Reversal of Focal “Misery-Perfusion Syndrome”
By Extra-Intracranial Arterial Bypass
in Hemodynamic Cerebral Ischemia
A Case Study with \(^{16}\)O Positron Emission Tomography

J. C. BARON, M.D., M. G. BOUSSER, M.D., A. REY, M.D.,
A. GUILLARD, M.D., D. COMAR, PH.D., AND P. CASTAIGNE, M.D.

SUMMARY Tomographic images of cerebral blood flow (CBF) and oxygen extraction fraction (OEF) using the \(^{16}\)O continuous inhalation technique, and positron emission tomography, were obtained from a patient with cerebral ischemia distal to an occluded left internal carotid artery. There was a focal mismatch between CBF and oxygen metabolism in the brain supplied by the middle cerebral artery where CBF was decreased and OEF increased (“misery-perfusion syndrome” as opposed to “luxury-perfusion syndrome”). These abnormalities were most marked in the parieto-occipital watershed area. After left superficial temporal to middle cerebral artery anastomosis, the clinical attacks ceased and a repeat study did not demonstrate the previous CBF and OEF abnormalities. This suggests that this pattern of abnormalities indicates potential viable tissue. The concept of “misery-perfusion” may be of some importance in the pathophysiological mechanisms of hemodynamic cerebral ischemia and serve as a rational basis for revascularization procedures.

RECURRENT SYMPTOMS of cerebral ischemia in the brain supplied by a previously demonstrated occluded internal carotid artery (ICA) is an unusual but not a rare problem. Present evidence suggests that symptoms may be due to recurrent embolization or to a fall in cerebral perfusion pressure without arterial embolism. When this problem is clinically suspected, it is believed to be an indication for an extracranial-intracranial arterial bypass (EIAB).

This report is of a patient with hemodynamic post-occlusion cerebral ischemia which was alleviated by EIAB and who was found to have inadequate perfusion relative to the oxygen requirements of cerebral tissue, i.e. “misery-perfusion syndrome.” The underlying concept of this syndrome will be discussed.

Presentation of Patient

A 65-year-old right-handed hypertensive man with mild diabetes, treated with hydralazine and beta-blocking agents, in March, 1978, sustained 4 episodes of either right lower limb or right hand weakness (the latter associated with dysphasia) lasting seconds to minutes. A similar episode occurred after admission to a first hospital, following which an emergency cerebral angiogram was performed. Occlusion of the left internal carotid artery (ICA) was found above the bifurcation of the common carotid artery (CCA). At operation the sole finding was an organized thrombus, and no attempt was made to restore flow. Despite effective anticoagulation, symptoms of transient cerebral ischemia continued unexpectedly and their frequency increased to multiple daily attacks which were clearly related to the orthostatic position.

The patient complained of transient right arm weakness lasting a few seconds after standing up abruptly and he had 2 orthostatic syncopal episodes. His heart was unremarkable with a resting rate of 80. His arterial pressure was 170/100 lying down, 120/80 directly after standing up and 120/80 after a few minutes and was associated with heart rate acceleration. The neurological examination showed a questionable motor deficit in the right hand and an unequivocal right Babinski sign. A \(^{99m}\)Tc brain scan was normal. The symptoms of transient ischemia in brain distal to an occluded ICA and triggered by postural hypotension, led to the diagnosis of “orthostatic cerebral ischemia.”

Medication Change

Anticoagulation was stopped, the dosage of hydralazine was decreased, dipyridamole and aspirin were prescribed and the patient was instructed to stand up with caution. He was discharged home but continued to have postural episodes of isolated, right arm weakness, although these were notably less frequent.

Additional Episodes

In December, 1978, and January, 1979, 2 severe episodes occurred while the patient had been standing for some time. These consisted of marked right lower limb weakness and moderate right arm weakness. An even more severe episode, not clearly postural, occurred on February 1, 1979, while he was sitting eating. He dropped his fork and became pale and mute. He recovered completely within a few minutes but 15 min-
utes later had a second attack in which he sank to the floor, was pale and sweated profusely. He had clouding of consciousness, complete right hemiplegia, deviation of mouth and eyes to the left and inability to talk. He recovered within minutes but during the next few days his right arm and leg were mildly weak and he had some difficulty finding words. Although it was estimated that a sufficient time had elapsed for maximum collateral flow to develop following the left ICA occlusion, hemodynamic cerebral ischemia with threatened stroke persisted.

Neurological Examination

The patient was readmitted in March, 1979. The neurological examination showed increased tendon reflexes, a Babinski sign and slight leg circumduction, localized to his right side. There were no cervical or ocular bruits. The blood pressure was 175/105 lying, and 145/80 standing, but on 2 occasions standing BP was recorded at 90/65. His dosage of hydralazine was further reduced. Four-vessel angiography, by retrograde catheterization of the femoral artery, showed an occlusion of the left ICA one cm above its origin, with faint filling of the distal ICA siphon and of the middle cerebral artery (MCA) through the external carotid-ophthalmic system (fig. 1). When the contrast medium was injected in the right CCA, a smooth, small atherosclerotic plaque was visualized in the right ICA just above its origin; there was limited passage of the contrast medium to the contralateral hemisphere, the left anterior cerebral artery filled, but not the left MCA. The left vertebral artery was unremarkable and there was a moderate stenosis of the intracranial right vertebral artery. No filling of the left middle cerebral artery occurred from the vertebral-basilar circulation. The angiographic findings suggested that the left MCA blood flow depended solely on a retrograde flow through the left ophthalmic artery.

Surgery

On June 8, 1979, the patient had surgery to anastomose the left superficial temporal artery to a parieto-temporal branch of the left MCA. Following surgery the attacks of right arm weakness associated with standing up disappeared. On June 19, the BP was 155/90 lying and 90/65 standing. On July 10, circumduction of the right leg had disappeared. A directional Doppler study suggested a patent STA-MCA anastomosis with diastolic flow. An angiogram on October 8, 1979, showed a considerable enlargement of the left STA with a patent anastomosis and good filling of most of the left MCA branches (fig. 2). A CT scan, performed before and after I.V. contrast injection, revealed a moderate widening of the cortical sulci over the left hemisphere with some ipsilateral ventricular enlargement but without evidence of cerebral infarction (fig. 3). When last seen, in 1981, the patient stated that no attack had occurred since surgery.

Figure 1. Preoperative left common carotid artery (CCA) angiogram. There is occlusion of the left internal carotid artery (curved arrow) with faint filling of its intracranial part (arrow-head) through the ophthalmic artery. The superficial temporal artery (STA) is indicated by the straight arrow.

Figure 2. Postoperative left CCA angiogram. The left STA has considerably increased in size (broad arrow). The anastomosis is patent (arrow-head) and there is excellent filling of most of the middle cerebral artery branches (small arrows).
only neurological abnormality still present was a right Babinski sign.

**1\(^{15}\)O Continuous Inhalation Study**

Our particular interest in the study of this patient were the tomographic images of cerebral blood flow (CBF) and oxygen extraction fraction (OEF) using the \(^{15}\)O continuous inhalation technique\(^1\) coupled with positron emission tomography (PET).\(^10\) These studies were carried out on 2 occasions, the first 45 days before surgery, and the second 32 days after surgery.

The non-invasive \(^{15}\)O continuous inhalation technique provides images that allow assessment of CBF and OEF.\(^11\)\(^-\)\(^18\) The oxygen extraction fraction (OEF) is the arteriovenous oxygen difference, \(Ca-Cv\), divided by the arterial oxygen content (\(Ca\)); and is related to the cerebral metabolic rate of oxygen (\(CMRO_2\)) by the following equation: 

\[
CMRO_2 = CBF \cdot OEF \cdot Ca.
\]

The methods have been described in detail elsewhere.\(^10\) The technique consists of continuous inhalation to equilibrium of the short-lived positron emitter \(^{15}\)O in the form of \(^{15}\)O\(_2\) and \(^{15}\)O\(_2\) consecutively. For each horizontal brain level studied, a set of 3 different images is obtained: 1) A \(^{15}\)O\(_2\) image that represents CBF; 2) A \(^{15}\)O\(_2\) image that represents both oxygen metabolism and CBF; 3) A \(^{15}\)O\(_2\) ratio image which is linearly proportional to the OEF.

Each of these images was obtained in this patient but only semi-quantitative data were available. Count rates per unit volume were calculated for various regions of interest, and compared to the values obtained from contralateral homologous regions. The side-to-side percent difference was considered abnormal if it lay outside the confidence limits defined for similar regions in 14 patients without known brain pathology (Baron et al., unpublished). The values obtained indicate real differences in CBF and OEF that, according to the mathematical model, would be of much larger magnitude.

**Results**

The results are shown on the table and figure 4. The preoperative \(^{15}\)O inhalation study revealed highly significant changes that indicated a large decrease in CBF in the brain supplied by the left MCA combined with an increased OEF; both abnormalities were predominant in the parieto-occipital watershed area. The postoperative study showed entirely normal images, especially in those areas previously involved, and both CBF and OEF now appeared symmetrical. Pre- and postoperative arterial \(Pco_2\) were 41.5 and 44 mm Hg, respectively.

**Discussion**

This patient had symptoms due to reversible ischemia related to an occluded left ICA and mostly triggered by orthostatic hypotension. These attacks were alleviated by a left EIAB procedure. Preoperatively, a \(^{15}\)O PET study showed decreased CBF in the brain supplied by the left MCA together with an
increased oxygen extraction fraction (OEF), a situation termed the "misery-perfusion syndrome." Following the EIAB, a repeat inhalation study showed complete resolution of these abnormalities. A focal decrease in CBF observed distal to symptomatic ICA occlusion is not surprising; this has frequently been reported in patients presenting with repeated ischemic attacks and significant ICA disease.\(^{14-18}\) CBF tends to return to normal or near-normal values following either ICA endarterectomy\(^{19,20}\) or EIAB.\(^{21-23}\) Similarly, large ipsilateral reductions in CBF frequently occur in patients subjected to carotid artery clamping.\(^{24}\) Significant decreases in ipsilateral pial artery pressure (monitored in the MCA branches) have been reported both in primate studies of the effects of carotid ligation\(^ {25}\) as well as in patients undergoing EIAB for symptoms referable to inaccessible occlusive carotid artery disease.\(^ {26}\) Experimental and clinical investigations have demonstrated a loss of CBF autoregulation and CO\(_2\) reactivity distal to carotid artery ligation,\(^ {27-29}\) a phenomenon also reported in some patients presenting with severe symptomatic carotid artery disease but without infarction.\(^ {30-32}\) The hypothesis advanced widely is that in order to compensate for the decrease in perfusion pressure, there is near-maximal vasodilatation of the cerebral resistance vessels which may or may not be sufficient to maintain CBF in the normal range. This situation results in an impairment of autoregulation and an inability to withstand a further decrease in perfusion pressure.\(^ {33}\)

The pattern of abnormalities observed preoperatively in our patient consisted of a focal OEF increase concomitant with CBF decrease. These findings are consistent with published evidence that an increased OEF is common in a number of low flow states in the brain. The ability of the brain to increase its fractional extraction of oxygen in the face of a primary CBF reduction has been consistently observed in both global ischemia (i.e., secondary to acute reduction in cerebral perfusion pressure,\(^ {34-36}\) marked hypocapnia,\(^ {37}\) or subarachnoid hemorrhage\(^ {38}\)) and acute focal experimental ischemia (i.e., MCA occlusion which induces an immediate darkening of the pial veins in the affected cortical territory\(^ {39-41}\)). In recent brain infarction of man studied with the \(^{15}O\) inhalation technique, well-defined areas showing acute "misery-perfusion syndrome" are commonly observed.\(^ {33,42}\) In patients with transient ischemic attacks, Lenzi et al.\(^ {43}\) reported a decreased perfusion rate with an increased OEF. Concomitant increase in the arteriovenous oxygen difference (AVDO\(_2\)) and decrease in CBF have been reported ipsilaterally to carotid artery clamping.\(^ {44}\) In 3 patients selected for EIAB because of symptoms attributed to inaccessible lesions in the carotid-MCA system, Grubb et al.\(^ {45}\) reported that "oxygen was being utilized at a higher rate than would be predicted from the level of rCBF", i.e., the OEF was focally increased, and that "postoperative studies showed a significant improvement in rCBF and rCMRO\(_2\)." Our findings are similar to those of this earlier study.

<table>
<thead>
<tr>
<th>Table: Results of Continuous Inhalation Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Whole Hemisphere</td>
</tr>
<tr>
<td>Pre-op</td>
</tr>
<tr>
<td>Post-op</td>
</tr>
<tr>
<td>Whole Cortex</td>
</tr>
<tr>
<td>Pre-op</td>
</tr>
<tr>
<td>Post-op</td>
</tr>
</tbody>
</table>

The values observed are the relative percent change between left and right hemispheres. The relative decrease in OEF during preoperative state is significant (P < 0.05).
When there is a decrease in CBF concomitant with an OEF increase, the implication is that perfusion is inadequate relative to the oxygen demand of the tissue. When focal, this state of uncoupling has been defined as the "misery-perfusion syndrome." In such a situation, cell oxygenation — and, hence, function — could range from normal to inadequate, depending on the extent that OEF increase compensates for the CBF decrease. If the OEF is near its upper limits, any additional decrease in perfusion pressure is likely to further diminish cell oxygenation and to induce or worsen cell dysfunction. If transient, such an event may lead to transitory focal neurological episodes; if long-lasting a protracted clinical deficit may follow. Acute "misery-perfusion syndrome" in ischemic stroke sometimes correlates with a favorable outcome. In migraineous infarction, the "misery-perfusion syndrome" was noted in a structurally intact area remote from the infarction itself, as judged by clinical and CT scan evidence. In our patient, as well as in the 3 patients reported by Grubb et al., the protracted focal "misery-perfusion syndrome" was reversed by an EIAB procedure, suggesting that this state may indicate tissue viability. The latter situation is reminiscent of the concept of "penumbra" where function is impaired but structure is (relatively) preserved. However, "penumbral" areas may not always display the "misery-perfusion syndrome." In 2 other patients OPOET studies suggested the presence of a matched decrease in CBF and oxygen utilization surrounding watershed necrosis which was corrected by EIAB. Similar observations reported by Thomas et al. and Grubb et al.

In the patient reported here, the EIAB resulted in a dramatic improvement in the clinical state and disappearance of the "misery-perfusion syndrome." Because of its potential reversibility — and, hence, favorable prognosis — protracted "misery-perfusion syndrome" emerges as a pathophysiological entity of some importance. Were such a situation identified, the rational management would clearly be to restore CBF to adequate values before permanent damage had occurred; EIAB is one way of improving the cerebral perfusion pressure and, in turn, the CBF.

Acknowledgement

We wish to thank Dr. E.T. MacKenzie for helpful discussions, Professor G. Du Boulay (The National Hospital, London) for reviewing the CT Scan, and N. Duquesnoy, J. Sastre and C. Loc' h for their skilled technical assistance.

References

23. Little JR, Yamamoto YL, Feindel W, Meyer E, Hodge CP: Superficial temporal artery to middle cerebral artery
PET STUDY OF BYPASS TO REVERSE "MISERY-PERFUSION SYNDROME"/Baron et al. 459


Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with 15O positron emission tomography.

J C Baron, M G Bousser, A Rey, A Guillard, D Comar and P Castaigne

doi: 10.1161/01.STR.12.4.454

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/12/4/454

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/