Pattern of collaterals, type of infarcts, and haemodynamic impairment in carotid artery occlusion

H Yamauchi, T Kudoh, K Sugimoto, M Takahashi, Y Kishibe, H Okazawa

Methods: We studied 42 patients with symptomatic ICA occlusion. The presence of Willismian, ophthalmic, or leptomeningeal collaterals was evaluated by conventional four vessel angiography. The infarcts on magnetic resonance imaging were categorised as territorial, border zone (external or internal), striatocapsular, lacunar, and other white matter infarcts. The value of OEF in the affected hemisphere was measured with positron emission tomography as an index of haemodynamic impairment.

Results: Using multivariate analysis, the presence of any ophthalmic or leptomeningeal collaterals and the absence of striatocapsular infarcts were significant and independent predictors of increased OEF.

Conclusions: In patients with symptomatic ICA occlusion, the supply of collateral flow, which is affected by the pattern of collateral pathways, and the metabolic demand of the brain, which is affected by the type of infarct, may be important factors determining the severity of haemodynamic impairment.

In patients with occlusion of the internal carotid artery (ICA), the collateral circulation plays a pivotal role in the pathophysiology of cerebral ischaemia. Insufficient collateral blood flow results in a marginally adequate blood supply relative to metabolic demand (misery perfusion), which may increase the risk of cerebral ischaemia. Patients with misery perfusion can be identified by increased oxygen extraction fraction (OEF), which is directly measured using positron emission tomography (PET). Increased OEF has been demonstrated to be a powerful and independent predictor of subsequent stroke in patients with symptomatic ICA occlusion. The need for a randomised clinical trial of extracranial to intracranial bypass for patients with ICA occlusion and increased OEF has been proposed, and such a study using PET has been started in the US. Therefore, knowledge of the critical determinants of collateral blood flow is essential for the management of patients with ICA occlusion.

Inadequate collateral blood flow distal to the ICA occlusion may be caused by poor function of collateral pathways. In ICA occlusion, the circle of Willis, including the anterior and posterior communicating arteries, may be the major collateral pathway that can rapidly compensate for decreased cerebral perfusion pressure. On the other hand, collateral pathways through the ophthalmic artery and leptomeningeal vessels may be recruited when collateral flow through the circle of Willis is inadequate. Thus, poor function of Willisian collaterals, which may lead to the recruitment of ophthalmic or leptomeningeal collaterals, may cause haemodynamic impairment. However, the association of the presence of ophthalmic or leptomeningeal collaterals with haemodynamic impairment is controversial.

The variability of the decrease in metabolic demand due to ischaemic lesions among patients may have a confounding effect on the relationship between patterns of collaterals and haemodynamic impairment. Primary minor ischaemic change or secondary metabolic change through deafferentation may decrease metabolism in the normal appearing cerebral cortex. The recruitment of ophthalmic or leptomeningeal collateral pathways, which may be associated with haemodynamic impairment in the brain with normal metabolism, may not be correlated with haemodynamic impairment when the metabolic needs of the brain are reduced due to ischaemic changes. However, few studies have evaluated the metabolic status, which may be related to the type of ischaemic lesions, with regard to the development of haemodynamic impairment in relation to poor function of collateral pathways in symptomatic ICA occlusion in the chronic stage.

In this study, we investigated the correlation of the severity of haemodynamic impairment assessed by OEF on PET with the pattern of collateral pathways and the type of infarcts in symptomatic ICA occlusion. Incomplete information regarding collaterals is obtained unless conventional angiography with multivessel injections is performed, and most previous studies suffered from this problem. Therefore, we selected patients in whom potential collateral routes were fully assessed on conventional, four vessel cerebral angiography. The purpose of this study was to determine whether the pattern of collateral pathways and the type of infarcts are independent predictors of OEF in symptomatic ICA occlusion.

Abbreviations: ACoA, anterior communicating artery; CBF, cerebral blood flow; CBV, cerebral blood volume; CMRO_2, cerebral metabolic rate of oxygen; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; OEF, oxygen extraction fraction; PcoA, posterior communicating artery; PET, positron emission tomography; ROI, region of interest; TCD, transcranial Doppler; TE, echo time; TIA, transient ischaemic attack; TR, repetition time.
METHODS

Patients

We studied 42 patients (34M, 8F) with symptomatic ICA occlusion, and a mean (SD) age of 62 (9) years. All subjects were selected from 45 consecutive patients with symptomatic atherothrombotic occlusion of the ICA who had been referred to our PET unit for evaluation of the haemodynamic effects of ICA occlusion for the first time between March 2000 and December 2002. Inclusion criteria were as follows: (a) occlusion of the ICA documented by conventional angiography; (b) transient ischaemic attacks (TIAs) or minor stroke with mild disability in the arterial distribution distal to the ICA occlusion; and (c) potential collateral routes fully assessed on conventional, four vessel cerebral angiography. Three patients who did not undergo conventional, four vessel cerebral angiography were excluded from the analyses.

Ten patients had had a transient ischaemic attack (TIA), and 32 had had a minor hemispheric stroke with mild disability. The interval between the latest ischaemic event and the evaluations by PET was 4 (9) months (range 10 days to 5 years). Recurrent symptoms prior to PET after angiographic demonstration of ICA occlusion were identified in three patients. In four of the patients with TIA, the magnetic resonance imaging (MRI) scan was normal. There were 38 patients who had infarcts in the hemisphere with symptomatic ICA occlusion, of whom 11 also had infarcts in the hemispheres contralateral to symptomatic ICA occlusion. Conventional angiography revealed, on the side contralateral to the symptomatic ICA occlusion, asymptomatic stenosis of more than 50% (including two occlusions) in the ICA in 13 cases. Asymptomatic stenosis of more than 50% in the vertebral artery was found in seven cases. None had stenosis of more than 50% in the middle cerebral artery (MCA) on the side ipsilateral to the symptomatic ICA occlusion. The interval between the angiography and PET study was 19 (15) days (range 1 to 64 days).

PET measurements

All the subjects underwent PET scans with a whole body PET scanner (Advance; General Electric Medical System, Milwaukee, WI, USA), which permits simultaneous acquisition of 35 image slices, with interslice spacing of 4.25 mm. Written informed consent was obtained from each subject under the guidance of the ethics committee of Shiga Medical Center. Performance tests showed the intrinsic resolution of the scanner to be 4.6 mm full width, half maximum in the superficial arterial system of the MCA and the ACA in the corona radiata or between the territory of the anterior cerebral artery and the MCA;17 posterior external border zone infarcts (wedge shaped, cortico-subcortical lesions in the posterior cortical border zone between the territory of the anterior cerebral artery and the MCA);17 posterior external border zone infarcts (wedge shaped, cortico-subcortical lesions in the posterior cortical border zone between the supply territory of the MCA and the posterior cerebral artery),18 cortical territorial infarcts (cortical lesions not assigned as external border zone infarcts); internal border zone infarcts (multiple or confluent white matter lesions located between the deep and superficial arterial system of the MCA in the corona radiata or between the superficial arterial system of the MCA and the ACA in the centrum semiovale);20 lacunar infarcts (single, well demarcated lesions with a diameter <20 mm in the basal ganglia, thalamus, internal capsule, corona radiata, or centrum semiovale); other white matter lesions (subcortical white matter lesions not assigned as internal border zone infarcts or lacunar infarcts); and striatocapsular infarcts (large subcortical lesions with a diameter >20 mm, in the territory of the lenticulostriate arteries, sometimes extending into the territory of the Heubner’s recurring artery or the anterior choroidal artery).21 Proton and FLAIR images were used to distinguish infarcts from dilated perivascular spaces. All scans were reviewed by a single investigator who was blinded to the clinical status of the patients, including other imaging data.

Data analysis

We analysed 10 tomographic planes from 46.25 to 84.5 mm above and parallel to the orbitomeatal line, which corresponded to the levels from the basil ganglia and thalamus to cerebral ischaemic lesions as hypointense lesions on T2 weighted MRI. They were classified as anterior external border zone infarcts (wedge shaped, cortico-subcortical lesions in the anterior cortical border zone between the territory of the anterior cerebral artery and the MCA);17 posterior external border zone infarcts (wedge shaped, cortico-subcortical lesions in the posterior cortical border zone between the supply territory of the MCA and the posterior cerebral artery);18 cortical territorial infarcts (cortical lesions not assigned as external border zone infarcts); internal border zone infarcts (multiple or confluent white matter lesions located between the deep and superficial arterial system of the MCA in the corona radiata or between the superficial arterial system of the MCA and the ACA in the centrum semiovale);20 lacunar infarcts (single, well demarcated lesions with a diameter <20 mm in the basal ganglia, thalamus, internal capsule, corona radiata, or centrum semiovale); other white matter lesions (subcortical white matter lesions not assigned as internal border zone infarcts or lacunar infarcts); and striatocapsular infarcts (large subcortical lesions with a diameter >20 mm, in the territory of the lenticulostriate arteries, sometimes extending into the territory of the Heubner’s recurring artery or the anterior choroidal artery).21 Proton and FLAIR images were used to distinguish infarcts from dilated perivascular spaces. All scans were reviewed by a single investigator who was blinded to the clinical status of the patients, including other imaging data.
the centrum semiovale. The region of interest (ROI) was placed on the CBF images. Each image was examined by placing a total of 10 to 12 circular ROIs 16 mm in diameter compactly over the grey matter of the outer cortex in each hemisphere. According to the atlas prepared by Kretschmann and Weinrich,\textsuperscript{21} the ROIs in all 10 images covered the distribution of the MCA as well as the watershed areas between the anterior cerebral artery and MCA and between the MCA and posterior cerebral artery.\textsuperscript{22} The same ROIs were transferred to the other images. The mean hemispheric values in each hemisphere were calculated as the average of the values of all circular ROIs. In 17 patients with infarction in the cerebral cortex, the circular ROIs that overlapped a well demarcated area of decreased CMRO2 corresponding to low intensity areas on T1 weighted MR images were excluded from the analysis. Previous studies have shown that the mean hemispheric value of OEF determined by this method is an independent predictor of stroke risk in patients with symptomatic major cerebral arterial occlusive disease.\textsuperscript{4,44}

Normal control values of the PET variables were obtained from seven normal volunteers (4M, 3F; mean (SD) age 47 (7) years) who had normal routine neurological examinations and MRI scans. The OEF value in the 14 hemispheres of the controls was 44.5 (3.8)%. Absolute hemispheric OEF values beyond the upper 95% limit defined in normal subjects (>52.9%) were considered to be increased OEF.

No subject showed a significant change in PaCO\textsubscript{2} during PET scanning. Data analysis was performed by a single investigator who was blinded to the clinical status of the patients, including other imaging data.

### Statistical analysis

We compared the values of PET variables or the frequency of the pattern of collateral pathways between each pair of groups by using Student’s \textit{t} test or Fisher’s exact test, as appropriate. Stepwise multiple linear regression analysis was used to test the independent predictive value of the pattern of collateral pathways and the type of infarcts with respect to the values of PET variables in the hemisphere with symptomatic ICA occlusion. Significance was established at \( p < 0.05 \).

### RESULTS

Table 1 shows the prevalence of collateral pathways on angiography. Increased OEF in the hemisphere with symptomatic ICA occlusion was not significantly correlated with the simple presence of any collateral pathway (table 2). However, the value of OEF was significantly higher in patients with ophthalmic or leptomeningeal collaterals than in patients without them (\( p < 0.05 \)) (tables 2 and 3). The value of CBF/CBV also showed a significant difference between the two groups.

#### Table 1: Prevalence of angiographic collateral pathways

<table>
<thead>
<tr>
<th>Circle of Willis</th>
<th>Other pathways</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Oph only</td>
<td>LM only</td>
<td>Both</td>
<td></td>
</tr>
<tr>
<td>ACoA only</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>PCoA only</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Both ACoA and PCoA</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No collateral flow</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td>42</td>
</tr>
</tbody>
</table>

Values are mean (SD). ACoA, anterior communicating artery; PCoA, posterior communicating artery; Oph, ophthalmic artery; LM, leptomeningeal anastomosis.

Of the 42 patients, 18 were categorised as having increased OEF values on the side of ICA occlusion compared with normal subjects. Of these, 17 (94%) had ophthalmic or leptomeningeal collaterals, while 17 of the 27 patients (63%) with ophthalmic or leptomeningeal collaterals showed increased OEF (Fisher’s exact test, \( p = 0.0004 \)). Specifically, OEF was increased in eight of the nine patients (88%) in whom the collateral supply to the MCA territory ipsilateral to the ICA occlusion was the ophthalmic artery only or leptomeningeal collaterals only (\( p = 0.0025 \)). Only one of the 15 patients (7%) without any ophthalmic or leptomeningeal collaterals (with Willisian collateral pathways only) had an increased OEF value. This patient had anterior communicating artery collaterals with severe contralateral ICA stenosis.

Table 4 shows the prevalence of cerebral ischaemic lesions on MRI. The presence of striatocapsular infarct, anterior external borderzone infarct, and contralateral lesions was significantly correlated with decreased CMRO2 in the hemisphere with symptomatic ICA occlusion (table 5).

#### Table 2: Angiographic collateral pathway and values of oxygen extraction fraction (%) in the hemisphere with symptomatic ICA occlusion

<table>
<thead>
<tr>
<th>Collateral circulation</th>
<th>Yes (n = 27)</th>
<th>No (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACoA</td>
<td>49.9 (8.7)</td>
<td>52.0 (6.0)</td>
</tr>
<tr>
<td>PCoA</td>
<td>51.4 (6.6)</td>
<td>50.8 (7.9)</td>
</tr>
<tr>
<td>ACoA or PCoA</td>
<td>50.4 (7.7)</td>
<td>53.1 (5.8)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>52.5 (9.2)</td>
<td>50.5 (6.0)</td>
</tr>
<tr>
<td>Leptomeningeal</td>
<td>51.6 (6.9)</td>
<td>50.8 (7.7)</td>
</tr>
<tr>
<td>Ophthalmic or leptomeningeal</td>
<td>53.2 (7.6)</td>
<td>47.3 (5.0)</td>
</tr>
</tbody>
</table>

Values are mean (SD). ACoA, anterior communicating artery; PCoA, posterior communicating artery. \( p < 0.05 \) versus corresponding value in the ‘‘No’’ group (Student’s \textit{t} test).

#### Table 3: Values of PET variables in patients with and without collaterals other than the circle of Willis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ophthalmic or leptomeningeal collaterals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 27)</td>
</tr>
<tr>
<td>CBF (ml/100g/min)</td>
<td>29.7 (7.36)</td>
</tr>
<tr>
<td>CBF/CBV (/min)</td>
<td>7.60 (2.30)*</td>
</tr>
<tr>
<td>CMRO\textsubscript{2} (ml/100g/min)</td>
<td>2.68 (0.55)</td>
</tr>
<tr>
<td>OEF (%)</td>
<td>53.2 (7.61)*</td>
</tr>
<tr>
<td>CBV (ml/100g)</td>
<td>4.05 (0.86)</td>
</tr>
</tbody>
</table>

Values are mean (SD). CBF, cerebral blood flow; CMRO\textsubscript{2}, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CBV, cerebral blood volume. \( * p < 0.05 \) versus corresponding value in the ‘‘No’’ group (Student’s \textit{t} test). Comparative values for CBF, CMRO\textsubscript{2}, OEF, CBV and CBV/CBV in normal volunteers were 44.6 (4.5), 3.43 (0.33), 44.5 (3.8), 3.98 (0.48), and 11.4 (1.8), respectively.
Using stepwise multiple linear regression analysis, the model that was produced included the presence of any ophthalmic or leptomeningeal collaterals and the presence of striatocapsular infarcts, and accounted for a significant proportion of the variance of the value of OEF (p<0.005, R² = 0.25). The other variables examined, including the patient age, the interval between the ischaemic event and PET, the time between PET and angiography, the presence of contralateral ischaemic lesions, and the presence of contralateral ICA stenosis of more than 50%, did not significantly contribute to the magnitude of the correlation. The presence of any ophthalmic or leptomeningeal collaterals and the absence of striatocapsular infarcts were significant and independent predictors of increased OEF (table 5). The patient in whom the collateral supply to the MCA territory ipsilateral to the ICA occlusion was leptomeningeal collateral only but whose OEF was normal had a striatocapsular infarct.

**DISCUSSION**

This study showed that in patients with symptomatic ICA occlusion, the supply of collateral flow (affected by the pattern of collateral pathways) and the metabolic demand of the brain (affected by the type of infarcts) are important factors determining the severity of haemodynamic impairment. The presence of any ophthalmic or leptomeningeal collaterals was associated with increased OEF, but this association was confounded by the presence of ischaemic lesions, particularly striatocapsular infarcts.

Several studies using various methods for the assessment of collateral patterns and haemodynamic status have shown that the presence of ophthalmic or leptomeningeal collaterals is associated with haemodynamic impairment, but not necessarily predictive. An earlier report by Powers et al., in which patients with ICA disease and normal CT scan were studied using angiography and PET demonstrated the close association of ophthalmic or leptomeningeal collaterals with abnormality of haemodynamic parameters. However, recent PET studies from the same laboratory showed that neither these nor other prospectively recorded angiographic findings identified patients with increased OEF (abnormal OEF asymmetry) in a larger number of patients with ICA occlusion. In those studies, patients were selected independently of the presence of neurological deficit or infarction, and more than 60% of the studied patients had cerebral infarction. From the results of the present study, we suggest that the characteristics of patients studied by Powers et al., lack of neurological deficit and normal CT scan might have led to the good correlation between ophthalmic or leptomeningeal collaterals and haemodynamic impairment, and that this correlation may not be generalised in all symptomatic patients with ICA occlusion and variable ischaemic lesions.

The recruitment of ophthalmic or leptomeningeal collateral pathways, which may be related to haemodynamic impairment at the time of symptoms or the acute stage of infarction, may no longer result in haemodynamic impairment when the metabolic needs of the tissue are reduced and are matched to even low collateral flow through these pathways during the time before the assessment of haemodynamic status. Such changes of haemodynamics and metabolism may be typical in patients with striatocapsular infarcts and ICA occlusion. Severe ischaemia in the distribution of the lenticulostriate arteries may result from ICA occlusion with aplasia of the A1 segment of the anterior cerebral artery due to a haemodynamic mechanism or MCA occlusion caused by an embolus from ICA disease, with little involvement of haemodynamic phenomena. In any case, in the acute stage there is less severe ischaemia in the superficial territory of the MCA because of collateral flow via leptomeningeal Anastomosis, if the occluded MCA is not recalculated. Striatocapsular infarcts may result in decreased CMRO₂ in the normal appearing cerebral cortex via two mechanisms: incomplete brain infarction and deafferentation. Selective neuronal loss of the cortex may occur because of prolonged ischaemia, depending on the inadequacy of collateral flow. Deafferentation through the tract between the basal ganglia or thalamus and cerebral cortex may cause functional deactivation of the cerebral cortex, then, the reduced metabolic demand is matched to collateral flow, even if the normal appearing cerebral cortex is perfused through leptomeningeal pathways.

This study indicated that evaluation of the collateral pathways may not be useful as an alternative parameter for predicting severe haemodynamic impairment for the clinical assessment of stroke risk in symptomatic ICA occlusion, which concurs with the findings of previous studies. The simple presence of ophthalmic and/or leptomeningeal collateral pathways is not an accurate indicator of increased OEF. In patients without infarcts, demonstration of the ophthalmic artery or leptomeningeal vessels as the sole collateral pathway to the MCA territory could be used as a sign of severe haemodynamic impairment. However, multivessel conventional angiography, which is impractical to perform for all subjects, is needed to demonstrate these findings. Advances in MR angiography (MRA) and transcranial Doppler (TCD) ultrasonography have made it possible to evaluate noninvasively some parts of collateral pathways. However, these noninvasive approaches can only assess the simple presence or absence of Willisian or ophthalmic collaterals and cannot assess the extent of collateral filling of each pathway or the contribution of leptomeningeal anastomosis. The lack of flow through either the circle of Willis or ophthalmic artery corresponds to the finding of sole leptomeningeal vessels as a collateral pathway to the MCA, and a few studies with MRA and/or TCD have shown that in symptomatic ICA occlusion, this finding is related to a severely deteriorated haemodynamic state and increased risk of future stroke. Therefore, in noninvasive methods, the finding of lack of flow through either the circle of Willis or

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO₂</td>
<td>Striatocapsular infarct (no = 0, yes = 1)</td>
<td>−0.576</td>
<td>0.153</td>
<td>−3.76</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td>Anterior external borderzone infarct (no = 0, yes = 1)</td>
<td>−0.994</td>
<td>0.266</td>
<td>−3.73</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td>Contralateral lesion (no = 0, yes = 1)</td>
<td>−0.286</td>
<td>0.139</td>
<td>−2.06</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>OEF</td>
<td>−0.005</td>
<td>0.007</td>
<td>−0.73</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Ophthalmic or leptomeningeal collaterals (no = 0, yes = 1)</td>
<td>5.983</td>
<td>2.089</td>
<td>2.864</td>
<td>0.0067</td>
</tr>
<tr>
<td></td>
<td>Striatocapsular infarct (no = 0, yes = 1)</td>
<td>−5.203</td>
<td>2.216</td>
<td>−2.348</td>
<td>0.0241</td>
</tr>
</tbody>
</table>

CMRO₂, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction.
ophthalmic artery could be used as a marker of severe haemodynamic impairment and high stroke risk, if infarcts are not present. However, the frequency of this finding without infarcts is probably too low to be clinically useful.\textsuperscript{10} The strength of our study is the assessment of all potential collateral routes by using conventional, four vessel cerebral angiography in all patients and the measurement of oxygen metabolism. However, our study is limited by the selected nature of our patients. Because of the PET referral bias and the angiography bias, patients with haemodynamic impairment may have been more likely to be included. All of the three patients who did not undergo conventional, four vessel cerebral angiography and were excluded from the analysis had normal OEF values. Therefore, the positive predictive value of the presence of ophthalmic or leptomeningeal collaterals for increased OEF might be overestimated. A delay between angiography and PET may cause errors in the correlation of collateral patterns and haemodynamic status. In all patients studied here, both conventional four vessel angiography and PET were performed within 64 days of each other in the chronic stage and the MCA was patent. Thus, it is not highly likely that major changes in collateral patterns or haemodynamic status occurred during the delay.\textsuperscript{10,14} In conclusion, in patients with symptomatic ICA occlusion, the recruitment of ophthalmic or leptomeningeal collaterals is associated with haemodynamic impairment. However, this association is confounded by the variability of the decrease of metabolic demand due to ischaemic lesions among patients. Therefore, the pattern of collaterals is not an accurate indicator of haemodynamic impairment. The concept of changes in the metabolic demand is helpful for understanding the development of haemodynamic impairment in relation to collateral circulation in symptomatic ICA occlusion in the chronic stage.

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