Acute occlusion of the retinal arteries: current concepts and recent advances in diagnosis and management

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Abstract
Purpose/Background—Central retinal artery occlusion (CRAO) is usually a blinding event, and is not an infrequent presentation to the accident and emergency (A&E) department. The evidence-base in support of current treatment options is weak.
Methods—This paper reviewed the literature germane to the diagnostic, therapeutic and prognostic aspects of retinal arterial occlusive disease.
Results—The visual prognosis associated with CRAO remains poor, and current therapeutic practices are of unproven benefit. The non-ophthalmologist in the A&E department should lie the patient flat and give a stat dose of intravenous acetazolamide in an attempt to improve the retinal perfusion pressure.
Conclusion—The management of acute occlusion of the central retinal artery has not changed over the past 30 years, although the potential benefits of superselective intra-arterial fibrinolytic therapy warrant evaluation in a randomised controlled trial. The identification of underlying pathology is an essential component of medical care, and all cases should be followed up by an ophthalmologist because of the possibility of ocular rubecrosis.

Keywords: atheroma; embolus; fibrinolysis; retinal artery occlusion

Pathophysiology
ANATOMICAL CONSIDERATIONS
The retina receives its blood supply from two sources, both of which must be intact to maintain retinal function. The choriocapillaris of the choroid nurtures the outer retina, whereas the central retinal artery (CRA) and its end artery branches feed the inner retinal layers. These circulations both originate from the ophthalmic artery, the CRA being its first branch and the ciliary arteries giving rise to the choriocapillaris. Occasionally, a cilioretinal artery arises from the ciliary circulation and supplies a portion of the papillomacular bundle.

The central retinal artery enters the globe at the optic disc where it bifurcates into superior and inferior branches, each of which in turn bifurcates into nasal and temporal branch retinal arteries. Therefore, occlusion of the central retinal artery deprives the entire inner retina of its blood supply unless a cilioretinal artery is present (15–30% of eyes).

PATHOLOGICAL CONSIDERATIONS
Arterial occlusive disease of the retina is the result of either arteriosclerotic thrombosis, vasculitis, embolic impaction, vasospasm or systemic hypotension. Over 75% of patients with CRAO suffer from generalised atheromatous disease, which is frequently associated with hypertension or diabetes mellitus, or both. Narrowing of the arterial lumen is typically seen at the level of the lamina cribrosa, and a final thrombotic episode is believed to account for the acute obstruction. However, obliteration of the retinal arterial lumen is also seen in the systemic vasculitides, most notably giant cell arteritis where an embolism can arise from an inflamed proximal vessel.

Retinal emboli may consist of a variety of materials including platelet aggregates, cholesterol, calcium, fat, parasites, air and even prosthetic heart valves. The platelet-fibrin and cholesterol emboli typically arise from atheromatous plaques at the carotid bifurcation or the internal carotid artery, whereas calcific and septic emboli are usually of cardiac valvular origin.

Evaluating the patient with acute occlusive disease of the retinal arterial circulation
HISTORY AND EXAMINATION
The visual symptoms associated with retinal artery occlusion depend on the vessel involved. Acute CRAO presents with a sudden, painless
and profound drop in vision, usually with an initial Snellen acuity of counting fingers or worse, unless a cilioretinal artery is present in which case central vision may be preserved. Acute BRAO most commonly affects the temporal vessels, and the presenting visual acuity can vary from hand movements to 6/5. A careful history aimed at identifying all aetiopathogenic mechanisms involved in the occlusive event should be taken. Particular attention should be directed to the presence of hypertension, diabetes mellitus, atherosclerotic cardiovascular and cerebrovascular disease and symptoms suggestive of giant cell arteritis. The clinician should also inquire after cigarette smoking, palpitations, valvular heart disease and a history of transient ischaemic attacks.

In patients with a “negative” history, and particularly in subjects less than 40 years of age, other aetiological factors should be considered and these include systemic vasculitis, migraine, sickle cell haemoglobinopathy, myeloproliferative disorders, hypercoagulable states, use of oral contraceptives and intravenous drug abuse (table 1).

Ocular examination
The ophthalmoscopic features of acute CRAO include a whitish, oedematous retina attributable to infarction, especially at the posterior pole where the nerve fibre layer and ganglion cell layer are thickest. As these layers are absent in the fovea, the underlying choroidal vascular bed can be seen in this area thus giving rise to the classic cherry-red spot (fig 1). In the presence of a patent cilioretinal artery, the retinal region served by the unobstructed vessel is not involved (fig 2). Disc pallor and retinal vascular narrowing are also characteristic of CRAO, although normal appearing retinal vessels do not rule out a complete occlusion of the central retinal artery. BRAO results in retinal oedema in the distribution of the affected vessel only (fig 3). Obstruction of a cilioretinal artery, or even a macular branch arteriole, gives rise to oedema of that region of the macula served by the occluded vessel and usually affects central vision.

Although a diagnosis of retinal arterial occlusion is usually obvious, a careful examination of the affected eye may provide important clues relating to aetiological factors. Ocular characteristics causally linked with retinal artery occlusion include acutely raised intraocular pressure, pre-retinal arterial loops and drusen of the optic nerve head (table 1). The presence of hypertensive, diabetic or sickle cell retinopathy is suggestive of small vessel disease. The clinical and morphological appearance of retinal emboli can also be of diagnostic value. Cholesterol emboli, also known as Hollenhorst plaques, are small, yellow and refractile (fig 4). Calcific emboli are single, white and non-scintillating plaques located in the proximal retinal vasculature whereas fibrino-platelet emboli are small, pale bodies. However, interobserver agreement with respect to the categorisation of retinal emboli is poor, and therefore a comprehensive systemic evaluation is indicated in all cases of acute obstruction of the retinal arteries (table 2).
Non-ocular examination

The physical examination is directed toward the possible causes of the acute occlusive event and should include a complete cardiovascular assessment. Of particular interest is the rate and rhythm of the radial pulse, and the blood pressure. Auscultation is useful in the detection of carotid bruits and heart murmurs. If giant cell arteritis is a possibility, nodular temporal arteries and scalp tenderness should raise the clinician’s index of suspicion. In the absence of an obvious cause of the retinal artery occlusion, especially in young patients, you should also be attentive for vasculitic rashes.

INVESTIGATIONS

Ophthalmical investigations

Fundus fluorescein angiography (FFA) is not routinely indicated in the acute phase of retinal arterial occlusive disease unless the diagnosis is in doubt. Angiographic findings associated with CRAO and BRAO include delayed filling of the affected vessels, reduced arterial calibre and “cattle-trucking” of the blood column in the branch arteries.

Systemic investigations

The following investigations are recommended in all cases of retinal artery occlusion: electrocardiography; urine analysis; fasting blood glucose; fasting blood cholesterol; fasting serum triglycerides; full blood count. An erythrocyte sedimentation rate and C reactive protein levels are justified in all cases to exclude giant cell arteritis.

In patients less than 40 years of age additional investigations are indicated to investigate whether a vasculitic process or a hypercoagulable state has contributed to the occlusive event. Brown et al have found evidence of a coagulation disorder in one third of young patients with retinal artery occlusive disease.17 The mechanisms involved are complex and include thrombocytosis,8 an increase in coagulation factor or platelet activity,17 deficiencies of protein C and protein S,16,22 resistance to activated protein C,23 and the interaction of lupus anticoagulant and anticardiolipin antibodies with phospholipids.19 Routine coagulation screening tests, including prothrombin time and partial thromboplastin time, as well as the more specialised platelet activity and coagulation factor studies are therefore indicated in unexplained retinal artery occlusions in young subjects. A screen for vasculitis should include the following: anticardiolipin antibodies;8 anti-nuclear antibodies17; anti-double stranded DNA antibodies;10

Hyperhomocystinemia has been reported in several patients with CRAO and BRAO25 26 and this is attributed to its toxic effect on the vascular endothelium. Consequently, in suspected homocystinuria or heterozygosity for homocystinuria an oral methionine loading test is recommended as hyperhomocystinaemia can be successfully treated with appropriate vitamin supplements.17

Finally, and only if there are strong clinical indications, testing for human immunodeficiency virus (HIV) may be indicated, as retinal arterial occlusive disease has been described in young people with HIV infection.15 28

Doppler studies of the carotid arteries are recommended in all cases of CRAO and BRAO, as there is a reported 19% incidence of haemodynamically significant carotid artery stenosis among these patients.21 Transthoracic echocardiography should be performed in all young patients with occlusive disease of the retinal arteries, and in older patients with any of the following cardioembolic risk factors: subacute bacterial endocarditis; rheumatic heart disease; mitral valve prolapse; recent myocardial infarction; prosthetic valve; intravenous drug abuse; cardiac tumour; heart murmur; ECG abnormalities including atrial fibrillation, acute ST elevation and Q waves.29 30 Cardiac abnormalities detected by
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Ophthalmic management, if seen within 48 hours of the occlusive event

A Lie the patient flat
Ocular massage
Stat intravenous acetazolamide, 500 mg
and/or
Paracentesis
Inhalation of carbogen
or
B Intraocular artery fibrinolysis, followed by 2 to 3 days of intravenous heparinisation. This therapeutic option should only be considered in a clinical setting that offers appropriate neuroradiological support and expert supervision.

Non-ophthalmic management
Cessation of cigarette smoking
Dietary advice in the presence of hypercholesterolaemia and hypertriglyceridaemia
Management of any coexisting hypertension, diabetes mellitus or hyperlipidaemia
Oral aspirin therapy
Specialist referral in the presence of systemic vasculitis, significant carotid artery stenosis, hypercoagulable states, valvular heart disease and complex arrhythmias.

Table 3 Management options in patients with acute central retinal artery occlusion

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Acute ophthalmic management

The variety of reported management options for CRAO and BRAO reflects the lack of a safe and efficacious treatment for this vascular occlusive event. The aim of treatment is to increase the perfusion pressure of the retinal circulation, or to dislodge or lyse the obstructing thrombus/embolus. Currently accepted practice in the management of acute CRAO or BRAO is dictated largely by the level of available expertise. For example, the non-ophthalmologist in a general A&E department should lie the patient flat, give a stat dose of acetazolamide (500 mg) intravenously, and instruct the patient to perform ocular massage. The ophthalmologist in the same environment may also wish to perform anterior chamber paracentesis. In a few centres, appropriate neuroradiological and ophthalmic support to consider selective intra-arterial fibrinolytic therapy may be available (table 3). The rationale and evidence base for these therapeutic approaches is discussed in this section.

The length of time the human retina can tolerate ischaemia before irreversible damage occurs remains uncertain. Although significant visual recovery has been reported up to 72 hours after the occlusive event, the visual prognosis tends to worsen with increasing duration of the visual symptoms. Hayreh et al reported on the reversibility of the fundoscopic, angiographic, electrophysiological and morphological findings after clamping of the CRA in 63 Rhesus monkeys, and concluded that the retinal tolerance time was approximately 100 minutes. However, it is probable that the degree of retinal ischaemia induced by clamping of the central retinal artery is greater than in the clinical setting as filling of the arterial system, albeit delayed, is seen on FFA in cases of CRAO.

Increasing the retinal perfusion pressure

The perfusion pressure of the retinal circulation can be increased by one of the following mechanisms: reducing intraocular pressure (IOP); dilating the ophthalmic and central retinal arteries; increasing the ophthalmic artery pressure.

Reducing IOP

The combination of ocular massage and intravenous acetazolamide (500 mg) can achieve an IOP as low as 5 mm Hg within a short period of time, and is probably the most widespread form of treatment for cases of CRAO and BRAO that present within the acute stage. Ocular massage is achieved by asking the patient to digitally apply pressure to the globe through the closed eyelids of the affected eye for a period of 15 to 30 minutes. The importance of ocular massage and intravenous acetazolamide rests on the fact that these steps can be undertaken by non-ophthalmic staff of the A&E department.

The role of anterior chamber paracentesis is, however, more controversial. This is achieved by inserting a 27 gauge needle into the anterior chamber via the limbus and withdrawing 0.1 to 0.2 ml of aqueous fluid. Paracentesis falls within the remit of the ophthalmologist, as it is an intraocular procedure, and should never be attempted by non-ophthalmic staff of the A&E department. The potential benefits of paracentesis include a dramatic drop in IOP, and dilatation of the retinal arteries because of the vascular tortuosity resulting from distortion of the globe. However, a maximum increase in retinal arterial volume flow of only 20% has been estimated from animal studies, and a rise in perfusion pressure of less than 15% is expected when the IOP falls from 15 mm Hg to 5 mm Hg. In addition to a lack of clinical efficacy, other factors that discourage ophthalmologists from performing paracentesis in cases of CRAO include the risk of complications and the need to repeat the procedure on a two hourly basis to maintain the low IOP.

Dilating the ophthalmic and retinal arteries

Several techniques to induce retinal arterial vasodilatation have been reported and these include ocular massage, retrobulbar administration of vasodilator drugs and inhalation of carbogen. In addition to reducing the IOP, ocular massage can increase the retinal arterial flow volume by 180% as a result of the vasodilatation that occurs on release of digital pressure. A small rise in ophthalmic artery pressure, which will also influence retinal
perfusion pressure in a favourable way, is
achieved by lying the patient flat.\(^9\) Retrobulbar
injections of vasodilator drugs and the inha-
lation of carbogen are of doubtful clinical
benefit, and are therefore not in widespread
use.\(^{33}\)

DISLODGING THE THROMBUS/EMBOLUS
Ocular massage is known to cause retinal arte-
rional dilatation and large fluctuations in IOP. It
has been postulated that this activity may
mechanically facilitate the disintegration of a
thrombus, or dislodge an impacted embolus
into a more peripheral part of the retinal
circulation.\(^6\)

LYSING THE THROMBUS/EMBOLUS
The limited success,\(^{39}\) and risk of intracerebral
haemorrhage,\(^{17}\) associated with systemic ad-
ministration of thrombolytic agents for CRAO
has resulted in its discontinuation in favour of
selective intra-arterial fibrinolytic therapy.

Selective intra-arterial fibrinolytic therapy
Considerable success has been reported after
injection of urokinase or tissue plasminogen
activator (TPA) into the ophthalmic artery via
a microcatheter in cases of CRAO.\(^{19, 30}\) How-
ever, the practice of selective intra-arterial
fibrinolysis is not widespread as specialist
neuroradiological support is required and seri-
ous complications can occur.

In a recent meta-analysis, we have reported a
final visual acuity of 6/12 or better in 27% of
subjects after selective intra-arterial fibrinolytic
therapy for CRAO compared with 18% to 21%
for conventional approaches.\(^{12, 40, 41}\) Also, a poor
visual outcome of 3/60 or worse was seen in
60.6% of eyes treated with intra-arterial
fibrinolytic therapy, and this compares with
62.5% to 66% for conservative treatment modalities.
\(^{12, 42}\) It seems, therefore, that this
treatment may be of marginal benefit. Should
the visual results improve with advances in
neuroradiological techniques, this treatment
option is likely to become increasingly avail-
able. We believe that a substantial proportion
of patients would consent to undergo this
emergency procedure as a recent survey has
shown that 37% of binocular adults with
CRAO would risk a cerebrovascular accident
or death to triple their chances of recovering a
visual acuity of 6/36 or better in one eye, and
this rose to 80% for monocular subjects.\(^{85}\)

SYSTEMIC ANTICOAGULATION
After regional thrombolytic therapy for CRAO,
intravenous heparin is administered for two to
three days. The value of therapeutic heparini-
sation alone in this group of patients remains
uncertain.\(^{45}\) Recently Liu et al have reported an
improvement in retinal function, as evaluated
by electroretinography, in rats after temporary
occlusion of the CRA using certain coumarin
derivatives.\(^{45}\) However, the clinical application
of these findings has yet to be investigated.

SYSTEMIC ANTIPLATELET THERAPY
To our knowledge, the value of oral aspirin
after CRAO and BRAO has not been investi-
gated. However, in the absence of contraindi-
cations, it seems clinically prudent to prescribe
this antiplatelet drug in an attempt to reduce
the risk of further thrombotic occlusive events
affecting the retina and other organs.

Ophthalmic follow up
Although the visual acuity is unlikely to
improve more than one week after an acute
obstruction of a retinal artery, follow up by an
ophthalmologist is essential because of possible
retinal and iris neovascularisation. The patho-
genesis of ocular neovascularisation after these
acute vascular occlusive events remains poorly
understood, but there is a general consensus
that chronic retinal ischaemia plays an impor-
tant aetiological part.\(^{46}\) The incidence of ocular
neovascularisation after CRAO lies between
16.6% and 18.75%, and the majority of these
go on to develop rubeotic glaucoma (67.5% to 83.3%).\(^{47, 48}\) The time interval between the
occlusive event and the development of neo-
vascularisation ranges from 10 days to 10
months, but the vast majority occur within
three months of the arterial obstruction.\(^{49}\)
Panretinal photocoagulation has been shown to
reduce the risk of rubeotic glaucoma and a
painful eye, and close ophthalmic follow up is
therefore recommended for a minimum period
of three months after the occlusive event.\(^{50}\)

Non-ophthalmic follow up
Systemic management in cases of CRAO and
BRAO is aimed at reducing morbidity and
mortality associated with predisposing and
related conditions. Measures recommended in
all cases include cessation of smoking, appro-
priate dietary advice, managing blood pressure
and oral aspirin therapy. Otherwise, associated
disorders should be treated on their own mer-
ts, and specialist referral is indicated in the
presence of: systemic vasculitis, significant
carotid artery stenosis, hypercoagulable states,
valvular heart disease and complex arrythmias
(table 3).

Prognosis

VISUAL PROGNOSIS
In those eyes where the macula is not served by
ciliary arterial, the visual outcome after
obstruction of the central retinal artery is gen-
erally poor. CRAO is associated with a poor
final acuity of counting fingers or worse in
62.5% to 66% of cases, and with a good final
acuity of 6/12 or better in 18% to 21% of
affected eyes.\(^{42}\) The visual outcome is related
to the presenting acuity and the duration of
visual impairment,\(^{12}\) and seems to be improved
in patients receiving intra-arterial fibrinolytic
therapy.

SYSTEMIC PROGNOSIS
The most common cause of death in subjects
who have suffered acute occlusive events of the
retinal arteries is cardiovascular disease.\(^1\)\(^4\)
Although the survival prognosis for this entire
group of patients is statistically comparable to
age and sex matched controls, the subgroup
with visible retinal emboli do have a signifi-
cantly shorter life expectancy.\(^{3, 50}\) Of the 152
patients with retinal arterial obstructions reported by De Potter and Zografos, 26% died during a mean period of follow up of 9.7 years. 29

Conclusion
Sudden loss of vision is a common presentation to the A&E department, and acute occlusive events of the retinal arterial circulation account for a substantial proportion of cases. All patients with CRAO or BRAO should be appropriately investigated, and particular attention should be directed to the possibility of conditions that require immediate treatment such as giant cell arteritis. A variety of therapeutic options are available in the acute phase, none of which are of proven benefit. In all cases, ophthalmological advice is indicated regarding acute management and follow up.

Contributors
Stephen Beatty saw a need to review the current evidence germane to diagnostic and therapeutic aspects of retinal arterial occlusive disease, initiated this project, and was the principal author of the paper. Kah-Guan Au Eong discussed core ideas, germane to diagnostic and therapeutic aspects of retinal arterial occlusion.

Conflicts of interest: none.

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