Regional cerebral blood flow (rCBF) and cerebral vasoreactivity in patients with retinal ischaemic symptoms

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SUMMARY Regional cerebral blood flow (rCBF) and cerebral vasoreactivity were assessed in 28 consecutive patients who presented with retinal ischaemic symptoms, without clinical or cerebral CT evidence of cerebral ischaemia. rCBF was measured using xenon-133 inhalation and single photon emission computed tomography before and 20 minutes after the intravenous administration of 1 g acetazolamide. The findings suggest that patients with retinal ischaemic symptoms alone due to carotid atherosclerosis often have a carotid lesion which is of haemodynamic significance with regard to cerebral perfusion and vasoreactivity. Furthermore, localized areas with reduced cerebral perfusion may also be present in some patients, without evidence of precerebral carotid occlusive disease.

Retinal ischaemic symptoms often suggest the presence of an embolic source in the ipsilateral carotid artery.¹⁻³ Although these symptoms may present without clinical evidence of cerebrovascular disease they predict an increased risk for cerebral TIAs and ischaemic stroke.⁴⁻⁵ The status of cerebral perfusion and intracranial haemodynamics in these patients is therefore of interest.

The purpose of this study was to assess regional cerebral blood flow (rCBF) and cerebral vasoreactivity in patients with retinal ischaemic symptoms who did not have a history of cerebral transient ischaemic attacks (TIA) or stroke, or cerebral CT evidence of cerebral ischemia.

Patients and methods

Twenty-eight consecutive patients who presented with amaurosis fugax or acute monocular visual field defects took part in the study. There were 17 males and 11 females, aged 23-78 years (mean 55). Patients were excluded if they had a history of cerebral TIAs or stroke, or evidence of infarction on cerebral CT examination. None of the patients suffered from migraine and they were not regularly taking medication of any kind.

All patients underwent a detailed neurological, neuro-ophthalmological and cardiological examination including ECG. Echocardiography was carried out in 24 patients and coagulation status was assessed in 22. Pulsed Doppler spectral analysis (SD 100 Vingmed Inc, Oslo, Norway) was carried out on the precerebral carotid arteries of all 28 patients. Details regarding this examination and the assessment of results have been reported previously.⁶ Angiography was carried out in 15 of the patients; conventional arteriography in 11 patients, intravenous digital subtraction angiography in two and intra-arterial digital subtraction angiography in two patients.

rCBF measurements

rCBF was measured using xenon-133 inhalation and single photon emission computed tomography (Tomomatic 64, Medimatic Inc, Copenhagen, Denmark). This method has been described in detail elsewhere.⁷ Using high sensitivity collimators three slices of the brain are studied simultaneously. The slices are 2 cm thick and routinely positioned 2, 6 and 10 cm above the orbitomeatal plane (OM). The resolution in the plane of each slice is 1.7 cm (full width, half maximum). The interval between the last retinal ischaemic episode and the rCBF measurements was from 1-90 days, mean 51 SD 1.3 days.

rCBF values were calculated in standardised regions of interest in slice 2 (OM + 6 cm) corresponding approximately to the perfusion territory of the anterior cerebral (ACA), the anterior (aMCA) and posterior branches (pMCA) of the middle (MCA) and of the posterior cerebral artery (PCA).⁷ This was obtained by using a software package for automatic calculation of flow values in regions of interest.

Each rCBF study consisted of two measurements. Follow-

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ing a baseline examination, 1 g acetazolamide was given intravenously, and the rCBF measurements were repeated approximately 20 minutes later. End-expiratory pCO₂ was measured by an infra-red capnograph (Datex CD 102 Normocap, Datex Instrumentation Corp, Helsinki, Finland). Correction of rCBF values for PCO₂ was not carried out.

rCBF values in patients were compared to those in 25 healthy control subjects, 12 of whom had been given acetazolamide.⁷

Statistical methods

The results are presented as mean, SEM (standard error of the mean) or mean with a 95% confidence interval. The Student procedure was used for calculating the confidence intervals.⁸ One-tailed statistical tests were found to be the most appropriate. Differences or changes were considered statistically significant if the p value was less or equal to a level of 5%. For differences in the same patient the Student test for paired comparison was used. The two sample Student test was used for comparison between groups.

In individual patients reduced baseline rCBF or a reduced response to acetazolamide was considered to be present if side-to-side asymmetry in a region of interest exceeded the 95% fractile for the controls.

Results

Clinical findings

Eighteen (64%) patients had experienced amaurosis fugax and 10 (36%) had suffered permanent visual disturbances. Fourteen patients had symptoms on the left side and 14 on the right. The amaurosis fugax attacks had lasted for a few minutes in the majority of patients, and in all less than one hour. In all 18 patients with amaurosis fugax the neuro-ophthalmological examination was normal.

Neuro-ophthalmological examination in the 10 patients with permanent visual disturbances showed that three had an occlusion of the central retinal artery on the symptomatic side with reduced visual acuity. The remaining seven patients had branch occlusion of this artery with normal or only slightly reduced visual acuity and permanent sector-shaped visual field defects. Neurological examination was otherwise normal in all patients.

The cardiological assessment including echocardiography (n = 24) was normal in all patients, and assessment of coagulation status, carried out in 22 patients, was normal in 20. One patient had protein-S insufficiency and another decreased factor VII with a slightly increased bleeding time.

Doppler and angiographic findings

The Doppler and angiographic examinations detected an atherosclerotic lesion in the precerebral internal carotid artery (ICA) ipsilateral to symptoms in 11 (39%) of the 28 patients (Patient group A). These lesions reduced the diameter of the ICA by < 50% in

Kerty, Russell, Bakke, Nyberg-Hansen, Rootwelt two, > 75% in six and in three patients the ICA was occluded. In the ICA contralateral to symptoms, four patients had an atherosclerotic lesion which reduced the diameter of the vessel by < 25%. Findings in the vertebral arteries were normal.

In 17 (61%) patients the Doppler (n = 17) and angiographic (n = 4) examinations showed normal findings in the carotid and vertebral arteries on both the symptomatic and the contralateral side. (Patient group B)

Correlation of clinical and Doppler/angiographic findings

The 11 patients with carotid occlusive disease ipsilateral to symptoms (Group A), consisted of seven men and four women, aged 44–77 years, mean 63, SEM 2.7 years. Seven of these patients had experienced amaurosis fugax, one had central retinal artery occlusion and three had branch occlusion of this artery.

The remaining 17 patients who did not have evidence of carotid occlusive disease (Group B), were ten men and seven women, aged 23–73 years, mean 50, SEM 3.7 years. Eleven of these patients had experienced amaurosis fugax, two central retinal artery occlusion and four branch occlusion of this artery.

rCBF findings

Group A: Patients with carotid occlusive disease (n = 11). Mean baseline rCBF values in the 11 patients with carotid occlusive disease ipsilateral to symptoms were significantly (p < 0.01) lower in all regions of interest on the symptomatic compared with the contralateral side (table 1, fig 1). Values in all regions of interest were also significantly lower on both the symptomatic (p < 0.005) and the contralateral (p < 0.05) side when compared with those in the control group (95% confidence interval). Mean pCO₂ values in these patients and the controls were not significantly different (table 1).

The mean response to acetazolamide in these patients was significantly (p < 0.01) reduced in all regions of interest on the symptomatic compared with the contralateral side (table 1, fig 1). When compared with control values (95% confidence interval) the acetazolamide response was significantly (p < 0.05) reduced in all regions of interest on the symptomatic side and in the ACA perfusion territory on the contralateral side (table 1, fig 1). The side-to-side asymmetry of the acetazolamide response was also significantly (p < 0.05) greater in the ACA and aMCA perfusion territories compared with the controls (table 2, fig 2). This was not the case for the pMCA and PCA territories. There was no significant difference with regard to the decrease in pCO₂ after acetazolamide administration in these patients and the

Table 1 Baseline rCBF values and the acetazolamide response (mean, SEM) in the perfusion territory of the anterior cerebral (ACA), the anterior (aMCA) and posterior (pMCA) branches of the middle cerebral, and the posterior cerebral artery (PCA) in 11 patients with retinal ischaemic symptoms alone who had ipsilateral precerebral carotid occlusive disease (Group A)

Perfusion territory	rCBF values (ml/100 g/min)					
	Baseline values			Acetazolamide response		
	Symptom side	Contralat side	Control values (n = 25)	Symptom side	Contralat side	Control values (n = 12)
ACA	48.7, 2.4	51.0, 2.5	56.0, 1.3	7.4, 2.2	9.5, 2.0	13.5, 1.2
aMCA	55.1, 2.7	58.0, 3.3	65.9, 1.5	8.7, 2.1	13.5, 2.2	15.6, 1.6
pMCA	50.8, 2.5	53.3, 2.6	58.1, 1.3	9.0, 1.6	12.6, 2.1	15.0, 1.4
PCA	48.6, 2.2	51.4, 2.2	54.5, 1.1	10.9, 1.9	11.7, 2.4	15.0, 2.1
pCO ₂ (mmHg)	39.9, 1.5		40.9, 1.1	36.2, 1.3		37.8, 1.0

controls (patients: 3.7, SEM 1.2 mmHg, controls 3.1, SEM 1.2 mmHg).

Assessment of the results in each of the patients in this group showed the following in the MCA and/or ACA territories ipsilateral to their symptoms and carotid occlusive disease: three patients had normal baseline rCBF and a reduced acetazolamide response; two reduced baseline rCBF and a normal acetazolamide response and in three both baseline values and the acetazolamide response were reduced. **Group B: Patients without carotid occlusive disease (n = 17).** Mean baseline rCBF values for the 17 patients without evidence of carotid occlusive disease did not differ significantly on the symptomatic compared with the contralateral side (table 3). However, flow values were significantly ($p < 0.05$) lower in all regions of interest on both sides when compared with

the 95% confidence interval for the control group. Mean pCO₂ values and the decrease in pCO₂ after acetazolamide administration (patients: 2.8, SEM 1.2 mmHg, controls: 3.1, SEM 1.2 mmHg) were not significantly different in these patients and the controls (table 3). The response to acetazolamide was normal in all regions of interest in these patients. The side-to-side asymmetry of the acetazolamide response did not differ from the controls in any region of interest (table 2).

Four (24%) of the 17 patients in this group had regions of interest with reduced baseline rCBF on the symptomatic compared with the contralateral side. In two patients this reduction was in the ACA perfusion territory, in one both the ACA and aMCA and in one patient in the aMCA and pMCA perfusion territories. The response to acetazolamide was normal in all

Fig 1 Baseline rCBF values (left) and the acetazolamide response (right) in the anterior cerebral artery perfusion territory (ACA) of 11 patients with ipsilateral carotid occlusive disease who had retinal ischaemic symptoms alone. Flow values are given as mean with a 95% confidence interval of the patients two sides. The grey area shows mean and 95% confidence interval for controls. p values compare the symptomatic and the contralateral side.

Fig 2 Side-to-side asymmetry of the acetazolamide response in the perfusion territory of the anterior branches of the middle cerebral artery (aMCA) in 11 patients with (Group A) and in 17 patients without (Group B) carotid occlusive disease. Flow values are given as mean with a 95% confidence interval. The grey area shows mean and 95% confidence interval for controls.

regions of interest in these patients. Cerebral magnetic resonance imaging (MRI) was carried out in these four patients, and in one showed small high intensity areas on T₂ weighted images consistent with ischaemic lesions which had the same location as the reduced rCBF. This patient was a 56 year old woman who presented with left-sided branch occlusion of the central retinal artery. In the remaining three patients the MRI findings were normal.

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Table 2 Side-to-side asymmetry of the acetazolamide response (mean, SEM) in group A and B patients. Perfusion territories as in table 1. Statistical comparison with control values.

Perfusion territory	rCBF values (ml/100 g/min)		
	Asymmetry of the acetazolamide response		
	Group A (n = 11)	Group B (n = 17)	Controls (n = 12)
ACA	2.2, 1.0**	0.2, 0.8*	0.3, 0.7
aMCA	4.7, 2.1**	0.5, 1.1*	0.7, 0.8
pMCA	3.6, 2.1*	1.5, 1.0*	1.1, 0.6
PCA	0.8, 1.1*	-0.4, 1.0*	-0.6, 0.7

*not significant, **p < 0.005.

Discussion

All of the 28 patients in this study presented with retinal ischaemic symptoms alone, and did not have clinical or cerebral CT evidence of cerebral ischaemia or infarction. Angiography and Doppler examinations revealed, however, that 11 (39%) had an atherosclerotic lesion in the precerebral ICA ipsilateral to their visual symptoms (Group A). In these patients mean baseline rCBF values and the response to acetazolamide were significantly lower in the hemisphere ipsilateral to symptoms compared with the contralateral side. The side-to-side asymmetry of the response was significantly greater than in controls. Baseline rCBF values in all regions of interest contralateral to symptoms and the response to acetazolamide in the ACA perfusion territory on that side were also significantly lower than control values.

In the 17 patients with no evidence of precerebral carotid occlusive disease (Group B), baseline rCBF values in all regions of interest on both the symptomatic and the contralateral side were significantly lower than those in the control group. However, values for the two sides did not differ significantly, and the acetazolamide response in all regions of interest as

Table 3 Baseline rCBF values and the acetazolamide response (mean, SEM) in the same perfusion territories as in table 1, in 17 patients with retinal ischaemic symptoms alone who had normal precerebral carotid arteries (Group B). Perfusion territories as in table 1.

Perfusion territory	rCBF values (ml/100 g/min)			Acetazolamide response		
	Baseline values					
	Symptom side	Contralateral side	Control values (n = 25)	Symptom side	Contralateral side	Control values (n = 12)
ACA	49.8, 2.3	49.4, 2.3	56.0, 1.3	13.4, 0.8	13.6, 1.0	13.5, 1.2
aMCA	56.8, 3.0	57.8, 3.2	65.9, 1.5	15.8, 1.1	16.4, 1.3	15.6, 1.6
pMCA	53.4, 2.8	53.5, 2.6	58.1, 1.3	14.2, 1.1	15.6, 1.0	15.0, 1.4
PCA	51.4, 2.4	50.3, 2.2	54.4, 1.1	14.1, 1.3	13.6, 2.4	15.0, 2.1
pCO ₂ (mmHg)	40.1, 1.2		40.9, 1.1	36.3, 1.2		37.8, 1.0

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well as the asymmetry of the response were within normal limits.

Before discussing the results of this study in detail we would like to stress that caution should be used when interpreting results based on a comparison between absolute rCBF values in patients with those in a control group. Findings may, at least partly be due to differences in pCO₂ levels and to age. Several studies have demonstrated a decrease in CBF with increasing age, especially after the age of 60 years.^{9,10} In addition the individual response to acetazolamide may show considerable variations. The assessment of side-to-side asymmetry in baseline rCBF values and the response to acetazolamide makes interpretation easier. Changes in baseline flow and in flow pattern after acetazolamide are then independent of random changes in flow and of pCO₂ values.

The rCBF findings in group A suggest that these patients often have impaired cerebral haemodynamics even though they have not experienced symptoms of cerebral ischaemia. The clinical implications of these findings are at present unclear but may partly explain the increased risk for cerebral TIAs and stroke.^{4,5} In addition information regarding the cerebral haemodynamic significance of ICA lesions may indirectly be of help in predicting the risk of developing chronic ischaemic retinopathy.^{11,12}

Retinal ischaemic symptoms in patients with ipsilateral carotid occlusive disease are most often due to emboli which have their origin in atheromatous ICA lesions.¹³ Four of the 11 patients in the present study with carotid occlusive disease ipsilateral to symptoms (Group A) had clinical evidence on ophthalmological examination suggesting emboli. One had central retinal artery occlusion and three patients had branch occlusion of this artery.

The occurrence of retinal ischaemic symptoms alone, without cerebral TIAs, is difficult to explain if the source of the emboli is an ipsilateral carotid lesion. It has been suggested, however, that an embolus in this situation may be of insufficient size or the arterial branches involved may be too small to cause clinical evidence of cerebral ischaemia.¹⁴

Reduced retinal perfusion pressure may have played a role in the development of symptoms in at least some of our patients with carotid occlusive disease (Group A). The rCBF examinations showed that cerebral vasoreactivity was reduced ipsilateral to the carotid lesion and it would therefore seem reasonable to assume that these lesions may also be of haemodynamic significance with regard to retinal blood flow. Although several studies have provided evidence which suggests that the eye and the brain have a similar autoregulation,¹⁵ it is possible that the retina is more sensitive to changes in perfusion pressure.¹⁶ Furthermore, the ICA was occluded in three of the 11 patients in group A who presented with amaurosis fugax. This may suggest that their visual symptoms were due to

haemodynamic changes rather than emboli. However, the proximal and distal parts of the ICA occlusion may be a potential source of emboli in some patients in whom the emboli may reach the eye via the external carotid artery or from the stump of the occluded ICA.¹⁷

Baseline rCBF values were lower and the response to acetazolamide in the ACA territory was reduced in the cerebral hemisphere *contralateral* to the retinal symptoms in group A patients compared with controls. However, the patients with carotid occlusive disease were older (63, SEM 2.7 years) compared with controls (41, SEM 2.6 years) which may at least partly be responsible for the results. An alternative explanation is that contralateral cerebral vessels contributed to perfusion in the cerebral hemisphere ipsilateral to the carotid lesion.¹⁸ Conventional arteriography was carried out on all of these patients without the detection of atherosclerotic lesions in the intracranial arteries, except in two patients who had a slight stenosis of the carotid siphon contralateral to symptoms.

The patients in group B were examined by Doppler and IVDSA alone and we do not therefore have information regarding possible atherosclerotic lesions in the intracranial arteries. Four of these 17 patients had reduced baseline rCBF values in the MCA and/or ACA territories ipsilateral to symptoms, compared with the contralateral side. The response to acetazolamide was, however, symmetrical and within normal limits in these regions. Cerebral CT examination was normal in all patients. One possible explanation for the low-flow areas in these four patients is ischaemic damage with selective neuronal loss, which has been termed incomplete infarction.^{19,20}

Mean baseline rCBF values for the 17 patients who did not have evidence of carotid occlusive disease were reduced on both the symptomatic and contralateral sides compared to controls. The response to acetazolamide was within normal limits on both sides in all regions. Patients in this group were also older (50, SEM 3.7 years) than the controls (41, SEM 2.6 years) which again may at least partly explain the rCBF findings. Although these results merit extreme caution in their interpretation, they suggest the presence of unilateral or bilateral areas with reduced rCBF in at least some patients with normal precerebral carotid arteries who present with retinal ischaemic symptoms alone.

A few authors have previously described localised areas with reduced cerebral perfusion in patients presenting with amaurosis fugax alone, and with no history of cerebral TIAs. Rees *et al*²¹ found cerebral low flow areas ipsilateral to amaurosis fugax attacks in one patient who had normal conventional arteriographic findings. A further four cases were reported by Harrison and Marshall.²² In the latter study information regarding possible atherosclerotic changes in the

precerebral carotid arteries was not provided. Neither of these two studies included cerebral CT examination. Vorstrup *et al*²³ described three patients with a normal cerebral CT examination and low flow areas in the MCA perfusion territory ipsilateral to their amaurosis fugax attacks. Two of these patients had angiographically demonstrated ipsilateral ICA stenosis and one severe stenosis of the innominate artery with subclavian steal.

There is some evidence suggesting that there may be an increased incidence of silent cerebral infarctions and cerebral atrophy, in patients who have experienced amaurosis fugax without cerebral symptoms. Grigg *et al*²⁴ reported cerebral CT findings in 70 patients who presented with amaurosis fugax alone. Forty-three per cent of these patients had findings consistent with infarction, and 25% of localised or generalised cortical or central atrophy when the CT examinations were assessed independently. In 29 cerebral hemispheres without evidence of ipsilateral precerebral carotid occlusive disease assessed by Duplex scanning, they found that 17% had cerebral CT evidence of infarction and 14% localised or generalised cortical or central atrophy.

Confirmation of areas with reduced cerebral perfusion in patients with retinal ischaemic symptoms alone, who do not have evidence of carotid occlusive disease, may suggest the presence of an embolic source other than the carotid artery. This is especially true if the findings are present in both cerebral hemispheres. Six (35%) of the 17 patients in the present study without precerebral carotid occlusive disease (Group B), had clinical evidence suggesting emboli on ophthalmological examination. One possibility is that these patients have a cardiac source for embolism. Necropsy studies had shown that patients with embolic stroke often have a potential cardiac source.²⁵ However, in clinical studies it has proved to be difficult to diagnose cardiogenic emboli with certainty.²⁶ Cardiological evaluation in the present study did not reveal abnormalities. Another possibility is that these patients may have a coagulation defect or haematological disease, which may provoke thrombosis or the formation of emboli.^{27,28}

In conclusion, the results of this study suggest that patients with retinal ischaemic symptoms alone due to carotid atherosclerosis often have a carotid lesion which is of haemodynamic significance with regard to cerebral perfusion. Furthermore, localised areas with reduced cerebral blood flow may also be present in at least some patients who do not have precerebral carotid occlusive disease.

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