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OCULAR ARTERIAL OCCLUSIVE DISORDERS AND CAROTID ARTERY DISEASE

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Abstract

Objective—To compare prevalence of carotid artery disease and its various types of lesions in different types of ocular arterial occlusive disorders.

Design—Cohort study.

Subjects—614 consecutive patients (728 eyes) with ocular arterial occlusive disorders.

Methods—At first visit, all patients had a detailed ophthalmic and medical history, comprehensive ophthalmic evaluation, and carotid artery evaluation (by Doppler/angiography) on the side of ocular arterial occlusion, and echocardiography. The same ophthalmic evaluation was performed at each follow-up visit. Ocular arterial occlusive disorders were divided into central (CRAO) and branch (BRAO) retinal artery occlusion, ocular ischemic syndrome (OIS), non-arteritic anterior ischemic optic neuropathy (NA-AION) and amaurosis fugax (AF).

Main Outcome Measures—Carotid artery and echocardiographic abnormalities, and incidence of transient ischemic attack (TIA)/stroke and myocardial ischemia.

Results—The study consists of a cohort of 266 eyes with NA-AION, 203 with CRAO, 127 with BRAO, 80 with OIS and 52 with AF. Carotid artery stenosis on the involved side was worse in AF and OIS compared to BRAO, CRAO, and NA-AION ($p<0.0001$). Presence of carotid artery plaques on the involved side was significantly higher in OIS, AF, and CRAO compared to NA-AION ($p=0.002$, $p=0.003$, and $p=0.0003$, respectively). Echocardiography revealed an embolic source in 61% of CRAO and 53% of BRAO compared to only 3% of NA-AION patients ($p<0.0001$). TIA/stroke before or after onset of ocular condition occurred in 17% of OIS, 11% of AF, 7% of CRAO, 6% of NA-AION, and 3% of BRAO patients. Kaplan-Meier estimate of the incidence of TIA /stroke within 3 months after onset was 6% (95% CI: 2%, 17%) for OIS, 3% (95% CI: 0.4%, 19%) for AF, and 1% (95% CI: 0.3%, 4.1%) for CRAO. Report of myocardial

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ischemia before or after onset of ocular condition was 52% in AF, 22% in OIS, 22% in BRAO, 21% in CRAO, and 6% in NA-AION patients.

Conclusions—The incidence of carotid artery stenosis and plaques, cardiac embolic source, TIA/stroke and myocardial ischemia differ among various ocular arterial occlusive disorders. The role of embolism and hemodynamic disturbances caused by carotid artery disease in these disorders is discussed.

a. The role of carotid artery disease in the development of various types of ocular arterial occlusive disorders has often been reported in the literature. However, there has been no planned study, based on a large cohort of patients with various ocular arterial occlusive disorders, dealing with the comparative prevalence of carotid artery disease in each of them; various types of carotid artery lesions separately in different types of these disorders; and systemic complications associated with carotid artery disease in each of these disorders. To investigate all these issues, we conducted this planned study in 614 consecutive patients (728 eyes) with central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), ocular ischemic syndrome (OIS), non-arteritic anterior ischemic optic neuropathy (NA-AION), and amaurosis fugax, in patients who also had carotid artery disease.

Material and Methods

a. We conducted this study in 614 consecutive patients (728) eyes with various types of ocular arterial occlusive disorders (CRAO, BRAO, OIS, NA-AION and amaurosis fugax) seen in our Ocular Vascular Clinic, at the University of Iowa Hospitals & Clinics, a Tertiary Care referral center, as a part of National Institute of Health funded (RO1) systematic studies on ocular vascular occlusive disorders, approved by the Institutional Review Board. The study consists of a cohort of 266 eyes with NA-AION, 203 with CRAO, 127 with BRAO, 80 with OIS and 52 with amaurosis fugax, which met our inclusion and exclusion criteria.

Inclusion criteria for the study

a. The study included only those patients with definite diagnosis of various types of ocular arterial occlusive disorders (NA-AION, CRAO, BRAO, OIS and amaurosis fugax), and carotid artery disease.

Diagnostic Criteria for Various Ocular Arterial Occlusive Disorders

a. These were based on our detailed studies in each disease, as discussed below.

For NA-AION: Findings of our detailed studies on NA-AION are summarized elsewhere.[1] Based on those studies, following diagnostic criteria were used:

1. A history of sudden visual loss, and an absence of other ocular, systemic or neurological diseases that might influence or explain the patient's visual symptoms.

2. In our study[2] of 839 episodes of NA-AION, in at least 73.3%, the visual loss was discovered in the morning, and in the rest they were not sure of the time of onset; this indicates that in NA-AION in the vast majority the visual loss is discovered in the morning.

3. Optic disc edema at onset, a classical finding, must have been documented in our Ocular Vascular Clinic.

4. Our study[3] of 312 eyes with NA-AION showed that initially these eyes most commonly show absolute inferior nasal visual field defect, and next common is absolute inferior altitudinal defect; less commonly are other types of optic disc-related visual field defects.

5. There was no neurologic, systemic or ocular disorder, which could account for the optic disc edema and visual impairment.

For CRAO: Following well-established diagnostic criteria were used.

1. There was a history of sudden loss of vision in one eye.

2. On initial ophthalmic evaluation, there was 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 showed absence or marked stasis of the retinal arterial circulation, except in eyes with transient CRAO.

For BRAO: Following diagnostic criteria were used.

1. There was a history of sudden onset of visual loss in the involved segment of the retina in the eye.

2. On initial ophthalmic evaluation, there was evidence of acute retinal ischemia in the distribution of the occluded branch retinal artery.[4]

3. The eye had corresponding visual field defect.

4. Fluorescein fundus angiography, performed soon after the onset, showed absence or marked stasis of circulation in the involved branch retinal artery, except in eyes with transient BRAO.

For OIS: Our detailed study[5] of 39 eyes with OIS showed following diagnostic criteria of OIS.

1. Evidence of ocular ischemia indicated by low central retinal artery pressure, and ocular vascular hypoperfusion demonstrated by fundus fluorescein angiography, particularly of the choroidal vascular bed.

2. Evidence of anterior segment ischemia, usually manifested by iris and angle neovascularization.
3. History of amaurosis fugax and/or gradual or sudden visual loss.
4. Presence of carotid artery disease, particularly stenosis.
5. Patients were excluded if they had any other potential cause for NV, such as a history of ischemic central retinal vein occlusion, proliferative diabetic retinopathy, uveitis, retinal detachment, or tumor.

For amaurosis fugax: Based on our detailed study[6] of amaurosis fugax in ocular vascular occlusive disorders, we used the following diagnostic criteria.

a. Amaurosis fugax was defined as sudden, transient visual loss or transient blurring or obscuration of vision in an eye, with normal recovery of vision after the episode. The visual loss or blurring mostly involved the entire visual field, although in some cases it only corresponded to the area of the retina involved. It was not a scotomatous defect. Only those cases were included who had no other ocular lesions associated with it. There was no evidence of non-vascular causes, such as, anterior segment, lens or vitreous causes to explain it.
b. As indicated above, amaurosis fugax can be a symptom of OIS, so that cases of OIS were excluded in this category.

Exclusion criteria for the study

a. All patients with doubtful diagnosis or inadequate information about the carotid artery lesions were excluded. The study was started in 1973, but 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; therefore, all patients seen before 1987 were excluded. Patients with giant cell arteritis were excluded.

Examinations performed

a. 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. Medical history included arterial hypertension, diabetes mellitus, transient ischemic attack (TIA), stroke, hyperlipidemia, any cardiac problem, smoking, or any other systemic problem. 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 performed.
b. In persons older than 55 years, erythrocyte sedimentation and C-reactive protein evaluation were tested to determine whether ocular arterial occlusive disorders

were due to giant cell arteritis, because giant cell arteritis can cause anterior ischemic optic neuropathy, CRAO, amaurosis fugax and rarely OIS. It is well established that giant cell arteritis is an ophthalmic emergency and requires immediate, intensive systemic corticosteroid therapy to prevent any further visual loss. None of the patients without giant cell arteritis had any treatment.

c. In our study, a diagnosis of stroke was based entirely on evaluation by the patient's physician/neurologist.

Carotid and cardiac evaluation—For this, the patients at the initial visit were referred for consultation to the vascular surgery department for carotid evaluation and to the cardiology department for cardiac evaluation.

Carotid artery evaluation

a. The patients had carotid Doppler and/or carotid angiography performed, depending upon the discretion of the vascular surgeon. Catheter angiography was done by the cardiovascular surgeons primarily for diagnosis only, and not for treatment. Only those patients who had the modern high resolution carotid Doppler capable of determining the degree of stenosis and presence of plaque in the carotid arteries were included in the study.

b. The degree of carotid artery stenosis was graded by the surgical vascular laboratory as follows: 0–15%, 16–49%, 50–79%, 80–99%, and 100%.

c. The plaques were classified by the surgical vascular laboratory as follows: calcific, ulcerated, dense, soft, minimal, heterogeneous, smooth, irregular, moderate and unspecified.

Echocardiography

a. In addition to the carotid artery evaluation, we also performed echocardiography to determine if the heart was the source of embolism. Also, in carotid artery disease, the association of myocardial ischemia is well known. For echocardiography and cardiac evaluation, the patients were referred to the cardiology department of our hospital at their initial visit.

b. While we were able to perform carotid studies in the vast majority of our eligible patients with ocular arterial occlusive disorders (Table 1), that was unfortunately not possible in a few cases for the following reasons. (i) The most important factor was that medical insurance coverage of some patients did not pay for these tests, which made them reluctant to undergo them. (ii) The University of Iowa Hospitals and Clinics are a tertiary care center, and the vast majority of our patients travel from 100 to 350 miles to reach our clinic. Also we have arctic winters in our area; these factors make travel inconvenient, particularly hazardous during winter. These factors created big logistic problems for some of these patients from undergoing these studies. That applied also to cardiac assessment, with the additional difficulty of scheduling appointments in a busy cardiology department at patient's convenience.

The Follow-Up Evaluation

a. The ophthalmic follow-up evaluation was performed by one of us (SSH), and was identical to that described at the initial visit examination, except for the fluorescein fundus angiography which was performed only at the initial visit, to document the state of retinal, choroidal and optic disc circulation at onset. The follow-up protocol was individualized for each patient for various logistic reasons. At each visit, all patients were repeatedly questioned for any episode of TIA, stroke or myocardial ischemia.

Statistical Analysis

a. The diagnosis groups were compared using one-way ANOVA for age of first onset, and by logistic regression for the presence of an embolic source. For stenosis (>50%) and presence of plaque in the involved side, the logistic model fitted by the generalized estimating equations (GEE) method was used to compare among the diagnosis groups. Since there were subjects who had both sides involved, the GEE method was used to account for the correlation of responses at each side from the same subject. The Kaplan-Meier estimator was used to calculate the incidence of TIA/stroke after onset of ocular condition.

Results

a. This study included a total of 614 consecutive patients, 191 with NA-AION, 44 with amaurosis fugax, 119 with BRAO, 196 with CRAO, and 64 with OIS. The demographic characteristics of these patients are shown in Table 1. Onset of NA-AION and BRAO was at a significantly younger mean age compared to CRAO ($p<0.0001$ and $p=0.034$) and OIS ($p<0.0001$ and $p=0.012$).

b. Assessment of carotid artery stenosis and plaque was done by carotid Doppler/angiography on the side of arterial occlusion (Table 2). The stenosis finding in the involved side was worse in those with amaurosis fugax and in those with OIS than in those with BRAO, CRAO, and NA-AION ($p<0.0001$). There was >50% stenosis in 72% (95% CI: 57%, 83%) of those with amaurosis fugax, and 64% (95% CI: 52%, 75%) of those with OIS. In contrast, this was 31% (95% CI: 24%, 40%) for BRAO, 29% (95% CI: 23%, 36%) for CRAO, and 11% (95% CI: 8%, 16%) for NA-AION. The presence of plaques in the involved side also differed among the diagnosis groups ($p<0.0001$), significantly higher for OIS, amaurosis fugax, and CRAO compared to NA-AION ($p=0.002$, $p=0.003$, and $p=0.0003$, respectively) (Table 2). Since the groups differed in age at diagnosis, test comparisons were also performed adjusting for age, which produced similar results.

c. Echocardiography could be performed in 52% of NA-AION patients, 52% of BRAO patients, and 59% of CRAO patients. Of those tested, an embolic source was found in 53% (41%, 65%) of BRAO and 61% (52%, 69%) of CRAO patients compared to only 3% (1%, 9%) of NA-AION patients ($p<0.0001$).

TIA/stroke events before or after onset of ocular condition was reported in 6% (n=11) of NA-AION, 11% (n=5) of amaurosis fugax, 3% (n=4) of BRAO, 7% (n=14) of CRAO, and 17% (n=11) of OIS patients. For TIA/stroke after onset, the Kaplan-Meier estimate of the incidence of TIA/stroke within 3 months after onset was 3% (95% CI: 0.4%, 19%) for amaurosis fugax, 1% (95% CI: 0.3%, 4.1%) for CRAO, and 6% (95% CI: 2%, 17%) for OIS. Among BRAO and NA-AION patients, each had 2 patients who had a stroke/TIA more than 5 years after the onset.

a. A report of myocardial ischemia before or after onset of ocular condition was 6% (n=11) for NA-AION, 52% (n=23) for amaurosis fugax, 22% (n=26) for BRAO, 21% (n=41) for CRAO, and 22% (n=14) for OIS.

b. Embolism is the main source of occlusion in CRAO and BRAO. Since, unfortunately, echocardiography could not be performed in all these patients (for logistic reasons discussed above), we compared the findings of carotid artery stenosis (>50%) and of plaques in those with and without echocardiography. In CRAO, there was no significant difference in the proportion with stenosis between those who had echocardiography (26.3%) and those who did not (33.2%) (p=0.304), nor in the proportion of plaques between those who had echocardiography (72.0%) and those who did not (78.5%) (p=0.343). Similarly, in BRAO, there was no significant difference in the proportion with stenosis between those who had echocardiography (26.7%) and those who did not (36.7%) (p=0.243); however, those who had echocardiography showed lower proportion (56.1%) with plaques than those who did not (75.3%) (p=0.032).

Discussion

a. It is vital to make clear at the outset that not all ocular arterial occlusive disorders are acute disorders causing acute vision loss; some of them may be chronic in nature. Since this study included OIS, which is a chronic arterial occlusive disorder (primarily caused by arterial hypoperfusion[5]), that is precisely why, in this study, we used the term "ocular arterial occlusive disorders" and not "acute ocular arterial occlusive disorders". In previously published studies dealing with the pathogenesis of NA-AION, we have reported that, although NA-AION is mostly due to arterial hypoperfusion in the posterior ciliary artery circulation in the optic nerve head[1,2], in some cases, it is definitely due to embolism into the posterior ciliary arteries (as revealed by fluorescein fundus angiography at onset).[1,7]

b. Carotid artery disease can produce ocular arterial occlusive disease by two mechanisms: (i) by embolism and (ii) by hemodynamic disturbance (i.e. poor arterial perfusion).

Embolic disorders

a. It is well established that the major source of embolism in the carotid artery is the plaque it contains. The data in our Table 2 shows that plaque is the most common finding in these disorders. Based on that, it becomes evident that

embolism is the most common cause of CRAO, BRAO, and amaurosis fugax; and our studies revealed that NA-AION in some eyes is also definitely due to embolism into the posterior ciliary arteries (as revealed by fluorescein fundus angiography at onset).[1,7] Although, in OIS, our study showed plaques in the carotid artery (because of severe carotid artery atherosclerosis), ocular hypoperfusion was actually the primary etiological factor in its development.

b. Thus, our findings indicate that the most common source of embolism in CRAO, BRAO and amaurosis fugax (and much less commonly in NA-AION), is plaque in the carotid artery; a much less common source is the severity or prevalence of stenosis in the artery. These emboli may go to the retina, choroid or optic nerve head.

c. The emboli are usually of three types: (i) cholesterol (Hollenhorst plaques), (ii) platelet-fibrin and (iii) calcific emboli, and very rarely of other nature. Arruga and Sanders[8] in their study of retinal emboli showed cholesterol emboli in 74%, platelet-fibrin in 15.5% and calcific emboli in 10.5%. In determining the severity of vascular occlusion, the characteristic of the embolus is important; for example, platelet-fibrin emboli, being smooth, usually migrate easily in the vessels and tend to produce transient occlusion more often than permanent occlusion. By contrast, calcific emboli are rough in texture, so they get impacted and do not migrate, resulting in permanent occlusion. Cholesterol emboli also tend to migrate but much less frequently than the platelet-fibrin emboli; in some cases the cholesterol emboli may not occlude the vessel completely, as has been demonstrated by fluorescein fundus angiography.

Hemodynamic disturbances

a. In carotid artery disease, this plays an independent role, unrelated to embolism, in producing ocular ischemic lesions. To understand this, one has to determine the factors which control the ocular blood flow. Ocular blood flow is calculated by using the following formula:

$$\text{Blood Flow} = \frac{(1)\ \text{Perfusion pressure}}{(1)\ \text{Resistance to blood flow}}$$

Perfusion pressure can be calculated in two ways.

Perfusion pressure = Mean arterial blood pressure (BP) minus venous BP in the retinal/choroidal vessels.

Perfusion pressure = Mean arterial BP in the retinal/choroidal vessels minus intraocular pressure. Normally the BP in the central retinal vein at the optic disc is slightly higher than the intraocular pressure, so that for all practical purposes, intraocular pressure is usually a good index of the ocular venous pressure.

$$\text{Mean BP} = \text{Diastolic BP} + 1/3(\text{systolic minus diastolic BP}).$$

a. Carotid artery stenosis results in a fall of BP in the ocular vascular bed, and consequently in hemodynamic disturbances. The severity of a fall of BP depends upon the degree of stenosis; a mild amount of stenosis may not cause any appreciable hemodynamic disturbance. There is, however, an important caveat here, because anatomical studies by one of us (SSH)[9] showed that sometime the ophthalmic artery originating from an atherosclerotic internal carotid artery has a markedly stenosed lumen at its origin from the internal carotid artery, with little or no stenosis of the internal carotid artery itself; in such a case it is the ophthalmic artery stenosis which is primarily responsible for the fall of BP in the ocular vascular bed.

b. In carotid artery disease, hemodynamic disturbances can also be produced by another mechanism. Our study[10] showed that serotonin (5-hydroxytryptomine) released by platelets aggregation on atherosclerotic plaques in the carotid artery may trigger transient vasospastic occlusion of the central retinal artery and/or posterior ciliary artery. This transient spasm of the ocular arteries may play a role in the development of amaurosis fugax or even permanent ocular ischemic lesions.

c. Our study showed that carotid artery stenosis was significantly more marked in OIS and amaurosis fugax compared to CRAO, BRAO and NA-AION ($p<0.0002$) – 80% to 100% occlusion of the internal carotid artery was seen in 61% in OIS and in 54% in amaurosis fugax (Table 2). This indicates that severe stenosis or complete occlusion of the carotid artery plays a major role in OIS and amaurosis fugax. Therefore, hemodynamic disturbance causing hypoperfusion in the ocular arterial bed is an important cause of the development of OIS, amaurosis fugax, and occasionally of CRAO[11]. In amaurosis fugax, this fall in ocular perfusion pressure, can play a role by the following mechanism. Carotid artery stenosis of 80% to 100% results in a marked fall of BP in the ocular vascular bed. In such a situation, since ocular perfusion pressure is equal to mean BP minus the intraocular pressure, if there is a transient fall of systemic blood pressure (as in orthostatic hypotension) and/or a rise in intraocular pressure (as by rubbing or squeezing the eye or stooping down), that can transiently result in fall of ocular perfusion pressure and compromise ocular circulation, resulting in amaurosis fugax. Release of serotonin (see above) can also cause amaurosis fugax in some cases. Amaurosis fugax can be due to either retinal ischemia or optic nerve head ischemia.

Association of Carotid Artery Disease with TIA/Stroke

a. The risk of development of TIA/stroke in patients with retinal artery occlusion and amaurosis fugax is well-known but its incidence is controversial, as is evident from the following very brief review.

b. In our study, TIA/stroke before or after onset of ocular arterial occlusive disorder, was reported by 3% of BRAO, 6% of NA-AION, 7% of CRAO, 11% of amaurosis fugax, and 17% of OIS patients. The Kaplan-Meier estimate of the incidence of TIA/stroke within 3 months after onset was 3% for amaurosis

fugax, 1% for CRAO, and 6% for OIS; among BRAO and NA-AION patients, each had 2 patients who had a stroke/TIA more than 5 years after the onset.

c. In 2014, a retrospective study by Lee et al.[12] from South Korea, based on 33 patients with acute retinal artery occlusion (18 with CRAO and 15 with BRAO), reported evidence of acute ischemic stroke in 8 (24.2%) subjects. This is in sharp contrast to the findings in our study, which showed: (a) stroke/TIA before or after onset of ocular condition in 3% of 119 BRAO and 7% of 196 CRAO patients, and (b) the Kaplan-Meier estimate of the incidence of TIA/stroke within 3 months after onset was 1% in 196 CRAO and only 2 of 119 BRAO patients had a stroke/TIA more than 5 years after the onset. This difference between the two studies seems to be due to problems with the study by Lee et al.[5]; they had 53 subjects with retinal artery occlusion but they give data about 33; it also seems their patient population was biased for neurological problems, resulting in that unusually high incidence of stroke/TIA. Lee's group in a 2015 study[13], based on a review of 2009–2010 database of the "National Health Insurance Review and Assessment Service of Korea" found reports of 1585 patients with CRAO; their stroke incidence one year before and one year after onset of CRAO was 9.18%. However, they admitted there were multiple limitations in their National Health Insurance Review study, which included: (i) "the study cannot provide the absolute risk of ischemic stroke in patients with incident CRAO"; (ii) "we could not validate the diagnostic codes in the claims data by reviewing the medical records", and (iii) "we could not assess the effect of cardiovascular and neurologic evaluations and subsequent interventions in patients with incident CRAO and stroke/AMI (acute myocardial infarction)."

d. In contrast to the studies by Lee and colleagues.[12,13], as mentioned above, in our study, TIA/stroke events before or after onset of CRAO was 7% and of BRAO 3%. Study design determines study outcome. The study designs of Lee's group[13] and that of ours differ markedly; therefore, the findings of the two studies cannot be compared. Our study reports the absolute incidence of stroke/TIA among these ocular conditions, based on the data carefully collected by a single investigator (SSH). Their data were based on the "National Health Insurance Review and Assessment Service", and they compared relative risk of stroke at time intervals from onset of the CRAO, but that does not provide the absolute risk. From their data, the risk of ischemic stroke was 3% within 90 days after the onset of CRAO in patients who were followed, while in our study it was 1%.

e. In the literature there are other studies reporting the prevalence of stroke/TIA in patients with retinal artery occlusion or amaurosis fugax. For example, Trobe[14] reported that the risk of future stroke in untreated patients with amaurosis fugax, retinal plaques, and infarcts is less than 3% per year, far lower than that expected for cerebral (hemispheric) TIAs. Hankey et al.[15], in a study of 99 patients with retinal artery occlusion, over the following five years found the actuarial average absolute risk of stroke 2.5% per year. Dunlap et al.[16] in 130 consecutive patients with a diagnosis of Hollenhorst plaques, central or branch retinal artery occlusion, found that the presence of a plaque or retinal artery occlusion is

associated with a low prevalence of extracranial cerebrovascular disease that requires intervention. The European carotid surgery trial[17] showed that the odds of stroke was decreased in patients with ocular ischemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral TIA or stroke. De Potter and Zografos[18], in a study of 151 patients with retinal arterial obstruction, reported that the survival rate of the entire group with retinal artery occlusion was not significantly different from that of the age- and sex-matched group (p= 0.29).

f. Thus, our study and others contradict the findings and conclusions of Lee's group[12,13] Also Brown and Vasudevan[19] pointed the following flaws in the study by Lee et al.[12]: (a) in that study there were no patients with amaurosis fugax, so their findings do not apply to amaurosis fugax, and (b) in their retrospective study, there is no mention of how many patients first presented with new neurological deficits and vision loss; also patients who had no neurological symptoms were unlikely to have an abnormal brain MRI, so it serves no useful purpose to subject them to MRI evaluation.

g. Thus, the high incidence reported by Lee et al.[12] does not represent what is seen in the sort of unselected, acute retinal artery occlusion cases commonly seen in ophthalmology clinics. If what Lee's study showed were typical, we should have had a large number of patients in our study develop stroke, which did not happen. In spite of the above limitations, Lee at al.[12] mistakenly advocated the practice of submitting all CRAO and BRAO patients to a detailed neurological workup, immediately and urgently. As discussed above, in our study of 196 CRAO and 119 BRAO patients, the Kaplan-Meier estimate of the incidence of TIA/stroke within 3 months after onset was 1% in CRAO, and among BRAO only 2 patients who had a stroke/TIA more than 5 years after the onset. Once the whole situation is seen in proper perspective, that mistake can be put aside.

h. Discussion of the pathogenesis of each condition investigated in this study is beyond the scope of this study, because it deals only with the role of carotid artery disease.

Association of Carotid Artery Disease with Myocardial Ischemia

a. The association of carotid artery disease with ischemic heart disease is well established. In the recent large study by Lee's group[1], based on a data of 1585 patients with CRAO, during a period of one year before and one year after onset of CRAO, the incidence of myocardial ischemia was 0.9%. In our study, incidence of myocardial ischemia before or after onset of ocular condition was 52% in amaurosis fugax, 22% in OIS, 22% in BRAO, 21% in CRAO, and 6% in AION. It was a surprise to find, for the first time, that the incidence of myocardial ischemia was highest in patients with amaurosis fugax. There is no selection bias in the patients seen with ocular arterial occlusive disease in our Ocular Vascular Clinic at Iowa City which would explain that.

b. The primary factor for this association between the carotid artery disease and myocardial ischemia seems to be hyperlipidemia, which results in widespread atherosclerosis, including atherosclerosis of the coronary and carotid arteries. Coronary artery atherosclerosis results in ischemic heart disease. Carotid artery disease and ischemic heart disease *per se* have no direct cause-and-effect relationship with each other.

c. Limitation in our study is that, while we were able to performed carotid studies in the vast majority of our eligible patients with ocular arterial occlusive disorders, that was unfortunately not possible in a few of them, for the reasons discussed above.

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Our study of 728 eyes in 614 consecutive patients with various ocular arterial occlusive disorders showed among them different incidences of carotid artery stenosis and plaques, and transient ischemic attack/stroke and myocardial ischemia.

Table 1

Demographic characteristics

Variable (Number of patients)	AION (n=191)	Amaurosis Fugax (n=44)	BRAO (n=119)	CRAO (n=196)	Ocular ischemic syndrome (n=64)
Sex (male)	112 (59%)	26 (59%)	80 (67%)	110 (56%)	43 (67%)
Age (at onset or visit1)					
Mean (SD)	60.8 (12.5)	65.9 (10.0)	62.9 (12.8)	67.1 (13.3)	69.5 (8.3)
Range	26–91	46–87	22–86	16–90	49–85
Involved side					
Right eye	63 (33%)	17 (39%)	52 (44%)	95 (48%)	23 (36%)
Left eye	53 (28%)	19 (43%)	60 (50%)	94 (48%)	25 (39%)
Both eyes	75 (39%)	8 (18%)	7 (6%)	7 (4%)	16 (25%)
Onset to first visit (wks)	(n=189)	(n=42)	(n=115)	(n=195)	(n=49)
Median [IQR]	2.4 [1.0–5.3]	8.0 [2,1–36.3]	1.1 [0.3–7.4]	1.0 [0.1–4.1]	9.7 [2.0–28.4]
Range	0–218	0–271	0–240	0–162	0–428
Follow-up (yrs)					
Median [IQR]	3.3 [1.2–8.2]	1.4 [0.2–3.4]	1.8 [0.2–4.7]	0.7 [0.2–3.4]	0.9 [0.1–3.8]
Range	0–20.7	0–21.8	0–24.1	0–20.4	0–17.4
<3 months	19 (10%)	11 (25%)	30 (25%)	66 (34%)	19 (30%)

Table 2

Doppler, Angiography, and Echocardiography findings

Variable	AION (191 patients, 266 eyes)	Amaurosis fugax (44 patients, 52 eyes)	BRAO (119 patients, 127 eyes)	CRAO (196 patients, 203 eyes)	Ocular ischemic syndrome (64 patients, 80 eyes)
Doppler/Angiography					
Doppler only	174 (91%)	19 (43%)	41 (34%)	94 (48%)	26 (41%)
Angiography only	1 (1%)	9 (20%)	16 (13%)	20 (10%)	23 (36%)
Doppler+Angiography	14 (7%)	14 (32%)	60 (50%)	79 (40%)	11 (17%)
Not done	2 (1%)	2 (5%)	2 (2%)	3 (2%)	4 (6%)
Stenosis (%) involved side	(n=261 eyes)	(n=48 eyes)	(n=122 eyes)	(n=199 eyes)	(n=73 eyes)
0–15%	201 (77%)	8 (17%)	66 (54%)	113 (57%)	11 (15%)
16–49%	33 (13%)	6 (13%)	19 (16%)	29 (15%)	15 (21%)
50–79%	12 (5%)	8 (17%)	20 (16%)	34 (17%)	2 (3%)
80–99%	4 (2%)	15 (31%)	10 (8%)	14 (7%)	9 (12%)
100%	11 (4%)	11 (23%)	7 (6%)	9 (5%)	36 (49%)
Plaque involved side	(n=250 eyes) 130 (52%)	(n=36 eyes) 31 (86%)	(n=118 eyes) 75 (64%)	(n=177 eyes) 131 (74%)	(n=35 eyes) 34 (97%)
Types of plaque	(n=250 eyes)	(n=36 eyes)	(n=118 eyes)	(n=177 eyes)	(n=35 eyes)
Calcific	40 (16%)	8 (22%)	15 (13%)	25 (14%)	7 (20%)
Ulcerated	6 (2%)	6 (17%)	22 (19%)	24 (14%)	8 (22%)
Dense	2 (1%)	6 (17%)	5 (4%)	7 (4%)	3 (9%)
Soft	0 (0%)	3 (8%)	2 (2%)	5 (3%)	5 (14%)
Heterogeneous	0 (0%)	2 (6%)	0 (0%)	3 (2%)	0 (0%)
Minimal	0 (0%)	2 (6%)	13 (11%)	24 (14%)	4 (11%)
Smooth	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Irregular	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Moderate	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Unspecified	81 (32%)	7 (19%)	19 (16%)	43 (24%)	11 (31%)
Echocardiography done	100 (52%)	4 (9%)	62 (52%)	117 (60%)	4 (6%)

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Variable	AION (191 patients, 266 eyes)	Amaurosis fugax (44 patients, 52 eyes)	BRAO (119 patients, 127 eyes)	CRAO (196 patients, 203 eyes)	Ocular ischemic syndrome (64 patients, 80 eyes)
With cardiac embolic source	(n=100) 3 (3%)	(n=4) 3	(n=62) 33 (53%)	(n=117) 71 (61%)	(n=4) 2
Location of embolus					
Mitral	1	0	21	50	1
Aortic	0	1	17	40	1
Patent Foramen ovale	2	0	4	4	0
Other	0	2	17	31	1
Doppler/Angio/Echo findings	(n=99)		(n=62)	(n=111)	
No stenosis, plaque and cardiac embolic source	48 (48%)	0	14 (23%)	16 (14%)	0
Stenosis*/plaque only	48 (48%)	0	15 (24%)	26 (24%)	2
Cardiac embolic source only	2 (2%)	1	10 (16%)	12 (11%)	0
With stenosis*/plaque and cardiac embolic source	1 (1%)	2	23 (37%)	57 (51%)	2

*At least >15% stenosis