Studies on Cerebral Blood Flow and Oxygen Metabolism in Patients with Established Cerebral Infarcts Undergoing Omental Transposition

Sigrid Herold, Richard S.J. Frackowiak, and Glenn Neil-Dwyer

Regional cerebral blood flow, blood volume, fractional oxygen extraction, and oxygen consumption were measured by positron emission tomography in 4 stroke patients prior to and 6 months following omental transposition surgery. Preoperatively, 3 patients showed the typical picture of established infarction with a matched reduction in flow and oxygen metabolism and a normal oxygen extraction fraction in the symptomatic hemisphere. One patient showed a chronically impaired perfusion reserve with a proportionally greater reduction in flow than oxygen metabolism and a compensatory rise in oxygen extraction ratio. No change in the physiological parameters was demonstrated in the postoperative studies. (Stroke 1987; 18:46-51)

In animal experiments it has been shown that when the intact omentum is placed on the surface of the brain, vascular connections are formed between the two tissues. The same authors demonstrated that, in dogs and monkeys, omental transposition performed several weeks prior to experimental middle cerebral artery (MCA) occlusion greatly decreased the incidence of ischemic infarction that otherwise invariably occurred. Regional cerebral blood flow (CBF) and sensory evoked potentials (SEP's) were measured in rabbits subjected to omental transposition; after MCA occlusion CBF dropped to 40% of its original value and SEP's disappeared in control animals, whereas flow remained at 75% of preocclusion values and SEP's were preserved in animals subjected to prior omental transposition. These experiments provide evidence that functioning omentum-brain anastomoses can be achieved and that these can effectively compensate for reductions in cerebral perfusion pressure. Recently, angiogenic factors from omental tissue have been shown to promote revascularization in the rabbit cornea.

In humans, omental transposition has so far mainly been performed in patients with established ischemic neurological deficits and frequent neurological improvement after the operation has been reported. One of the reasons for attempting to improve longstanding neurological deficit by this procedure is the assumption that even months and years after a stroke there might be a "chronic penumbra" at the borders of an infarct, consisting of viable but not functioning cells, whose function could be restored by improved substrate supply. There is another hypothesis that the omentum, which is rich in enzymes, lipids, and neurotransmitters, might exert a direct stimulating effect on the brain tissue via an as yet unknown biochemical transmitter.

Positron emission tomography (PET) allows the determination of CBF, fractional oxygen extraction (OER), oxygen utilization (CMRO₂), and cerebral blood volume (CBV) regionally and quantitatively. Mismatching between oxygen supply and demand is reflected by changes in the OER. In acute stroke, OER's far above the normal values of 35-45% indicate a shortage of oxygen supply in relation to metabolic requirements. Established infarcts, however, are characterized by a coupled reduction of CBF and CMRO₂ and normal or decreased OER, implying that blood flow, however low it may be in absolute terms, is adequate for the tissue's residual metabolic demands.

In view of this pathophysiological information in man, which is at variance with the rationale for revascularizing infarcted brain with omental transposition, we prospectively carried out PET studies in 4 patients pre- and postoperatively.

Subjects and Methods

Stroke patients (2 women and 2 men) were selected such that they had fixed, static ischemic neurological deficits and frequent neurological improvement after the operation has been reported. One of the reasons for attempting to improve longstanding neurological deficit by this procedure is the assumption that even months and years after a stroke there might be a "chronic penumbra" at the borders of an infarct, consisting of viable but not functioning cells, whose function could be restored by improved substrate supply. There is another hypothesis that the omentum, which is rich in enzymes, lipids, and neurotransmitters, might exert a direct stimulating effect on

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The scans were performed with an ECAT II (EG & G Ortec) PET scanner with a spatial resolution of 16.7 × 16.7 × 16 mm at full width half maximum (FWHM).\textsuperscript{13} CBF, OER, CMRO\textsubscript{2}, and CBV were measured using the oxygen-15 steady-state technique\textsuperscript{14} and the carbon-11 carboxyhemoglobin technique\textsuperscript{16} described previously.

In each study, emission and transmission scans were performed in 2 tomographic planes 2 cm apart, parallel to the orbito–meatal (OM) line. Levels above the OM line were chosen by reference to the largest extent of low attenuation seen on the CT scans. Thus, planes +4.0 and +6.0 cm above and parallel to the OM line were scanned in Patient 1, +4.5 and +6.5 cm in Patients 2 and 4, and +4.8 and +6.8 cm in Patient 3.

Positioning was performed by aligning the OM line with a laser beam, moving the patient on the scanner bed to the selected level above the OM line, projecting a grid of light on the patient’s forehead and marking its position on the skin. Any head movement could then be corrected. The procedure also permitted accurate repositioning in the repeat study so that comparable planes were scanned pre- and postoperatively.

**Data Analysis**

The method of cortical plotting, as previously described for the analysis of data from patients with acute and chronic cerebrovascular disease,\textsuperscript{9,17} was applied. This involves the semiautomatic placing of contiguous rectangular 15 × 7.5 mm regions of interest by computer over the highest mean pixel values in the cortical rim of high metabolic activity on the CMRO\textsubscript{2} images. Twenty to 26 such regions encompass the cortex of each hemisphere. The plots obtained from the CMRO\textsubscript{2} image are superimposed on the CBF, OER, and CBV images to obtain values from identical regions. The physiological variables are expressed in two ways:

1. Mean values were obtained from a strip of 12 contiguous regions in each plane and hemisphere corresponding to the superficial distribution of the MCA. The reported values represent the mean of both planes on each side.
2. Values of the individual rectangular regions were plotted against the distance around the cortex from frontal to occipital lobes.

Although the main objective was to assess differences between pre- and postoperative studies, some
comparisons were made with data from 15 normal volunteers of the same age range (35–64 years; mean age 50.7 years).

Statistical analysis was performed using Bonferroni t tests for multiple comparisons.

The study of patients with cerebrovascular disease was approved by the Hammersmith Hospital Ethics Committee. Permission for the administration of radioisotopes was given by the U.K. Administration of Radioactive Substances Advisory Committee. The informed consent of the patients was obtained prior to each study.

Results

Inspection of the physiological images in 3 patients indicated functional lesions with coupled reductions in CMRO₂ and CBF that were far more extensive than the structural lesions seen on the CT scans. The left internal capsule infarct of Patient 1 involved the posterior temporal and parietal cortex on both planes giving the picture of a middle–posterior cerebral artery watershed infarct. Additionally, an infarct in the right frontal lobe was clearly seen explaining the patient’s pseudobulbar symptoms. In Patient 2, in whom the CT scan showed a deep left hemisphere infarct, metabolic depression was seen in the whole of the left MCA territory. Patient 4, with a left frontal infarct on CT scan, showed coupled reduction in flow and oxygen metabolism in the whole area supplied by the left internal carotid artery (Figure 1). Only in Patient 3, who showed the most structural damage on CT scan, was the extent of the lesion similar on the functional images.

Thus, the focal lesions involved the whole of the cerebral cortex supplied by the left MCA in Patients 2, 3, and 4 and the posterior part of the MCA cortex in Patient 1. At operation, the 0.5- to 1.0-cm thick omentum was placed over most of the lateral surface of the brain covering an area of approximately 10 × 7 cm. As both the functional lesions and the transposed pieces of omentum encompassed large cortical areas, the standardized analysis of MCA territories via cortical plots provided an objective way of expressing the data. The presence of the omental ridge did not affect the postoperative measurements as the cortical regions were both pre- and postoperatively defined by the highest CMRO₂ values and were adjusted accordingly.

Table 3 and Figure 2 give the pre- and postoperative values of CBF, OER, CMRO₂, and CBV for the operated and contralateral hemispheres of the 4 patients. Additionally, the ratio CBF/CBV was calculated, which provides an index of cerebral perfusion pressure and hemodynamic reserve in noninfarcted brain tissue. None of the parameters showed a significant change in mean values from the first to the second study.

In the cortex of the symptomatic hemispheres, CBF and CMRO₂ were pathologically low in 3 patients preoperatively; in Patient 2, who was clinically the least severely affected, values for both parameters lay in the normal range but were reduced compared to the contra-
Table 3. CBF, CMRO₂, OER, CBV, and CBF/CBV Values in the MCA Cortex of Operated (Left) and Contralateral (Right) Hemispheres. Comparison Between Pre- and Postoperative Values.

<table>
<thead>
<tr>
<th>Patient</th>
<th>CMRO₂</th>
<th>CBF</th>
<th>OER</th>
<th>CBV</th>
<th>CBF/CBV</th>
<th>CMRO₂</th>
<th>CBF</th>
<th>OER</th>
<th>CBV</th>
<th>CBF/CBV</th>
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</thead>
<tbody>
<tr>
<td>Operated hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>3.5</td>
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<td>Mean ± SD</td>
<td>1.8 ± 0.7</td>
<td>22 ± 10</td>
<td>0.48 ± 0.03</td>
<td>3.5 ± 0.5</td>
<td>6.1 ± 2.1</td>
<td>1.7 ± 0.8</td>
<td>21 ± 10</td>
<td>0.47 ± 0.08</td>
<td>3.3 ± 0.5</td>
<td>6.2 ± 2.1</td>
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Contralateral hemisphere

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<th>OER</th>
<th>CBV</th>
<th>CBF/CBV</th>
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<th>CBF</th>
<th>OER</th>
<th>CBV</th>
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<td>3.6</td>
<td>8.0</td>
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<tr>
<td>Mean ± SD</td>
<td>2.6 ± 0.4</td>
<td>33 ± 6</td>
<td>0.43 ± 0.01</td>
<td>4.1 ± 0.4</td>
<td>8.2 ± 2.2</td>
<td>2.3 ± 0.3</td>
<td>31 ± 6</td>
<td>0.43 ± 0.05</td>
<td>3.6 ± 0.3</td>
<td>8.6 ± 2.0</td>
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</table>

lateral hemisphere. A normal OER in 3 patients suggested adequate oxygen supply in these cases. Only Patient 4 showed a proportionally greater reduction in CBF than CMRO₂, oxygen delivery to the tissues being maintained by a significant rise in OER (> 2 SD from the normal mean value). CBV values lay in the low normal range or below. However, in all patients except Patient 2, CBV was high in relation to the prevailing blood flow, so the ratio CBF/CBV was slightly reduced in Patient 1 and profoundly decreased in Patients 3 and 4.

In the contralateral hemisphere, CBF and CMRO₂ were in the low normal range or slightly below in all cases except Patient 1, in whom a reduction in CBF and CMRO₂ to values similar to the symptomatic hemisphere was indicative of his bilateral ischemic disease. OER and CBV were normal in all cases preoperatively, but CBF/CBV ratios were low in two cases.

Figure 2. Pre- and postoperative cortical values in middle cerebral artery territory for CMRO₂, CBF, OER, CBV, and CBF/CBV ratio in 4 stroke patients. Patients are represented by symbols: • = Patient 1, ○ = Patient 2, △ = Patient 3, ▲ = Patient 4. Plotted is also the mean ± SD of cortical values obtained from 15 normal volunteers.
Changes in the physiological parameters between pre- and postoperative studies were small in most instances and went in both directions. Changes in the operated hemispheres ranged from -25% to +6% for CMRO₂, -26% to +19% for CBF, -20% to +15% for OER, -20% to +15% for CBV, and -8% to +10% for the CBF/CBV ratio. In the contralateral hemisphere the range was -16% to -4% for CMRO₂, -19% to +2% for CBF, -10% to +14% for OER, -29% to -1% for CBV, and -18% to +61% for the CBF/CBV ratio.

In Figure 3, pre- and postoperative CMRO₂ and CBF values from the individual 15 x 7.5 mm regions of interest of the operated hemispheres are plotted against distance around the cortex. The plots indicate that the same general trends were seen regionally as for the MCA territory as a whole.

Neurological examination performed at the second PET study showed slight improvement in muscle power on the hemiparetic side in all patients. The impression was that the changes did not exceed the improvements that are frequently observed in the natural history of stroke patients in neurological practice.

Discussion

The finding that the physiological defect is frequently greater than the lesion seen on CT scanning has been described by others and corroborated by all groups studying cerebral infarction. The main issue that this paper addresses are changes in the measured variables in the same individuals following therapy. Unless a change from a clearly normal to a clearly pathological state, or vice versa, occurs, the significance of differences between pre- and postoperative values has to be seen in light of long-term reproducibility studies. Nine repeat measurements in normal volunteers were performed in our laboratory after intervals of 2-10 months; they showed a mean difference of 12% (range 1-35%) for CMRO₂, 16% (3-43%) for CBF, and 17% (0-38%) for OER in temporal gray matter. The changes seen in our patient group are well within these ranges and cannot therefore be considered significant. However, the bilateral increase in OER in Patient 1, with a change from normal to pathological on the left side, indicates a hemodynamic deterioration. Further, the focally elevated OER in Patient 4 did not fall postoperatively, indicating a failure of hemodynamic normalization. The reproducibility of CBV values in normal subjects has not been assessed in a systematic way. The CBF/CBV ratio is commonly very low in established infarction where, in the absence of a raised OER, its value as an indicator of hemodynamic reserve is questionable.

From basic physiological considerations our failure to demonstrate increases in CBF was not surprising in those 3 patients in whom a preoperatively normal OER indicated a normal flow–metabolism relation, the reduced flow reflecting the low metabolic demands of the surviving tissue. Only the preoperative scan of Patient 4 showed evidence of "critical perfusion" in the symptomatic hemisphere, a low CBF/CBV ratio indicating exhausted hemodynamic reserve and a rise in OER compensating for inappropriately low flow. PET studies have shown in similar cases that extracranial–intracranial (EC–IC) bypass surgery via superficial temporal–MCA anastomosis can reverse such hemodynamically compromised states: CBF increases and OER falls so that normal coupling between flow and metabolism is reestablished. If in Patient 4 omental transposition had established an effective EC–IC blood supply one would have expected this pattern of changes in CBF and OER to occur. There are two possible explanations for the lack of hemodynamic effect of omental transposition in this case: Either blood flow through the transposed omentum was not sufficient to increase flow to the critically perfused area, or a brain–omentum anastomosis did not form, as observed in a minority of animals subjected to omental transposition.

The second mechanism by which omental transposition might have improved cerebral function, namely, a "direct stimulating effect on the brain tissue", would have been expected to result in a postoperative parallel
rise in CBF and CMRO$_2$. This was not found. Although a recent report has unexpectedly described substantial increases in CBF and CMRO$_2$ in a small number of patients after EC–IC bypass surgery, the claimed reversal of a state of metabolic depression has not been observed in other studies and needs confirmation before it can be accepted as an effect of therapy rather than variation in serial measurements.

A final point to consider is the resolution of the PET scanner compared with the size of the cerebral structures. The 15-mm width of the cortical strips used for analysis represents a compromise between the 16-mm FWHM resolution of the ECAT-II scanner and the actual 4- to 5-mm width of the cortical ribbon. The individual 15 x 7.5 mm rectangular blocks contain variable amounts of subarachnoid space and white matter. Therefore, the findings reported need to be assessed in light of the spatial accuracy of the recorded data, the timing of the postoperative measurements, and the representative nature of the 4 patients studied.

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