Venous Stasis Retinopathy in Symptomatic Carotid Artery Occlusion
Prevalence, Cause, and Outcome

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Background and Purpose—Chronic ocular ischemia is a rare form of ischemia of the eye in patients with carotid artery occlusion (CAO). The early and often asymptomatic stage of chronic ocular ischemia is referred to as venous stasis retinopathy (VSR). The aim of this study was to gain insight into the prevalence, cause, and outcome of VSR in patients with symptomatic CAO.

Methods—In 110 patients with symptomatic CAO, we prospectively investigated the frequency of VSR, the association between the presence of VSR and impaired cerebral blood flow, and the proportion of patients who developed clinically manifest chronic ocular ischemia with ischemia of the anterior eye segment or blindness.

Results—At study entry, VSR was found in 32 patients (29%; 95% CI, 21 to 38), particularly in those with symptoms classically associated with a hemodynamic cause, such as limb shaking (relative risk, 2.4; 95% CI, 1.0 to 5.9). Patients with VSR had lower pulsatility indexes in the ophthalmic artery in case of reversed flow, lower cerebral CO2 reactivity, and lower cerebropetal blood flow than patients without VSR. On follow-up (mean, 29 months), clinically manifest chronic ocular ischemia developed in 4 patients (annual rate, 1.5%; 95% CI, 0.4 to 3.8); it tended to occur more often in patients in whom VSR was present at study entry (relative risk, 7.3; 95% CI, 0.8 to 68).

Conclusions—One third of patients with symptomatic CAO has VSR on ophthalmoscopy. VSR is associated with an impaired flow state of the brain. Development of clinically manifest chronic ocular ischemia is rare. (Stroke. 2002;33:695-701.)

Key Words: carotid artery occlusion ■ chronic ocular ischemia ■ venous stasis retinopathy

Ischemic symptoms of the eye are common in patients with occlusive disease of the carotid artery. Most often, these consist of sudden (transient) monocular blindness supposedly caused by entrapment of emboli in the retinal arterial tree. Less common is the chronic form of ocular ischemia; reported frequencies range between 5% and 21% in series of patients with carotid artery stenosis or occlusion.1–4 The chronic form of ocular ischemia is explained by a chronic low perfusion pressure that causes diffuse retinal ischemia, reflected by an increase in circulation time, which initially results in dilatation, irregularity of caliber, and tortuosity of retinal veins.5 Ophthalmoscopy may also show midperipheral microaneurysms, small dot-and-blot intraretinal hemorrhages, or nerve fiber layer splinter hemorrhages.1,5 This early stage of chronic ocular ischemia, often referred to as venous stasis retinopathy (VSR), may remain completely asymptomatic. Progression of the disease may lead to the clinical syndrome of chronic ocular ischemia with progressive visual loss through cotton wool spots; edema of the optic disc and macula; neovascularization of the optic disc, retina, and iris; and finally an uveitislike syndrome and neovascular glaucoma. This may be accompanied by pain around the eye.

It is unclear why only some patients with carotid occlusive disease develop chronic ocular ischemia. In patients with carotid artery occlusive disease, collateral blood flow via branches of the external carotid artery may result in reversal of flow in the ophthalmic artery (OphthA) to sustain cerebral blood flow, most likely at the expense of blood flow to the eye. If this “steal” phenomenon plays a role, one would expect VSR to develop more often in patients with a low flow state of the brain than in patients without compromised cerebral blood flow.

To gain insight into the prevalence, cause, and outcome of VSR in patients with transient or moderately disabling symptoms of retinal or cerebral ischemia associated with carotid artery occlusion (CAO), we investigated (1) the...
frequency of VSR at ophthalmoscopy, (2) the association between VSR and an impaired flow status of the brain, and (3) the rate of development over time of the clinical syndrome of chronic ocular ischemia with ischemic changes of the anterior segment of the eye.

**Patients and Methods**

**Patients**

Consecutive patients with an angiographically proven CAO and recent symptoms (<6 months) of sudden transient or at most moderately disabling (Rankin grade 3 or better) retinal or cerebral ischemia ipsilateral to the CAO were prospectively included between September 1995 and July 1998. Patients were excluded if they had suffered a severely disabling stroke (Rankin grade 4 or 5) or if the CAO was caused by dissection. One of 2 investigators (C.J.M.K., L.J.K.) interviewed patients in detail about symptoms and vascular risk factors as listed in Table 1. As clinical symptoms of an impaired flow status of the brain or eye, we regarded transient monocular blindness triggered by bright light; limb shaking; precipitation of symptoms by rising, exercise, transition from a cold to a warm environment, or documented low blood pressure; and ongoing symptoms after demonstration of CAO.

We performed the following investigations to assess blood flow to the brain: (1) reversal of blood flow in the OphthA assessed by transcranial Doppler (TCD) ultrasonography, (2) velocity and pulsatility index in the OphthA in case of reversed flow assessed by TCD, (3) TCD CO2 reactivity, and (4) magnetic resonance angiography quantitative flow measurements in the middle cerebral artery (MCA) and the cerebropetal arteries. All patients underwent a standardized ophthalmologic examination.

Patients with severe stenosis of the contralateral internal carotid artery (ICA) were offered endarterectomy, and those with recurrent symptoms of presumed hemodynamic origin were offered high-flow extracranial/intracranial (EC/IC) bypass surgery according to the method of Tulleken et al. A possible hemodynamic origin of symptoms was inferred from the presence of hemodynamic symptoms as defined above, the presence of a border zone infarct, a low CO2 reactivity, or a combination of these. Signs of VSR on the side of the CAO were never the primary indication for either type of operation. The indication for ophthalmologic treatment of the VSR was left to the judgment of the individual ophthalmologist. In all patients, antithrombotic medication was prescribed (low-dose aspirin in most patients), and vascular risk factors were rigorously treated.

All patients were followed up in the outpatient clinic until November 1, 1999. They were specifically questioned about any deterioration of vision or pain around the eye. Patients with retinal signs of VSR at the time of inclusion in the study underwent...
ophthalmoscopy 6 and 12 months after the initial examination. In patients without such signs at study entry, ophthalmoscopy was not repeated unless they developed symptoms of the eye.

The Institutional Review Board of the University Medical Center Utrecht approved the study protocol.

**Ophthalmoscopy**

All patients underwent a standardized ophthalmologic investigation, including measurement of visual acuity and intraocular pressure, slit lamp examination, and fundoscopy in mydriasis with emphasis on the presence of early retinal signs of VSR according to the definitions of Kearns and Hollenhorst! and Carter. Patients were diagnosed with VSR if they had ≥1 of the following early retinal signs ipsilateral to the symptomatic CAO: midperipheral microaneurysms; multiple small dot-and-blot intraretinal hemorrhages or nerve fiber layer splinter hemorrhages; or dilatation, irregularity of caliber, or tortuosity of veins for which no other cause was apparent. Signs of more advanced chronic ocular ischemia were neovascularization of the optic disc, retina, or iris (rubeosis iridis), with or without uveitis, or neovascular glaucoma in the absence of any other cause. Fluo-}

**TABLE 2. Investigations in Patients With Symptomatic CAO With or Without VSR**

<table>
<thead>
<tr>
<th></th>
<th>VSR, Mean±SD*</th>
<th>No (n=78)</th>
<th>Mean Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reversed flow in the OphthA† n (%)</td>
<td>29/31 (94)</td>
<td>47/56 (84)</td>
<td>2.8 (0.5 to 28)</td>
</tr>
<tr>
<td>BFV of the OphthA, cm/s‡</td>
<td>41±16</td>
<td>35±19</td>
<td>5 (−3 to 14)</td>
</tr>
<tr>
<td>Pulsatility index of the OphthA‡</td>
<td>0.82±0.24</td>
<td>0.97±0.37</td>
<td>0.16 (0.02 to 0.30)</td>
</tr>
<tr>
<td>CO₂ reactivity, %</td>
<td>8±15</td>
<td>20±25</td>
<td>12 (2 to 21)</td>
</tr>
<tr>
<td>MRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow in MCA ipsilateral to CAO, mL/min</td>
<td>64±22</td>
<td>75±28</td>
<td>11 (−1 to 21)</td>
</tr>
<tr>
<td>Total cerebropetal flow, mL/min§</td>
<td>375±108</td>
<td>445±131</td>
<td>70 (14 to 125)</td>
</tr>
</tbody>
</table>

MRA indicates magnetic resonance angiography.

*Unless otherwise indicated.
†Blood flow direction in the OphthA could not be reliably determined in 23 patients; data are expressed as n (%) and compared by means of the odds ratio with exact 95% CI.
‡In patients with reversed direction of blood flow in the OphthA.
§Flow in the basilar artery and contralateral ICA.

**Data Analysis**

The proportion of patients with VSR was calculated. Subsequently, characteristics listed in Table 1 and ancillary measurements listed in Table 2 were compared between patients with and without VSR. For dichotomous variables, proportions were compared between patients with and without VSR in terms of relative risk (RR) with corresponding 95% CIs. When for any of the dichotomous variables the expected value in 1 of the cells of the 2×2 table was ≤5, we calculated odds ratios with exact 95% CIs. For continuous variables, we determined mean differences and corresponding 95% CIs on the basis of Student’s t test. Subsequently, we calculated the proportions of patients who developed advanced chronic ocular ischemia with anterior segment changes during follow-up in the group of patients with and without VSR at baseline, as well as their RR of developing the syndrome of chronic ocular ischemia. Finally, we calculated the annual rate of development of advanced chronic ocular ischemia with ischemic changes of the anterior segment. All ophthalmologic data refer to the eye ipsilateral to the symptomatic CAO.

**Results**

Of the 112 eligible patients, 1 patient was excluded because severe cataract of the eye ipsilateral to the CAO precluded ophthalmoscopy. In another patient, ophthalmoscopy was erroneously omitted. Of the remaining 110 patients, 97 had an
extracranial occlusion of the ICA, and 13 patients had an occlusion of the common carotid artery (none of these showed an open ICA on the angiogram). Twenty-seven patients had had symptoms of transient cerebral ischemia, and 64 had had a mildly or moderately disabling stroke (Rankin grade 3 or better). Of the 91 patients with hemispheric symptoms, 23 also had ocular symptoms: transient monocular blindness in 22 and retinal infarction in 1. Nineteen patients had had symptoms only (transient monocular blindness in 17 and retinal infarction in 2). Of 27 patients with a severe stenosis of the contralateral carotid artery, 20 underwent endarterectomy, 6 patients chose not to be operated on, and the operation was not possible in 1 patient because the stenosis continued to the level of the carotid siphon. Sixteen patients underwent high-flow EC/IC bypass surgery.

Ophthalmoscopy showed VSR ipsilateral to the symptomatic CAO in 32 of 110 patients (29%; 95% CI, 21 to 38). Midperipheral hemorrhages were found in all 32: 1 to 5 per quadrant in 22 patients, 6 to 10 per quadrant in 7, and >10 per quadrant in 3. Dilatation of veins was observed in 16 of the 32 patients, and irregular or tortuous veins were seen in 6. Only 3 patients had microaneurysms, and 2 had cotton wool spots. Neovascularization of the posterior segment of the eye was not observed in any of the 32 patients. On average, visual acuity and intraocular pressure did not differ between the 32 patients with VSR (mean ± SD visual acuity, 0.8 ± 0.3; mean intraocular pressure, 14 ± 4 mm Hg) and the 78 without VSR (mean visual acuity, 0.8 ± 0.2; mean intraocular pressure, 15 ± 3 mm Hg; mean difference in visual acuity, 0.0; 95% CI, −0.1 to 0.1; intraocular pressure, 1 mm Hg; 95% CI, −1 to 2). In 1 of the 32 patients with VSR, focal laser therapy was started immediately after the first ophthalmoscopic examination because of large midperipheral avascular areas (Figure 1). Of the 32 patients with VSR, 6 underwent endarterectomy because of ≥70% stenosis of the contralateral carotid artery, and another 6 were treated with high-flow EC/IC bypass surgery.

Characteristics of patients with and without VSR at study entry are summarized in Table 1. Patients with VSR more often had symptoms suggesting a hemodynamic cause than those without VSR (RR, 2.4; 95% CI, 1.0 to 5.9). We found no differences in any of the other patient characteristics listed in Table 1, except for a higher proportion of patients with hypertension in the group with than in those without VSR (RR, 1.4; 95% CI, 1.0 to 2.0). Transient monocular blindness or retinal infarction had not occurred more frequently in patients with VSR than in those without (RR, 1.1; 95% CI, 0.7 to 1.8), and retinal claudication was a rare symptom (found in only 3 of the 110 patients).

Table 2 compares TCD and magnetic resonance angiography findings in patients with and without VSR. We found reversed flow in the OphthA in a large proportion of patients, both in the group with (94%) and in the group without (84%) VSR. In patients with reversed flow, BFV in the OphthA was similar in patients with and without VSR, but the pulsatility index was lower in patients with than in those without VSR. Patients with VSR had a lower CO₂ reactivity than those without such signs (mean difference, 12%; 95% CI, 2 to 21); they also had a lower total cerebroretinal blood flow than those without retinal abnormalities (mean difference, 70 mL/min; 95% CI, 14 to 125). In addition, MCA flow ipsilateral to the occluded carotid artery was lower in patients with than in those without VSR, but the difference did just not reach significance (Table 2).

The average time between the last symptoms a patient had and ophthalmoscopy, TCD, and MR investigation did not differ between patients with and without VSR (78 ± 68 and 72 ± 54 days; mean difference, 12 days; 95% CI, 19 to 30).

During follow-up for an average period of 29 months (SD, 12; range, 2 to 50 months), 3 of the 32 patients (9%; 95% CI, 2 to 25; average follow-up, 30 months; SD 14) with VSR at study entry developed the syndrome of chronic ocular ischemia with ischemic changes of the anterior segment. At study entry, 1 of these 3 patients had had episodes of transient monocular blindness (without retinal claudication), whereas the other 2 patients had had no eye symptoms. All 3 patients underwent panretinal laser therapy, and 1 had endarterectomy of a 90% stenosis of the contralateral carotid artery. Vision of the affected eye could be preserved in only 1 of the 3 patients. Only 1 of the 78 patients (1%; 95% CI, 0 to 7; average follow-up, 28 months; SD, 11 months) without VSR at study entry developed ischemic changes of the anterior segment (RR, 7.3; 95% CI, 0.8 to 68). This patient had complained of episodes of transient monocular blindness triggered by looking into bright light. A single hemorrhage and a single microaneurysm with dilated veins (Figure 2A) found at ophthalmoscopic examination at study entry had been diagnosed as a mild diabetic retinopathy. Fourteen months after inclusion in the study, this patient developed ruberosis iridis and diffuse ischemic leakage from vessels in the posterior pole, causing macular edema (Figure 2B). Visual acuity deteriorated to light perception only despite panretinal laser therapy. None of the 4 patients had been treated with EC/IC bypass surgery.

The annual rate of development of advanced chronic ocular ischemia with ischemic changes of the anterior segment for
all 110 patients was 1.5% (95% CI, 0.4 to 3.8). Because of the small number of patients (4 of 110) who developed the syndrome of chronic ocular ischemia with ischemic changes of the anterior segment, we refrained from formal analysis of prognostic indicators.

In the remaining 29 patients with VSR, the retinal signs remained stable in 21 patients and diminished in 8 during follow-up and in patients with extensive retinal abnormalities at the time of the first investigation (Figure 3). Of these 29 patients, 5 underwent endarterectomy of ≥70% stenosis of the contralateral carotid artery, and 6 underwent high-flow EC/IC bypass surgery. In addition, the remaining 77 of 78 patients without VSR at first examination did not develop symptoms consistent with the syndrome of chronic ocular ischemia during follow-up.

Discussion

We found that approximately one third of patients with CAO manifested by transient or mildly disabling retinal or hemispheric symptoms have VSR. Patients with VSR commonly had symptoms that have classically been associated with cerebral hypoperfusion. On average, patients with VSR had a relatively low pulsatility index in the OphthA in case of reversed flow, a low CO2 reactivity, and a low cerebropetal blood flow value. Retinal claudication appeared to be an unreliable guide to the presence of VSR because it was reported only rarely. Development of clinically manifest chronic ocular ischemia with ischemic changes of the anterior segment of the eye or loss of vision was rare but did occur, particularly in patients with VSR at study entry.

The proportion of patients with VSR in our study is higher than the 18% found in an earlier series of patients with CAO, although not to a significant extent (difference, 11%; 95% CI, 1 to 23). That study differs from ours in that the authors did not describe how patients were selected and all patients were treated with EC/IC bypass surgery. In 3 studies that included not only patients with CAO but also patients with carotid
artery stenosis, the proportion of patients with VSR ranged between 5% and 21%.1,3,4

Our observations support the hypothesis that development of VSR is related to a chronically impaired blood supply of the brain. The low pulsatility index in the OphthA with reversed flow in patients with VSR suggests a relatively low vascular resistance of the cerebral vessels in these patients. Low vascular resistance is likely to be caused by compensatory vasodilatation to maintain cerebral blood flow.16 This is corroborated by our finding that CO₂ reactivity is relatively low in patients with VSR because CO₂ reactivity reflects the residual capacity of the resistance of the cerebral arterioles after a vasodilatory stimulus, in this case CO₂. If vasodilatation is already maximal, CO₂ reactivity will be low or even absent. The relatively low cerebropetal blood flow in patients with VSR probably implies that in these patients dependency on collateral blood flow via the OphthA is relatively high. Some studies found an association between chronic ocular ischemia and reversal of flow in the OphthA and between chronic ocular ischemia and reduction of retrobulbar blood flow.17–19 Another study could not confirm these associations.20 Our findings suggest that in patients with CAO the hemodynamic state of the brain may be an important indicator of the development of VSR. We could not confirm the hypothesis that VSR in patients with CAO is an indication of more advanced atherosclerosis4 because we found no evident excess of vascular risk factors, manifestations of vascular disease of the heart or peripheral vessels, or contralateral carotid artery disease in patients with VSR.

The prognosis of vision in patients with the advanced syndrome of chronic ocular ischemia with ischemic changes of the anterior segment or deterioration of vision is highly variable.21 The presence of rubeosis iridis has been described as a particularly bad prognostic sign.21 Data on visual outcome of patients with VSR are lacking. We found that during an average follow-up of >2 years, ≈1 in every 10 patients with symptomatic CAO and VSR will develop the advanced syndrome of chronic ocular ischemia with ischemic changes of the anterior segment or deterioration of vision. Within the group of patients with VSR, we could not reliably determine prognostic indicators because the number of patients who developed clinically manifest chronic ocular ischemia was small. If indeed the development of the advanced syndrome of chronic ocular ischemia is related to a chronically impaired cerebral blood flow, one could hypothesize that in patients with VSR who do not develop clinically manifest chronic ocular ischemia, cerebral blood supply improves over time, whereas cerebral blood flow remains impaired in patients who will develop clinically manifest chronic ocular ischemia. Only 1 of the 78 patients without VSR developed the advanced syndrome of chronic ocular ischemia during follow-up, indicating that the risk of developing symptomatic chronic ocular ischemia is very small in the absence of VSR. This patient illustrates the diagnostic dilemma of distinction of VSR and mild diabetic retinopathy, particularly in diabetic patients with carotid artery occlusive disease.2,5 Because patients without VSR at study entry were not followed up by ophthalmologic examination in the absence of new symptoms, we may have missed the development of subclinical retinal ischemic changes. Furthermore, treatment with EC/IC bypass surgery and endarterectomy in patients with severe stenosis of the contralateral carotid artery may have affected the course of VSR in some patients. That the RR of VSR for development of the advanced syndrome of symptomatic chronic ocular ischemia showed a strong trend but did not reach significance (RR, 7.3; 95% CI, 0.8 to 68) is probably caused by the small number of patients. Observation over a longer time period might render a higher number of patients who develop clinically manifest chronic ocular ischemia.

On the basis of our findings, we recommend referral of patients with symptomatic CAO to the ophthalmologist on a routine basis, regardless of whether they have had visual symptoms. If VSR is present, both patient and physician should be keen on symptoms and signs of ischemia of the anterior eye segment indicating impending visual loss. In these patients, we recommend ophthalmologic follow-up. If VSR is absent, ophthalmologic follow-up is probably not necessary. A management strategy cannot be inferred from this study, but treatment should probably be started early.22 The finding that VSR occurs more frequently in patients with evidence of an impaired flow state of the brain supports the hypothesis that revascularization procedures may be effective in these patients. However, evidence other than from case reports23–27 and uncontrolled studies28 is not available and is unlikely to emerge because the disease is so rare.

We conclude that in patients with symptomatic CAO, VSR is common and related to a low flow state of the brain. Although development of clinically manifest chronic ocular ischemia is rare, follow-up of patients with VSR is recommended to prevent vision loss.

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