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Retinal Artery Occlusion:

Associated Systemic and Ophthalmic Abnormalities

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Abstract

Objective—To investigate systematically the various associated systemic and ophthalmic abnormalities in different types of retinal artery occlusion (RAO).

Design—Cohort study.

Participants—439 consecutive untreated patients (499 eyes) with RAO, first seen in our clinic from 1973 to 2000.

Methods—At first visit, all patients had a detailed ophthalmic and medical history, and comprehensive ophthalmic evaluation. Visual evaluation was done by recording visual acuity, using the Snellen visual acuity chart, and visual fields with a Goldmann perimeter. Initially they also had carotid Doppler/angiography and echocardiography. The same ophthalmic evaluation was performed at each follow-up visit.

Main Outcome Measures—Demographic features, associated systemic and ophthalmic abnormalities and sources of emboli in various types of RAO.

Results—RAO was classified into various types of central (CRAO) and branch (BRAO) artery occlusion. In both nonarteritic CRAO and BRAO the prevalence of diabetes mellitus, arterial hypertension, ischemic heart disease, and cerebrovascular accidents were significantly higher compared to the prevalence of these conditions in the matched US population (all $p < 0.0001$). Smoking prevalence, compared to the US population, was significantly higher for males ($p = 0.001$) with nonarteritic CRAO and for females with BRAO ($p = 0.02$). Ipsilateral internal carotid artery had $\geq 50\%$ stenosis in 31% of nonarteritic CRAO patients and 30% of BRAO, and plaques in 71% of nonarteritic CRAO and 66% of BRAO. Abnormal echocardiogram with embolic source was seen in 52% of nonarteritic CRAO and 42% of BRAO. Neovascular glaucoma developed in only 2.5% of nonarteritic CRAO eyes.

Conclusion—This study showed that in CRAO as well as BRAO the prevalence of various cardiovascular diseases and smoking was significantly higher compared to the prevalence of these conditions in the matched US population. Embolism is the most common cause of CRAO and BRAO;

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plaque in the carotid artery is usually the source of embolism and less commonly the aortic and/or mitral valve. The presence of plaques in the carotid artery is generally of much greater importance than the degree of stenosis in the artery. Contrary to the prevalent misconception, there is no cause-and-effect relationship between CRAO and neovascular glaucoma.

Retinal artery occlusion is a common, visually disabling, ocular vascular occlusive disorder. There is usually a sudden, dramatic onset of visual loss, particularly in central retinal artery occlusion (CRAO). von Graefe¹ in 1859 first described a case of CRAO caused by multiple systemic emboli from endocarditis. Since then a huge volume of literature has accumulated on various aspects of retinal artery occlusion (RAO); however, there are still several controversial areas on the subject. This is due to several factors. Most of the information is drawn from small studies, mostly retrospective in nature. Several misconceptions are prevalent² and are still being perpetuated. Moreover, all RAOs are often lumped together in the literature as if they were one clinical entity, when in fact RAO consists of multiple distinct entities differing in their etiology, pathogenesis, clinical features and management. For example, our recent studies have shown that CRAO consists of 4 categories [i.e., non-arteritic (NA) CRAO, transient NA-CRAO, NA-CRAO with cilioretinal artery sparing, and arteritic CRAO with giant cell arteritis]^{3,4} and branch retinal artery occlusion (BRAO) consists of BRAO and cilioretinal artery occlusion (CLRAO); furthermore, the latter comprises (i) NA-CLRAO alone, (ii) arteritic CLRAO associated with giant cell arteritis, and (iii) CLRAO associated with central retinal vein occlusion (CRVO)⁵. Thus, lumping them together into one category has resulted in misleading information and controversy. Therefore, to get valid information on various aspects of RAO, it is essential to classify it into its various categories. In the present study, we have conducted a systematic, longitudinal, prospective study, from 1973 to 2000, on various aspects of RAO in a cohort of 439 patients (499 eyes).

Material and Methods

We conducted this study in patients with CRAO and with BRAO seen in our Ocular Vascular Clinic, a Tertiary Care referral center at the University of Iowa Hospitals & Clinics, as a part of National Institute of Health funded (RO1) prospective studies on ocular vascular occlusive disorders, approved by the Institutional Review Board. The study consists of a cohort of 439 patients (499 eyes), with CRAO in 249 patients (289 eyes) and BRAO in 190 patients (210 eyes), seen consecutively from 1973 to 2000, who met our inclusion and exclusion criteria.

Inclusion criteria for the study

A definite diagnosis of CRAO or BRAO was based on the presence of the classical clinical findings. These were recorded either in our clinic, or by the local referring ophthalmologist for patients who were not seen by us within the first few days after the onset of visual loss.

Diagnostic criteria for CRAO

These were, principally: (1) A history of sudden loss of vision in one eye. (2) On initial ophthalmic evaluation, evidence of acute retinal ischemia, i.e. retinal opacity with cherry red spot or, in eyes with transient CRAO, multiple scattered patches of retinal opacity all over the posterior pole with or without intervening retina showing whitening or even a faint cherry red spot. (3) The presence of "box-carring" ("cattle trucking") of the blood column in the retinal vessels, except in those with transient CRAO. (4) Fluorescein fundus angiography performed at first consultation after the sudden onset of visual loss (either at the local referring ophthalmologist or in our clinic), showing evidence of absence or marked stasis of the retinal arterial circulation, except in eyes with transient CRAO. (5) No treatment, other than ocular massage in a few eyes by the local ophthalmologist.

Diagnostic criteria for BRAO

A definite diagnosis of BRAO was based on the presence of its various classical clinical findings. These findings included the following. (1) There was a history of sudden onset of visual deterioration in the eye. (2) On initial ophthalmic evaluation, there was evidence of acute retinal ischemia in the distribution of the occluded branch retinal artery. (3) Fluorescein fundus angiography, performed soon after the onset, showed evidence of absence or marked stasis of circulation in the involved branch retinal artery, except in eyes with transient BRAO. (4) No treatment was given for BRAO.

Exclusion criteria for the study

All patients with inadequate information or doubtful diagnosis were excluded. However, eyes with pre-existing unrelated retinal conditions, such as diabetic retinopathy, were not excluded. There was no built-in bias for the types of patients seen in the Ocular Vascular Clinic.

Examinations performed

At the initial visit to the Ocular Vascular Clinic, all patients were seen by one of us (SSH) and had a detailed ocular and medical history, as well as a detailed ocular evaluation. The ocular examination included a careful testing of the visual acuity, visual field plotting with a Goldmann perimeter, a detailed anterior segment examination, intraocular pressure recording with a Goldmann applanation tonometer, relative afferent pupillary defect, detailed fundus evaluation by indirect and direct ophthalmoscopy and if required by contact lens. All had stereoscopic color fundus photography and fluorescein fundus angiography. In persons older than 55 years, erythrocyte sedimentation and C-reactive protein evaluation (since 1985) were done to determine whether CRAO was due to giant cell arteritis^{6,7}, because giant cell arteritis represents an ophthalmic emergency and requires immediate, intensive systemic corticosteroid therapy to prevent any further visual loss.⁷ Giant cell arteritis was also excluded in all eyes with cilioretinal artery occlusion alone but not in BRAO, since giant cell arteritis cannot produce BRAO, because “retinal arteries” are actually arterioles and giant cell arteritis is a disease of medium and large arteries only. None of the patients without giant cell arteritis had any treatment, except in an occasional case where the local initial evaluating ophthalmologist massaged the eyeball.

In addition to these evaluations, almost all patients received carotid evaluation and echocardiographic study to determine the source of embolism at their first visit; however, some patients refused or did not undergo these testing for self-reported financial, transportation or other logistic reasons (patients have to travel long distance, some several hundred miles, to our tertiary care center). For carotid evaluation the patients were referred to the vascular surgery laboratory where carotid Doppler was first performed in all patients and then, at the discretion of the vascular surgeon, carotid angiography was performed, where it was indicated. The study was started in 1973, and the modern high resolution carotid Doppler capable of determining the degree of stenosis and presence of plaque in the carotid arteries was not available till 1987 – hence carotid Doppler information on the degree of stenosis and presence of plaque is not available in all patients. For echocardiography, they were referred to the cardiology clinic.

The follow-up ophthalmic evaluation (by SSH) was identical to those described in the initial visit examination, except for the fluorescein fundus angiography which was performed only once at the initial visit, to document the state of retinal circulation at onset. The follow-up protocol was individualized for each patient for various logistic reasons.

For data analysis, CRAO and BRAO were classified into the various categories listed in Tables 1 and 2 respectively.

Statistical data analysis

Descriptive statistics, mean±standard deviation and frequency and percentages, were obtained for the demographic characteristics, prevalence of systemic conditions, and findings of the carotid Doppler/angiography and echocardiography. The prevalence of diabetes mellitus, renal disease, ischemic heart disease, arterial hypertension, transient ischemic attacks (TIA) and cerebrovascular disease (CVA) was compared to the corresponding race, age and period matched subgroup of the US population using the exact test for a binomial proportion. The US prevalence used in the analysis was the computed weighted mean prevalence from those reported for 1982⁸ and 1990-92⁹ in the National Health Interview Survey (NHIS). The study was divided into 2 intervals, 1973-1985 and 1986-2000, with the weights used in computing the weighted mean prevalence for the matched US White population (population in our area is predominantly white) based on the proportion of the distribution of subjects in the 2 intervals. For prevalence of elevated cholesterol and current smoking, the comparison with the US population was done by gender. The reference prevalence rates of the age matched US population used for elevated cholesterol were those reported in NHANES¹⁰ for 1976-80 and 1988-94. For current smoking, the race and age matched prevalence rates in the US population were from 1979 and 1992 in Health United States 2005¹¹.

For the comparisons involving the carotid Doppler/angiography and echocardiography findings, the Pearson Chi-square test was used. Comparison of amount of carotid occlusion was done using the Wilcoxon rank-sum test.

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Central retinal artery occlusion—There were 234 NA-CRAO patients (271 eyes), 37 (16%) with bilateral involvement. More than half of the 271 eyes had NA-CRAO alone (156 eyes), with the rest having other types of CRAO (Table 1). The demographic characteristics of these patients are listed in Table 3. Development of CRAO was discovered at waking in 29.5% (80 eyes). In this cohort of CRAO patients, the natural history of visual outcome³ and fundus findings⁴ are described in detail elsewhere.

Branch retinal artery occlusion—There were 141 patients (160 eyes) with BRAO, including those with NA-CLRAO of whom 19 (13%) had bilateral involvement. Most of these patients (122 patients, 133 eyes) had permanent BRAO, with the rest having either transient BRAO or NA-CLRAO alone (Table 2). In 28% (45 eyes), the visual loss was discovered at waking. The demographic characteristics of these patients are listed in Table 3. In this cohort of BRAO patients, the natural history of visual outcome⁵ is described in detail elsewhere.

ASSOCIATED SYSTEMIC ABNORMALITIES

Central retinal artery occlusion—The prevalence of diabetes mellitus, renal disease, arterial hypertension, ischemic heart disease, and TIA/CVA in NA CRAO were significantly higher compared to the prevalence of these conditions in the matched US population (all $p<0.0001$, Table 4). Smoking prevalence in NA-CRAO compared to the US population was significantly higher for the male patients ($p=0.001$). The data also suggested a higher smoking prevalence for female patients ($p=0.06$) but that was not significant at the 0.05 significance level.

Branch retinal artery occlusion—Diabetes mellitus, arterial hypertension, ischemic heart disease, and TIA/CVA were more prevalent in the BRAO patients than in the matched US population (all $p<0.0001$, Table 5). Current smoking prevalence in BRAO compared to the US

population was significantly higher for the female patients ($p=0.02$). However, this was not evident for the male BRAO patients ($p=0.25$).

Comparison of systemic conditions between NA-CRAO and BRAO patients showed a slightly higher prevalence of diabetes mellitus in CRAO (20%) than in BRAO (13%) ($p=0.086$). No significant difference was seen for the rest of the systemic conditions listed in Tables 4 and 5 ($p>0.16$). Current smoking status did not differ significantly between the NA-CRAO and BRAO patients in either males (38% vs. 32%; $p=0.40$) or females (27% vs. 35%; $p=0.29$).

CAROTID DOPPLER/ANGIOGRAPHY AND ECHOCARDIOGRAPHY FINDINGS

Central retinal artery occlusion—The findings are summarized in Table 6. From the carotid Doppler/angiography, 34% had 50% or greater stenosis and 71% had plaque(s). Presence of plaque(s) did not differ significantly between those with TIA/CVA and without TIA/CVA (66% vs. 72%; $p=0.43$) or between those with ischemic heart disease and those without (69% vs. 72%; $p=0.755$).

Echocardiography findings showed 52% with abnormal echocardiogram of an embolic source. Of those with an embolic source, 26% were from the mitral valve, 38% from the aortic valve, and 36% from both mitral and aortic valves (Table 6). The mitral valve lesions comprised 57% calcified valve, 17% mitral valve prolapse, and 26% other types of lesions. The aortic valve lesions were 78% calcified valve and 22% of other types. Patent foramen ovale was detected in 6 patients. The finding of an abnormal echocardiogram with an embolic source was not significantly associated with TIA/CVA (59% in TIA/CVA vs. 50% without TIA/CVA; $p=0.480$) or ischemic heart disease (67% in ischemic heart disease vs. 48% without ischemic heart disease; $p=0.137$). Relating Doppler/angiography findings to echocardiography findings showed abnormal echocardiogram with embolic source in 62% of those with plaque and 36% of those without plaque ($p=0.04$).

Branch retinal artery occlusion—This group consists of combined BRAO and NA-CLRAO alone. The carotid Doppler/angiography findings (Table 6) on the side corresponding to the eye with BRAO showed that 30% had 50% or greater stenosis and 66% had plaque(s) present. The presence of plaque did not differ significantly between those with TIA/CVA and without TIA/CVA (76% vs. 64%; $p=0.27$); nor between those with ischemic heart disease and those without (76% vs. 62%; $p=0.16$).

The echocardiography showed 42% with abnormal echocardiograms of an embolic source, of which 31% were from the mitral valve, 28% from the aortic valve, and 41% from both valves (Table 6). The mitral valve lesions comprised 70% calcified valve, 4% with mitral valve prolapse, and 26% with other types of lesions. The aortic valve lesions were 68% calcified valve and 32% of other types. Patent foramen ovale was detected in 4 patients. Having an abnormal echocardiogram with embolic source did not significantly differ between those with and without TIA/CVA (70% in TIA/CVA vs. 38% without TIA/CVA; $p=0.18$) or between those with and without ischemic heart disease (50% in ischemic heart disease vs. 40% without ischemic heart disease; $p=0.69$). In the 58 patients with both Doppler/angiography and echocardiogram, there was a finding of abnormal echocardiogram with embolic source in 44% (15 of 34) of those with plaque(s) and 29% (7 of 24) of those without plaque(s) ($p=0.46$).

Comparison of the carotid Doppler/angiography in NA-CRAO and BRAO (Table 6) showed no significant difference in the level of carotid occlusion ($p=0.68$) or presence of plaque(s) ($p=0.33$). There was also no significant difference in the echocardiogram results with respect to abnormality ($p=0.20$) or type of lesion ($p=0.33$ for mitral valve; $p=0.38$ for aortic valve).

Cilioretinal artery occlusion associated with CRVO—Clinical findings are described in detail elsewhere.¹² Of the 38 eyes, 30 had nonischemic CRVO, 5 ischemic CRVO and 3 nonischemic hemi-CRVO. Patients with nonischemic CRVO were significantly younger (mean 45.3 ± 16.0 years) than those with ischemic CRVO (72.3 ± 9.2 years; $P=0.001$) and nonischemic hemi-CRVO (64.7 ± 7.5 years; $P=0.018$). Arterial hypertension was present in 5 of 30 nonischemic CRVO patients and 3 of 5 ischemic CRVO, ischemic heart disease in 2 of non-ischemic CRVO, 2 of ischemic CRVO, and stroke in one of ischemic CRVO and one of nonischemic hemi-CRVO. Of these patients, 12 with nonischemic CRVO smoked, 1 with ischemic CRVO and 2 with nonischemic hem-CRVO.

Cilioretinal artery occlusion associated with giant cell arteritis—There were 11 patients (12 eyes) in this group. In them, giant cell arteritis confirmed by temporal artery biopsy, caused occlusion of the posterior ciliary artery which in turn resulted in occlusion of the cilioretinal artery¹³. There were 4 males and 7 females, with age range 57 to 79 (mean 69.4 ± 6.8 SD) years. Of the 12 eyes, 10 had associated arteritic anterior ischemic optic neuropathy, one arteritic posterior ischemic optic neuropathy and in only one eye cilioretinal artery occlusion was not associated with optic neuropathy.

Non-arteritic CRAO with ocular neovascular glaucoma and/or ocular ischemia—Among the 14 patients (14 eyes) with NA-CRAO, 6 had neovascular glaucoma, 7 had ocular ischemia and one had both. Among these patients, 8 had arterial hypertension, 9 had diabetes mellitus, 2 had TIA/CVA, and two ischemic heart disease. Carotid Doppler/angiography results on the side of the involved eye was available for 13, and that showed 100% occlusion in 3, and stenosis of 50-79% in 3, 16-49% in 2 and 0-15% in 5. In the 6 eyes with ocular ischemia, the internal carotid artery on that side showed 100% occlusion in 1, a stenosis of 50-79% in 1, 16-49% in 2 and 0-15% in 2. In the 6 eyes with neovascular glaucoma, the internal carotid artery on that side showed 100% occlusion in 2, stenosis of 50-79% in 2, and 0-15% in 2. In one eye with both ocular ischemia and neovascular glaucoma the internal carotid artery on that side showed only 0-15% stenosis.

Discussion

There is a large volume of literature dealing with various aspects of RAO, including visual outcome, sources of retinal emboli, systemic diseases, hematologic abnormalities and other risk factors associated with RAO.

CAUSES OF RETINAL ARTERY OCCLUSION

Embolism is the most common cause. The carotid artery and the heart are the most common sources.

Carotid artery disease—Carotid artery disease is the most common cause of RAO. It can cause retinal arterial occlusion by three mechanisms:

(i) Embolism: This is by far the most common cause. The major source of emboli is plaques in the carotid arteries, and much less frequently stenosis. In the present study, carotid Doppler/angiography showed the presence of plaques in 71% in CRAO and 66% in BRAO (Table 6).

(ii) Hemodynamically: To produce hemodynamically induced retinal and/or ocular ischemia, by markedly reducing the ocular blood flow, the internal carotid artery has to be significantly stenosed (usually about 70% or more), or completely occluded; this can also occur, rarely, with spontaneous internal carotid artery dissection. A fall of blood pressure, particularly nocturnal arterial hypotension, with a markedly stenosed or occluded internal carotid artery, can result

in transient CRAO³. Anderson et al¹⁴ found that hemodynamic effects due to carotid artery stenosis do not appear to be more important in the pathogenesis of retinal events than hemispheric ones. Whereas severe stenosis of the extracranial internal carotid artery is the most common identified condition associated with retinal and ocular ischemia¹⁵⁻¹⁸. Sharma et al¹⁸ found hemodynamically significant carotid artery stenosis in only 18.7% of patients with acute RAO. In our study, $\geq 80\%$ stenosis of the internal carotid artery was seen in 18% of CRAO cases and 14% of BRAO (Table 6). We have found that the presence of retinal embolus is a poor predictor of hemodynamically significant carotid stenosis on carotid Doppler, as has also been pointed out by others.¹⁸⁻²⁰

(iii) Serotonin (5-hydroxytryptamine) induced arterial spasm: In our study on atherosclerotic monkeys, we found that Serotonin, in the presence of atherosclerotic lesions, can cause transient, complete occlusion or impaired blood flow in the central retinal artery by producing a transient spasm²¹. Serotonin, released by platelet aggregation on atherosclerotic plaques in the carotid artery, may produce vasospasm of the central retinal artery in atherosclerotics, and thus may contribute to CRAO and retinal ischemic disorders,

Retinal emboli—The most common cause of RAO is embolism. Retinal emboli are usually of three types: calcific, cholesterol and platelet-fibrin. The carotid artery and the heart are the sources of embolism to the retinal arteries. In the carotid artery, plaque is the most common source of that. In the heart, sources of emboli are aortic and mitral valvular lesions, patent foramen ovale, tumor in the left atrium²², and myxoma²². Table 6 summarizes the findings in our cohort for carotid Doppler/angiography as well as echocardiographic findings. It shows that the most common abnormality and source of embolism in the carotid arteries is the presence of plaque(s) (66%); significant carotid stenosis (i.e. $\geq 50\%$) was seen in only 30%. In our study, relating carotid Doppler/angiography findings to echocardiography findings showed an abnormal echocardiogram with embolic source in 62% of those with plaque in CRAO and in 44% with BRAO. This means that in such cases, the embolus could have come from either the carotid artery or the heart or possibly both. This indicates that one has to evaluate both sources for embolism in all patients with CRAO and BRAO.

There are some prevalent misconceptions about using the findings from carotid Doppler to evaluate the source of retinal artery embolism². There is a widespread misconception that the absence of any abnormality on Doppler evaluation of the carotid artery always rules that out as the source of embolism or cause of ocular ischemia. This is not always true for the following reasons.

- i. We have found that, when evaluating the carotid artery by Doppler, vascular surgeons, neurologists and other physicians are almost invariably interested in the degree of stenosis of the carotid artery, because their primary interest is hemodynamic insufficiency and carotid endarterectomy. However, arterial occlusions in the eye are due to microembolism in the vast majority of cases, and the major source of microemboli is plaque - which may be present with or without any significant carotid artery stenosis. Thus, the absence of significant stenosis or of plaque in the carotid artery does not necessarily rule out the carotid artery as the source of microembolism. Vascular insufficiency in the eye caused by a significant carotid artery stenosis is seen only rarely, and occurs primarily in ocular ischemic syndrome, but every patient with ocular ischemia does not show severe carotid artery stenosis or occlusion.^{15,16}
- ii. Carotid Doppler evaluates the artery only in the neck and not above and below that (in the skull and the thorax respectively) – the source of microembolism may be at those locations. Moreover, the resolution of Doppler is not always sensitive enough to detect plaques which, though, very small, may be enough to produce microembolism in the retina. We have observed patients with visible retinal emboli

who showed no abnormality on routine carotid Doppler or echocardiography. Similarly, we have previously reported that 26% of patients with ocular ischemia had no significant carotid Doppler stenosis on the side of the ocular ischemia.¹⁶ Likewise, Nicolaides et al²³ reported the presence of cerebral infarcts with no evidence of internal carotid artery stenosis on the side of the infarct. Based upon our current and previous data, we believe that most retinal occlusions are due to relatively small emboli ("microemboli"). Microemboli may be derived from non-hemodynamically significant obstruction, as it requires only a small intraluminal plaque(s) which may be present with or without any significant carotid artery stenosis. Thus, inability to find any abnormality on carotid Doppler does not rule out the carotid artery as the source of embolism.

Therefore, from the ophthalmic point of view, when evaluating the results of carotid Doppler study for ocular microembolism, the presence of plaques is usually of much greater importance than the degree of stenosis; and the absence of marked carotid artery stenosis on Doppler does not rule out ocular ischemia.

Table 6 summarizes echocardiographic abnormalities seen in our cohort in CRAO and BRAO. There is a common belief that echocardiography rules out the heart as the source of retinal microembolism, which is not always the case, because its resolution or the technique used may not be sensitive enough to detect very small valvular or other cardiac lesions. As has been pointed out by several studies, including ours, that when routine transthoracic cardiac echography shows no abnormality, transesophageal echography may reveal abnormalities.

When dealing with RAO, we have found another common misconception: that the absence of an embolus in the retinal artery means the occlusion was not caused by an embolus. This is not true at all. Migration of emboli in the retinal vascular bed is a characteristic feature. Thus, the axiom should be: if one sees an embolus, then that was responsible for the occlusion; but, if one does not see an embolus, that does not mean that embolism was not responsible for the occlusion. The embolus may have migrated and disappeared by the time the eye is examined. For example, of our 42 eyes with CRAO and multiple visits where an embolus was seen at least once, in 69% the embolus was not consistently present at all of the visits⁴; that means the actual incidence is likely to be much higher than is recorded. Thus, the apparent incidence of emboli so far recorded seems to underestimate their relationship to CRAO and BRAO. This phenomenon of migratory emboli has practical implications. Obviously, if one finds an embolus, it is highly likely to be responsible for retinal arterial occlusion. However, if one does not find an embolus in CRAO that may be due to two reasons. (a) If the embolus is impacted in the proximal part of the central retinal artery, it will not be seen. (b) The embolus may have caused CRAO but disintegrated, migrated and disappeared by the time the eye is examined, so that fluorescein angiography shows normal retinal circulation in spite of classical fundus findings of CRAO. In our study, when an embolus was seen, it was either on the disc at the bifurcation of the central retinal artery or in one of the branch retinal arteries. We found that calcific emboli usually get impacted and do not migrate, being rough in texture, whereas Hollenhorst emboli and especially platelet-fibrin emboli do frequently migrate.

SYSTEMIC RISK FACTORS

Systemic cardiovascular diseases have a well known association with RAO. Arterial hypertension, diabetes mellitus, hyperlipidemia, carotid artery disease, coronary artery disease, TIA/CVA and tobacco smoking have been described as significantly more common among these patients than in the general population.²⁴⁻³¹ Findings in our study are summarized in Table 4 for non-arteritic CRAO, and for BRAO + non-arteritic CLRAO in Table 5. In non-arteritic CRAO, compared to the age-period matched US population, there was a significantly higher prevalence of diabetes mellitus, renal disease, arterial hypertension, ischemic heart

disease, TIA/CVA, and smoking in males in NA CRAO (all $p < 0.0001$, Table 4). In BRAO+ non-arteritic CLRAO cases, diabetes mellitus, arterial hypertension, ischemic heart disease, and TIA/CVA were more prevalent in the BRAO patients than in the matched US population (all $p < 0.0001$, Table 5). Current smoking prevalence in BRAO compared to the US population was significantly higher for the female patients ($p = 0.02$). Compared to other studies, our study did not show hyperlipidemia in both types significantly different, which may be because some of the patients were already taking lipid lowering drugs, and possibly because the sample size was small due to missing data for that variable.

There are multiple anecdotal case reports of CRAO or BRAO associated with a variety of diseases, including systemic lupus erythematosus, polyarteritis nodosa, dengue fever, West Nile virus, AIDS, sickle cell disease, Takayasu's arteritis, after smallpox vaccination, Churg-Strauss syndrome, ocular Behçet's disease, Fabry's disease, head injury, migraine and other conditions. Giant cell arteritis is an important cause of CRAO and of CLRAO¹³ and should be excluded in all such cases in persons aged 50 and over, to prevent tragic bilateral visual loss which is preventable with early diagnosis and intensive corticosteroid therapy⁷. In many of these conditions, the primary factor responsible for CRAO or BRAO is most probably vasculitis. We have seen one case of BRAO associated with toxoplasma³² and another one due to herpes zoster³³. There are many case reports of Susac syndrome in the literature. This is characterized by the clinical triad of encephalopathy, hearing loss, and branch retinal artery occlusion, mostly in young women due to a microangiopathy affecting the precapillary arterioles of the brain, retina, and inner ear.^{34,35} There were two such cases in our current study on BRAO³⁶. There are several case reports of BRAO or CRAO or, rarely, of cilioretinal artery occlusion, attributed to migraine; however, a critical evaluation of the case reports does not definitely establish a cause-and-effect relationship between migraine and RAO. In our study two patients with NA-CRAO and 10 with BRAO gave a history of migraine but it did not have a temporal relationship with retinal arterial occlusion. In many cases, the attribution of retinal arterial occlusion to migraine is mostly presumptive, because transient loss of vision lasting for a few seconds to a few minutes that has been attributed to migraine may in fact be due to other causes, e.g., transient embolism or spasm of the artery due to serotonin.

Greven et al³⁷ reported 21 patients under 40 years old with retinal arterial occlusion. They found that cardiac valvular disease was the most commonly recognized etiologic agent (19%). Various associated factors leading to a hypercoagulable state or embolic condition were identified in 19 patients (91%). They concluded that retinal arterial occlusions in young adults occur via multiple mechanisms.

Hematologic abnormalities—These have been described associated with RAO. They include familial and acquired thrombophilia (low protein C, lupus anticoagulant) in patients with CRAO³⁸, antiphospholipid antibodies³⁹ and homocysteinemia^{38,40,41}; however, factor V Leiden, prothrombin 20210A and homozygosity for the MTHFR C677T have not been found to be associated with RAO^{27,40}. In our study we did not conduct hematological studies systematically; therefore, we have no information on this aspect of RAO.

CENTRAL RETINAL ARTERY OCCLUSION AND NEOVASCULAR GLAUCOMA

This is an important and a controversial subject. There is a prevalent misconception that CRAO can cause anterior segment neovascularization and neovascular glaucoma², similar to that seen following ischemic CRVO. For example, Duker et al⁴², based on a study of 33 eyes with CRAO, attributed the development of neovascular glaucoma in 18% to CRAO *per se*. They claimed that in the majority of cases, carotid artery disease was not responsible for ocular neovascularization in their series because in 5 of the 7 (71%) patients there was no "ipsilateral

hemodynamically significant carotid artery disease". There are several problems with that conclusion.

1. Findings in our study (in 232 eyes), as well as in our previous studies on the subject^{15,16}, show that ocular ischemia as well as neovascular glaucoma can be present when the internal carotid artery on that side does not show "hemodynamically significant" stenosis or complete occlusion on Doppler evaluation. For example, in our study on ocular ischemia¹⁶, 26% of the cases showed only 0-49% stenosis of the internal carotid artery in spite of definite ocular ischemia, and in the present study 10 of 13 (77%) with ocular ischemia had 70% or less stenosis (see above). As discussed above, this reflects the limitations of carotid Doppler evaluation.
2. In anatomical studies by Hayreh and Dass on the ophthalmic artery⁴³, the ophthalmic artery was markedly stenosed at its origin from the internal carotid artery in some cases, without any stenosis of the internal carotid artery at all. Similarly the ophthalmic artery or its ocular branches themselves may be markedly stenosed to produce ocular ischemia and ocular neovascularization.
3. In the study by Duker et al⁴² the incidence of development of neovascular glaucoma was 18% among 33 patients with CRAO, while in our study of 232 eyes with complete CRAO, it was only 2.5%. That shows that the sample of neovascular glaucoma in Duker et al's⁴² series must have been biased. Other factors must have been responsible for that high incidence of neovascular glaucoma in their series, e.g., diabetes mellitus.
4. It is invalid to consider ischemic CRVO and CRAO as being similar in nature, as for as the development of neovascular glaucoma is concerned. In CRVO, there is chronic retinal hypoxia, while in CRAO there is acute severe retinal ischemia and infarction. It is the chronically hypoxic retina that is thought to liberate vasoproliferative factor to cause ocular neovascularization, which is totally missing in CRAO. Thus, there is little scientific rationale for CRAO to cause ocular neovascularization per se. Moreover, if CRAO were causing ocular neovascular glaucoma, it should logically cause that in far more than only 2.5%. In ischemic CRVO, for example, neovascular glaucoma develops in about 45%⁴⁴.

In conclusion, our study showed that in CRAO as well as BRAO the prevalence of diabetes mellitus, arterial hypertension, ischemic heart disease, and TIA/CVA was significantly higher compared to the prevalence of these conditions in the matched US population (all $p < 0.0001$). Smoking prevalence, compared to the US population, was significantly higher for males ($p = 0.001$) with NA-CRAO and for females with BRAO ($p = 0.02$). Embolism is the most common cause of CRAO and BRAO; plaque in the carotid artery is the usual source of embolism (71% in CRAO and 66% in BRAO) and less commonly the aortic and/or mitral valve. The presence of plaques in the carotid artery is generally of much greater importance than the degree of stenosis in the artery. Contrary to the prevalent misconception, there is no cause-and-effect relationship between CRAO and neovascular glaucoma.

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Table 1

Types of Central Retinal Artery Occlusion in 249* patients (289 eyes)

Type of Central Retinal Artery Occlusion	n patients * (n eyes)
Non-arteritic CRAO alone	156 (169)
Non-arteritic CRAO with cilioretinal artery sparing	32 (34)
Transient non-arteritic CRAO	38 (39)
Non-arteritic CRAO with amaurosis fugax history	20 (20)
Non-arteritic CRAO with other ocular condition **	9 (9)
Arteritic CRAO	15 (18)

* There were 21 patients with bilateral involvement that had different types of CRAO in each eye, 19 with non-arteritic CRAO alone and non-arteritic CRAO with cilioretinal artery sparing; 1 with non-arteritic CRAO alone and transient non-arteritic CRAO; 1 with non-arteritic CRAO with cilioretinal artery sparing and transient non-arteritic CRAO.

** Other conditions include 7 with non-arteritic anterior ischemic optic neuropathy, 1 with non-arteritic posterior ischemic optic neuropathy, and 1 with non-arteritic CRAO following vitrectomy+scleral buckle surgery.

CRAO = Central retinal artery occlusion.

Table 2

Types of Branch Retinal Artery Occlusion in 190* patients (210* eyes)

Type of Branch Retinal Artery Occlusion	n patients * (n eyes)
Permanent BRAO	122 (133)
Transient BRAO	18 (18)
Cilioretinal artery occlusion alone	10 (11)
Cilioretinal artery occlusion with giant cell arteritis	11 (12)
Cilioretinal artery occlusion with CRVO	38 (38)

* There were 7 patients with bilateral involvement that had different types of BRAO in each eye (6 with Permanent BRAO and Transient CRAO; 1 with Permanent BRAO and Cilioretinal artery occlusion alone) and 2 patients with 2 episodes of different types of BRAO on the same eye (1 with Transient BRAO then Permanent BRAO; 1 with Cilioretinal artery occlusion alone then Permanent BRAO).

BRAO = Branch retinal artery occlusion.

CRVO = Central retinal vein occlusion

Table 3

Demographic characteristics

Demographic Variable	Non-arteritic CRAO n=234 patients	Arteritic CRAO n=15 patients	BRAO* n=141 patients	Cilioretinal artery occlusion with giant cell arteritis or CRVO n=49 patients
Gender (Male)	130 (56%)	8 (53%)	91 (65%)	21 (43%)
Age at initial visit (Mean±SD)	66±14	74±7	59±20	55±18
<u>Eye involvement</u>				
OD	104 (44%)	9 (60%)	59 (42%)	24 (49%)
OS	93 (40%)	3 (20%)	63 (45%)	24 (49%)
OU	37 (16%)	3 (20%)	19 (13%)	1 (2%)

* BRAO includes both permanent and transient BRAO and also cilioretinal artery occlusion alone.

BRAO = Branch retinal artery occlusion.

CRAO = Central retinal artery occlusion.

CRVO = Central retinal vein occlusion

OD = Right eye

OS = Left eye

OU = Both eyes

SD = Standard deviation.

Table 4
Prevalence of systemic conditions in non-arteritic CRAO*

Systemic condition	Non-arteritic CRAO n=234 patients	White Age-Period matched population	Non-arteritic CRAO vs. matched population p-value
Diabetes mellitus	47 (20%) (95% CI: 15%, 26%)	7.7%	<0.0001
Renal disease	17 (7%) (95% CI: 4%, 11%)	2.3%	<0.0001
Arterial hypertension	121 (52%) (95% CI: 45%, 58%)	30.1%	<0.0001
Ischemic heart disease	60 (26%) (95% CI: 20%, 31%)	10.7%	<0.0001
TIA/CVA	45 (19%) (95% CI: 14%, 25%)	4.3%	<0.0001
Cholesterol $\geq$ 240 mg/dL In males	(n=81, 49 missing) 25 (31%) (95% CI: 21%, 42%)	27.6%	0.580
Cholesterol $\geq$ 240 mg/dL In females	(n=56, 48 missing) 29 (52%) (95% CI: 38%, 65%)	41.5%	0.157
Current smoker In males	(n=109, 21 missing) 41 (38%) (95% CI: 29%, 47%)	23.6%	0.001
Current smoker In females	(n=79, 25 missing) 21 (27%) (95% CI: 17%, 38%)	17.7%	0.063

CI = Confidence limit

CRAO = Central retinal artery occlusion

CVA = Cerebrovascular accident

TIA = Transient ischemic attack

Table 5

Prevalence of systemic conditions in BRAO*

Systemic condition	BRAO* n=141 patients	White Age-Period matched population	BRAO* vs. matched population p-value
Diabetes	18 (13%) (95% CI: 8%, 19%)	6.1%	0.009
Renal disease	5 (4%) (95% CI: 1%, 8%)	2.2%	0.269
Hypertension	76 (54%) (95% CI: 45%, 62%)	26.4%	<0.0001
Ischemic heart disease	36 (26%) (95% CI: 19%, 34%)	9.0%	<0.0001
TIA/CVA	24 (17%) (95% CI: 11%, 24%)	3.4%	<0.0001
Cholesterol $\geq$ 240 mg/dL In males	(n=58, 33 missing) 13 (22%) (95% CI: 13%, 35%)	27.5%	0.479
Cholesterol $\geq$ 240 mg/dL In females	(n=33, 17 missing) 10 (30%) (95% CI: 16%, 49%)	37.5%	0.508
Current smoker In males	(n=77, 14 missing) 25 (32%) (95% CI: 22%, 44%)	26.0%	0.246
Current smoker In females	(n=42, 8 missing) 16 (38%) (95% CI: 24%, 54%)	21.9%	0.025

* BRAO includes permanent and transient BRAO and also cilioretinal artery occlusion alone.

BRAO = Branch retinal artery occlusion

CI = Confidence limit

CVA = Cerebrovascular accident

TIA = Transient ischemic attack

Table 6

Carotid Doppler/Angiography and Echocardiogram findings on the side of the involved eye

Test Finding	Non-arteritic CRAO	BRAO*
Patent foramen ovale	(n = 234) 6 (2%)	(n=141) 3 (2%)
Carotid Doppler/angiography:	(n=199)	(n=128)
<u>Occlusion</u>		
0-15%	109 (55%)	69 (54%)
16%-49%	23 (12%)	21 (16%)
50%-79%	32 (16%)	21 (16%)
80%-99%	13 (7%)	11 (9%)
100%	22 (11%)	6 (5%)
Carotid Doppler/angiography:	(n=187)	(n=123)
Plaque present	133 (71%)	81 (66%)
Echocardiogram	(n=131)	(n=76)
Normal	39 (30%)	32 (42%)
Abnormal, no embolic source	24 (18%)	12 (16%)
Abnormal, with embolic source	68 (52%)	32 (42%)
Echocardiogram:	(of n=68 with embolic source)	(of n=32 with embolic source)
<u>Abnormal embolic source</u>		
Mitral valve	18 (26%)	10 (31%)
Aortic valve	26 (38%)	9 (28%)
Mitral and aortic valves	24 (36%)	13 (41%)
Echocardiogram:	(of n=42 with mitral valve as embolic source)	(of n=23 with mitral valve as embolic source)
<u>Mitral valve lesion types</u>		
Calcified valve	24 (57%)	16 (70%)
Mitral valve prolapse	7 (17%)	1 (4%)
Other types of lesions	11 (26%)	6 (26%)
Echocardiogram:	(of n=50 with aortic valve as embolic source)	(of n=22 with aortic valve as embolic source)
<u>Aortic valve lesion types</u>		
Calcified valve	39 (78%)	15 (68%)
Other types of lesions	11 (22%)	7 (32%)

* BRAO includes permanent and transient BRAO and also cilioretinal artery occlusion

BRAO = Branch retinal artery occlusion

CRAO = Central retinal artery occlusion