluded side to a variable extent. The use of \(^{133}\)Xenon inhalation,\(^{17}\) and also the intravenous \(^{133}\)Xenon technique,\(^{18}\) partly circumvents the problem of isotope delivery encountered in patients with carotid occlusion. Moreover, its non-invasiveness facilitates sequential studies with time and during various conditions.
The definition of an ischemic focus must take into account the normal hyperfrontal distribution of the rCBF. Normally, parietal regions have a rCBF 4-7% below the hemispheric mean. In this study, an ischemic focus was defined from the normal intrahemispheric distribution and in all patients with minor stroke. In patients with a severe stroke rCBF was more markedly reduced on both sides. Although "cross-talk" tends to underestimate true side differences in blood flow, an inter-hemispheric asymmetry was generally observed. The inter-hemispheric rCBF differences mainly paralleled the clinical state of the patients.

The spontaneous return of an initially subnormal rCBF to the normal range was observed in two patients not subjected to surgery. This implies that the finding of an increased rCBF after a bypass procedure has to be cautiously interpreted, unless rCBF studies are performed close to the time of the operation.

The finding of a subnormal mean rCBF after induced hypercapnia, was found to be proportionally depressed. However, data by Grubb et al. show that this relationship may be deranged also in the chronic state. Presently, regional measurements of metabolic rate can only be obtained by positron emission tomography, the costs and practical aspects of which limit its broad use.

The third type of rCBF data analyzed in this report, the rCBF response to induced hypercapnia, was found to be the most informative.

Table 2. rCBF Results

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Time interval between initial symptom and rCBF study</th>
<th>ISI (mean of 7 detectors)</th>
<th>ISI-difference between sides</th>
<th>No. patients with ischemic focus</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 6 months</td>
<td>&gt; 1 year</td>
<td>Occluded side</td>
<td>Contralateral side</td>
</tr>
<tr>
<td>I</td>
<td>14</td>
<td>7</td>
<td>7</td>
<td>41.9</td>
<td>42.9</td>
</tr>
<tr>
<td>II</td>
<td>18</td>
<td>14</td>
<td>4</td>
<td>38.7</td>
<td>42.2</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>7</td>
<td></td>
<td>29.2</td>
<td>34.9</td>
</tr>
</tbody>
</table>

xx = p < 0.01 (Wilcoxon's test).

In this study, three types of rCBF data were specifically analyzed, viz., the resting rCBF values, the presence of an ischemic focus and the CO₂ response.

As compared to age-matched controls, subnormal rCBF values on the occluded side were found in about two-thirds of the patients with TIA or asymptomatic occlusion and in all patients with minor stroke. In patients with a stroke rCBF was more markedly reduced on both sides. Although "cross-talk" tends to underestimate true side differences in blood flow, an inter-hemispheric asymmetry was generally observed. The inter-hemispheric rCBF differences mainly paralleled the clinical state of the patients.

In this study, many patients with a low resting rCBF could increase flow substantially during induced hypercapnia. We believe that a subnormal rCBF mainly reflects an adaption to the reduced demands of the tissue. If so, a bypass procedure would not necessarily be of benefit. A more precise definition of the indications of therapy intended to increase the cerebral blood flow would require determining the relationship between the metabolic demands of the tissue and the available blood flow. In most stroke patients, rCBF and the metabolic rate have been found to be proportionally depressed. However, data by Grubb et al. show that this relationship may be deranged also in the chronic state. Presently, regional measurements of metabolic rate can only be obtained by positron emission tomography, the costs and practical aspects of which limit its broad use.

The rCBF response to various psychological activation procedures is mediated via the parenchyma, the state of which will be critical for the full effect of the activation. Normally the rCBF response to activation procedures is considerably less pronounced than to hypercapnia.

An abnormal CO₂ reactivity in stroke patients is mainly seen in the acute phase, and if no major arterial occlusion is present, the CO₂ response is usually later regained. In patients with only TIA or minor stroke and without major vessel pathology, a normal CO₂ response in the chronic phase has been found. In the present study, a decreased CO₂ reactivity was found in only three of the patients with the CT finding of an infarction, two of which were lacunar. In the corresponding rCBF areas, as well as in regions with an
In a previous study on pathophysiological mechanisms in the acute phase of carotid occlusion, the circle of Willis was found to be the most efficient collateral pathway, whereas a collateral supply via the ophthalmic artery was associated with more severe stroke symptoms. This study reveals a similar relationship between these two collateral pathways and the ability to increase blood flow during induced hypercapnia. In addition to patients with retrograde ophthalmic flow, patients with a collateral supply via the circle of Willis associated with a contralateral carotid stenosis exceeding 50% were found to have an impaired CO$_2$ response.

Considering collateral flow via the ophthalmic artery, the diameter of this vessel is about equal to a normal, patent anterior communicating artery. However, the considerable length of the ophthalmic collateral route probably is critical for its function as a full capacity collateral able to increase flow substantially.

The hemodynamic importance of even a moderate stenosis in the carotid artery contralateral to an occlusion is often not fully recognized. During normal conditions a carotid stenosis is of hemodynamic significance only when the cross-sectional area is reduced to about 80% or more. However, in patients with a carotid occlusion and collateral flow via the circle of Willis, flow in the contralateral carotid artery has been found to be increased about 40–60%. Since the pressure drop across a stenosis is strongly dependent on the flow rate through the vessel, stenoses also of lesser degree are hemodynamically significant when flow is increased. When a contralateral carotid artery serves both hemispheres, stenoses of about 65–70% reduction in cross-sectional
area, corresponding to about 40–55% decrease in diameter, will be critical.\(^4^4\) In patients with an impaired CO\(_2\) response a reduced peripheral resistance, i.e. a vasodilatation of intracerebral arterioles on an autoregulatory basis, may be present already in the resting condition. The contribution of this latter factor to the reduced CO\(_2\) response is not specifically answered by this study because the autoregulatory response to hypotension was not tested. However, the finding of low perfusion pressures (down to 9–15 mm Hg) in the middle cerebral artery or a cortical artery during intraoperative measurements in a proportion of patients with chronic carotid occlusion\(^3^6,3^6\) makes it reasonable to assume that in some patients the autoregulatory reserve may be diminished, making these patients susceptible to cerebral ischemia during transient drops in blood pressure due to decreased cardiac output or postural hypotension. While an induced hypotension test would be of interest in patients with carotid occlusion, the practical aspects of its safe execution limit its use.

Evaluation of the possible prophylactic benefit of bypass surgery must take into account the pathophysiological mechanisms of postocclusion ischemic events. These may be caused both by hemodynamic factors and by embolism. A transient drop in blood pressure due to decreased cardiac output or postural hypotension is often assumed as a cause, but has been clearly documented in only a few patients.\(^9^7–9^8\) However, due to its transient state, a drop in perfusion pressure may easily escape detection. It has recently been shown that post-occlusion ischemic events may also be of embolic origin. Possible sources of emboli are the "proximal" stump\(^9^9,10^0\) and distal "tail"\(^1^0^1\) of the occluded carotid artery, arterial lesions in the external carotid artery\(^4^5,4^6\) or other collateral pathways and concomitant intracranial lesions distal to the occlusion. In patients where the mechanism of ischemia is related to emboli, the possible benefit of a bypass would be a redistribution of flow in collateral pathways with an embolic source, or to an increase in the tolerance of a marginally perfused region to withstand emboli without the development of infarction.\(^1^8\)

The present finding, that a majority of the patients with carotid occlusion and no or only minor stroke have an adequate reserve capacity of the collateral circulation, should imply that a bypass operation in these patients is not required from a hemodynamic point of view. The finding of an impaired CO\(_2\) response does not provide full information about the adequacy of the collateral circulation to the occluded hemisphere in the resting condition, but identifies a subset of patients in whom further studies may reveal a possible role of bypass surgery. It also remains to be investigated whether a bypass is a more efficient collateral than the ophthalmic artery or simply would redistribute flow from the latter vessel.\(^4^5\) In patients with collateral flow via the circle of Willis associated with a significant contralateral carotid stenosis, an endarterectomy of the stenosis would be the procedure of choice also from a hemodynamic point of view, provided that this operation can be performed with sufficiently low morbidity.\(^4^8–4^8\)

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