

Management of acute central retinal artery occlusion

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SUMMARY

Central retinal artery occlusion (CRAO) is considered to be an acute stroke of the eye that results in profound visual loss. Spontaneous recovery rates are poor. Most CRAOs are caused by thromboembolism in the central retinal artery. Current standard therapies for CRAO that aim to restore perfusion to the retina and optic nerve head have not been shown to alter the natural course of the disease. Thrombolytic therapy for acute management of CRAO has shown promise in nonrandomized studies with regard to improving visual outcomes. A randomized controlled trial will be required to confirm the efficacy of thrombolytic therapy before it can be recommended for use in CRAO in daily clinical practice.

KEYWORDS central retinal artery occlusion, retina, stroke, thromboembolism, thrombolytic therapy

REVIEW CRITERIA

For this Review, we searched PubMed for articles published from 1990 to 2007, including early release publications. Search terms included "central artery occlusion", "retinal artery occlusion", "retinal vascular occlusion" and "thrombolysis", in conjunction with "eye" or "retinovascular". The abstracts of retrieved citations were reviewed and prioritized by relevant content. Full articles were obtained and references were checked for additional material where appropriate.

INTRODUCTION

Central retinal artery occlusion (CRAO) is considered to be an acute stroke of the eye. The most common etiology is a fibrin-platelet thrombus or embolus that occludes the central retinal artery (CRA), leading to ischemia of the retina and optic nerve head with resultant visual loss.^{1,2} The visual prognosis of CRAO is poor, with 61% of patients having a final visual acuity of 20/400 or worse. This degree of severe unilateral visual impairment can limit social functioning, lead to mental health problems,³ and increase the risk of experiencing falls and becoming dependent on others.⁴ In addition, CRAO might be the first manifestation of atherosclerotic disease, presaging either a cerebrovascular or a cardiovascular event and necessitating preventive therapy.⁵

Following diagnosis of CRAO, prompt acute and ongoing management strategies need to be instituted. Current acute therapy aims to increase both retinal and optic nerve head perfusion through arterial vasodilation, manually dislodging emboli, or increasing the perfusion pressure by decreasing intraocular pressure in relation to CRA blood pressure. None of these treatments, however, has been shown to improve visual acuity beyond that achieved if the disease is left to take its natural course.⁶⁻⁸

This Review will discuss the pathogenesis of CRAO and the efficacy of current acute treatments. The article will go on to outline the rationale behind a new treatment strategy for CRAO that involves local intra-arterial thrombolysis and survey the promising results that have been obtained with this approach to date.

WHAT IS CENTRAL RETINAL ARTERY OCCLUSION?

CRAO is an acute occlusion of the CRA that results in a sudden, painless monocular loss of vision. The patient's vision at presentation is usually only 'counting fingers' or less in the affected eye. The CRA branches off the ophthalmic artery and supplies blood to

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the prelaminar part of the optic nerve before branching into arterioles, which supply blood to two thirds of the inner retina.² In CRAO, infarction of the inner retina and intracellular edema give rise to a pale retina compared with its usual orange color (Figure 1). In acute CRAO, the choroid underlying the macula—the thinnest part of the retina—produces a dark orange-red color, described as a ‘cherry red spot’, against the pale retina (Figure 1B). Other signs in the affected eye include an afferent pupillary defect relative to the unaffected eye and a visual field defect. The retinal arterioles can show changes that reflect systemic arteriosclerosis, including narrowing of the arterioles and venules and ‘box-carrying’ of flow in both arterioles and veins (Figure 1B, arrowheads). Investigations with fundus fluorescein angiography show a marked delay in filling of the CRA and its branches (Figure 2). Venous filling is also slowed.

CRAOs can be divided into four subclasses: nonarteritic transient CRAO, nonarteritic permanent CRAO, arteritic CRAO, and nonarteritic CRAO with cilioretinal sparing.¹ Nonarteritic transient CRAOs, which are analogous to cerebral transient ischemic attacks, account for 15% of all CRAO cases, and they tend to have the best visual prognosis of all CRAOs. In the vast majority of CRAO cases, however, the occlusion is permanent, resulting in infarction of the retina. Nonarteritic permanent CRAOs account for more than two-thirds of all CRAO cases. Arteritic CRAO, which includes vasculitic etiologies such as giant cell arteritis (GCA), accounts for under 5% of the total number of CRAOs.¹

In 15–30% of the general population, a cilioretinal artery arises from the ciliary circulation to supply blood to a portion of the papillomacular bundle—the area that contains the maximum concentration of photoreceptors and is essential for central vision.⁹ In this subset of people, the macula can still be perfused during an acute CRAO (Figure 3), enabling good vision to be retained.

PATHOGENESIS OF CENTRAL RETINAL ARTERY OCCLUSION

Thromboembolism

The most common cause of CRAO is a thrombus or embolus that lodges in the CRA. The nature of the occlusion has been debated, although the general view is that CRAOs are more commonly caused by acute thrombi than by emboli.⁶ Emboli

are usually smaller than thrombi and are more likely to cause a branch retinal arterial occlusion than a CRAO. The occlusion in CRAO is usually located immediately posterior to the lamina cribrosa,⁷ the portion of the optic nerve adjacent to the sclera. If the occlusion is anterior to the lamina cribrosa, as occurs in fewer than 20% of CRAO cases, the embolus might be visible on fundoscopy.^{8,10}

Patients with CRAO caused by emboli have a higher mortality rate than those without emboli.^{11,12} The majority of emboli originate from the heart or carotid arteries. The composition of these emboli vary, and they include fibrin–platelet plugs, cholesterol plaques, and calcium fragments.¹³ In young patients (<45 years of age) with acute CRAO of embolic origin, a cardiac pathology such as an atrial myxoma or other cardiac tumor,¹⁴ or congenital or rheumatic heart disease, should be considered.¹⁵ In very rare situations, internal carotid artery emboli from a carotid artery dissection or aneurysm have been reported to cause CRAO.¹⁶

The risk factors for CRAO are the same as those for atherosclerosis, with hypertension and diabetes being the most common associations.¹⁷ Other atherosclerotic risk factors associated with CRAO include hypercholesterolemia, smoking, and a family history of macrovascular disease.^{18,19} In addition, coronary artery disease, atherosclerotic carotid disease, and peripheral vascular disease are associated with CRAO.

In young patients, proatherogenic states, such as hyperhomocysteinemia, and hypercoagulable states, such as those that occur in patients with factor V Leiden, with protein C, protein S or antithrombin III deficiencies, with antiphospholipid antibodies, or with Gly20210Ala mutations in the prothrombin gene, should be investigated.^{20–23} Other rare systemic diseases reported to cause CRAO include sickle cell disease²⁴ and paraneoplastic syndromes,²⁵ both of which contribute to a hypercoagulable state. Some patients have no notable atherosclerotic risk factors but do have a history of migraine, which suggests a possible role for vasospasm in CRAO.²⁶

Retinal vasculitis

Vasculitides that affect large-sized and medium-sized vessels can cause inflammatory occlusion of the CRA.¹ Fortunately, these vasculitides are uncommon and account for fewer than 5% of CRAO cases. Of these vasculitides, GCA is the

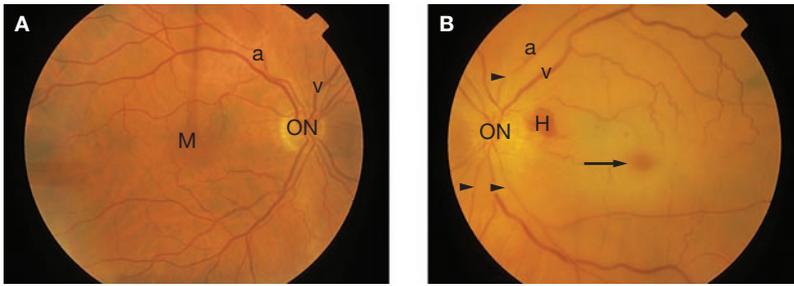


Figure 1 Color fundus photographs in a patient with acute central retinal artery occlusion. **(A)** The unaffected right eye. **(B)** Left eye showing signs of an acute central retinal artery occlusion. The left eye shows pallor of the retina compared with the right eye, and the macula, indicated by (M) in part A, is seen as a 'cherry red spot' (arrow) against the pale retina. The retinal arteries (a) and venules (v) are attenuated and there is box-carring of the arterioles (arrowheads). The optic nerve (ON) is swollen, resulting in blurred disc margins, and there is a peripupillary hemorrhage (H) temporal to the optic nerve.

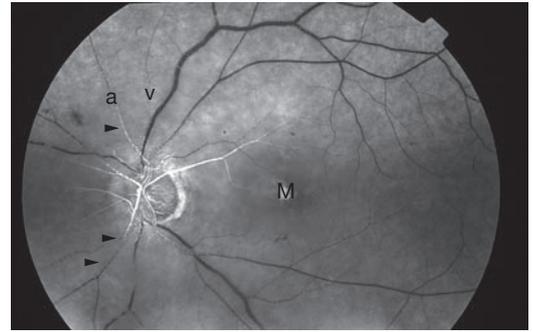


Figure 2 Fundus fluorescein angiography of an eye with acute central retinal artery occlusion. The image shows limited and sluggish filling (arrowheads) of the retinal arteries (a) 40 s after injection of fluorescein. The veins (v) were not yet filling. The macula (M) was not perfused.

most common and can produce unilateral or bilateral CRAO that is often, but not always, refractory to treatment with systemic corticosteroids. Other causes of vasculitic CRAO include systemic lupus erythematosus, polyarteritis nodosa, Takayasu's aortitis, Wegener's granulomatosis,²⁷ and, in rare cases, postviral syndromes such as herpes zoster.⁷

Iatrogenic causes

Iatrogenic causes of CRAO are rare but have been described in the context of autologous fat injection into the nasolabial groove,²⁸ intralesional steroid injection for eyelid capillary hemangioma,²⁹ and spinal surgery.³⁰ The pathogenesis of perioperative visual loss is not fully understood and is probably multifactorial. Postulated mechanisms include direct pressure on the eye and orbital structures during surgery owing to incorrect positioning of a firm headrest³¹—both hypovolemia and hypotension have also been hypothesized to be contributing factors in this scenario.³² Vinerovsky *et al.* reported two cases of CRAO resulting from peribulbar anesthesia, and they proposed that these were caused by the vasospastic effect of epinephrine on the retinal and optic nerve circulation.³³

CURRENT ACUTE MANAGEMENT

The rationale behind current acute treatments of CRAO is removal of the CRA blockage. There is no consensus regarding the precise strategy for acute management of CRAO, partly because there are many variables involved, including the degree of

vascular obstruction, the presence of a cilioretinal artery, and the underlying pathogenesis.

Opinions differ regarding the length of time it takes for permanent visual loss to occur after CRA occlusion.^{34–36} Early primate experiments suggested that the retina had an ischemic tolerance time of a mere 97–100 min.³⁵ By contrast, experiments in primate models with an increased burden of atherosclerosis showed that recovery of retinal function could occur at up to 240 min after occlusion, which is similar to the therapeutic window of the ischemic penumbra in cerebral stroke.³⁴ Clinical improvement with intervention 24–48 h after the onset of CRAO has also been reported.³⁷

The discussion that follows concentrates mainly on nonarteritic CRAOs of presumed thromboembolic origin, which represent the majority of CRAO cases. It is important to note that arteritic CRAOs, resulting from GCA or other vasculitides, carry the risk of bilateral visual loss and are associated with markedly increased mortality and morbidity.³⁸ Patients in whom arteritic CRAOs are suspected should be treated immediately, and efforts should be made to establish the underlying diagnosis. For example, if GCA is considered to be a likely diagnosis, erythrocyte sedimentation rate and C-reactive protein assays should be conducted, and the patient should then be treated immediately with high-dose intravenous corticosteroids, followed by confirmation of the diagnosis with a unilateral or bilateral temporal artery biopsy.

Current acute management strategies for nonarteritic CRAO can be divided into two categories: noninvasive standard therapy, and invasive local intra-arterial fibrinolysis (LIF). Noninvasive therapy can be grouped into four main areas, as described in the sections that follow.

Noninvasive therapy

Observation

If spontaneous recanalization of the occluded CRA occurs at all, it usually happens within 48–72 h of the occlusion. Retinal blood flow is often only partially restored after spontaneous recanalization,¹⁰ and current estimates of the spontaneous visual improvement rate in nonarteritic CRAO vary from 1% to 10%.^{6,39,40}

Debate exists among various groups as to what constitutes a significant improvement in visual acuity. Some authors have suggested that a two to three lines or greater visual improvement on a Snellen acuity chart is significant, as it is considered to be a doubling of visual angle,⁴¹ but this level of improvement occurs in fewer than 10% of individuals in whom reperfusion occurs spontaneously.²⁰ The attainment of a visual acuity of 20/200 or better could also be used as an arbitrary cut-off to represent a significant improvement in visual function, given that the majority of individuals with CRAO have a visual acuity of 20/200 or less. In addition, 20/200 vision is the definition for legal blindness in the US and also represents the level of visual acuity below which independent living is considered to be difficult, if not impossible.

Dilation of retinal arteries and increasing blood oxygen content

Noninvasive interventions such as administration of sublingual isosorbide dinitrate or systemic pentoxifylline, inhalation of carbogen (a mixture of 95% oxygen and 5% carbon dioxide), or rebreathing of expired carbon dioxide have been tried in patients with CRAO.^{20,42–44} These treatments are thought to vasodilate the CRA, thereby increasing retinal blood flow. Retinal Doppler ultrasonography has revealed increases in retinal blood flow when these approaches are used, but there has been no documentation of an association between clinical improvement, in terms of visual acuity or visual field changes, and increases in retinal blood flow.⁴⁵

Hyperbaric oxygen has also been tried in an attempt to increase diffusible oxygen content to the ischemic retina, but the results have been equivocal.⁴⁶

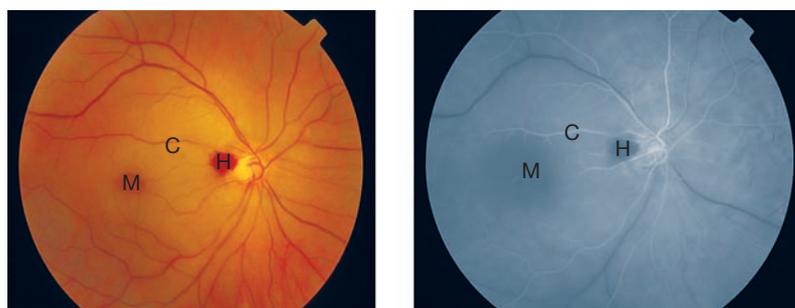


Figure 3 Central retinal artery occlusion with cilioretinal artery sparing. (A) Color fundus photograph. (B) Fundus fluorescein angiography. The cilioretinal artery (C) perfuses the superior part of the macula (M). The patient had vision of 20/80 at presentation. There is a peripupillary hemorrhage (H) temporal to the optic disc.

Attempts to dislodge emboli

Measures to dislodge emboli with ocular massage, either directly or through a contact lens to permit observation of the retinal circulation, have been described.¹⁰ Rumelt *et al.* assessed the success of using ocular massage with a three-mirror contact lens.⁴² The end point was improved retinal arterial blood flow, which was defined as the re-establishment of continuous laminar flow, an increase in the width of the blood column, and the disappearance of fragmented flow. All patients also received sublingual isosorbide dinitrate, intravenous acetazolamide, intravenous mannitol, and oral glycerol. Only one out of eight patients had improved retinal blood flow with this regimen, suggesting that ocular massage—alone or with measures to dilate the retinal arteries and reduce intraocular pressure—has a limited success rate.

Increasing retinal artery perfusion pressure by reducing intraocular pressure

On the basis of the fact that mean ocular perfusion pressure is the difference between mean arterial pressure and intraocular pressure, attempts have been made to reduce the intraocular pressure and thereby increase ocular perfusion. Measures that have been employed include the use of intravenous acetazolamide or mannitol to acutely reduce intraocular pressure, and anterior chamber paracentesis followed by the withdrawal of a small amount of aqueous fluid from the eye.^{19,20,42,47}

Most patients receive a combination of the above therapies. Atebara *et al.* compared the efficacy of anterior chamber paracentesis and carbogen inhalation with that of no acute treatment, and

they found no statistically significant differences in outcomes between the treated and untreated groups.²⁰ Rumelt *et al.* and Landa *et al.* both evaluated the effect of a systematic stepwise approach starting with ocular massage, globe compression, sublingual isosorbide dinitrate and intravenous acetazolamide, followed by intravenous mannitol, methylprednisolone, and, finally, intravenous streptokinase and retrobulbar tolazoline.^{42,48} The effect of the stepwise approach was compared with the response in controls, whose treatments were administered in an arbitrary nonsystematic manner. Both studies were limited by small patient numbers, but the studies showed a greater visual improvement in those who received the systematic stepwise approach than in the controls. Nevertheless, Landa *et al.* found that despite stepwise systematic implementation of standard therapies, their patients all had some residual deficits in visual function, supporting the argument that these 'standard therapies' are not truly effective.⁴⁸ These findings highlight the need for investigations into alternative treatments for CRAO.

Invasive therapy: thrombolysis

Rationale for thrombolytic therapy

By far the most exciting recent development in the treatment of CRAO is the use of thrombolytic therapy. Systemic and intra-arterial thrombolysis have been successful at restoring perfusion to ischemic tissue through fibrin-platelet clot lysis in cases of ischemic stroke and myocardial infarction.⁴⁹⁻⁵¹ The use of thrombolysis in CRAO relies on two assumptions: first, that the CRAO is of nonarteritic etiology, and second, that the material occluding the CRA is a fibrin-platelet thrombus or embolus that can be lysed.

In several open-label studies, LIF was efficacious in the treatment of CRAO, with up to 60-70% of treated individuals experiencing an improvement in visual acuity.^{39,40,52,53} By contrast, individuals treated with standard therapy had a poor visual outcome, comparable to that obtained in previous studies of the natural course of CRAO.^{7,8}

Administration of thrombolytic agents

The administration of streptokinase or tissue plasminogen activator (tPA), either intravenously or intra-arterially, has been attempted in patients with CRAO. Kattah *et al.* administered tPA intravenously and reported that 10 out of 12 patients with CRAO achieved some degree of improvement

in visual acuity, with no thrombolysis-related systemic or neurological complications.⁵⁴ Four of these patients, however, subsequently developed neovascular glaucoma.

Intra-arterial administration of thrombolytic agents delivered directly to the ophthalmic artery, and thence to the CRA, usually involves a continuous infusion of tPA, with a dose in the range 40-80 mg, or of urokinase, in a dose ranging from 300,000 to 1 million units.^{52,53,55} In several open-label studies, LIF was shown to be effective in CRAO, with up to 60-70% of treated subjects experiencing an improvement in visual acuity.^{40,52,53,56} Reported adverse effects included ischemic cerebrovascular accidents and both intracerebral and systemic bleeding.^{39,52,55} The US Nationwide Inpatient Survey of 2001-2003 found that intra-arterial thrombolysis was given to 1.9% of patients who presented with CRAO during those years, and the treatment was offered only in selected urban hospitals.⁵⁷ There was no in-hospital mortality or intracranial hemorrhaging reported among patients with CRAO who were treated with thrombolysis.

Several criticisms have been leveled at these early reports. The first is that a number of these studies deployed LIF beyond the 97-240 min that primate experiments showed was the maximum retinal ischemic tolerance time. The second is the assumption that CRAO is caused by lysable fibrin-platelet thrombi or emboli. One early report demonstrated that 50% of visible emboli consist of cholesterol, and such emboli would not respond to thrombolysis.⁵⁸ It is important to stress, however, that the majority of emboli in CRAO occur at the level of the lamina cribrosa and are consequently not visible on funduscopy. It cannot be assumed, therefore, that a study of visible emboli accurately represents the frequency distribution of retinal embolus types in CRAO.

The main controversy is whether the use of LIF results in an improvement in visual function above and beyond that found if the disease is allowed to take its natural course.¹ The studies listed to date have used various measures of outcome, one being an improvement in visual acuity of one line or more on a Snellen chart, and the studies have not necessarily included physiological secondary end points, such as the objective documentation of retinal blood flow shown by fundus fluorescein angiography.⁵⁹ The lack of consistency in even the primary

end point used, such as the number of lines of improvement of visual acuity, makes comparison between interventional and natural course studies difficult. In addition, the question still remains as to whether continuous infusion of a fibrinolytic agent is the best method of delivery with the lowest complication rate.

To address these issues, Eric Aldrich and colleagues at Johns Hopkins Hospital, Baltimore, MD, USA performed a nonrandomized study of super-selective catheterization of the ophthalmic artery followed by LIF by use of tPA given in aliquots until patency of the CRA was established clinically.⁶⁰ With thrombolytic therapy, the risk of hemorrhagic complications is related to the total dose of thrombolytic agent, and the risk of ischemic stroke is thought to be related to the total time during which an arterial catheter remains within the carotid artery. Consequently, it was hypothesized that the delivery of LIF in aliquots would result in a relatively small dose of thrombolytic agent being delivered within a short time period, thereby minimizing the risk of such complications.

From 1999 to 2006, 42 consecutive patients with CRAO that was diagnosed clinically by an ophthalmologist were recruited into the study. On the basis of the treating clinician's personal preference, the patients were assigned to receive either standard therapy plus LIF with tPA delivered in 3 mg aliquots, or standard therapy alone. Standard therapy could consist of any one or a combination of the following: observation; ocular paracentesis; inhalation of carbogen; and administration of agents such as acetazolamide to reduce intraocular pressure. The primary end point was an improvement in visual acuity by one line or more on a Snellen chart, as well as an improvement in visual acuity of three lines or more at final follow-up, 15 months after enrollment. All adverse events were recorded.

In this study, 76% of patients who received LIF compared with 33% of the standard therapy group had a visual acuity improvement of one line or more on a Snellen chart at final follow-up ($P=0.018$). The remaining patients in the LIF group showed no improvement in visual acuity. A third of the LIF group attained an improvement of three lines or more on a Snellen chart, compared with 4.8% of the standard therapy group ($P=0.018$). Multivariate regression analysis adjusted for age, sex, history of hypertension or hypercholesterolemia, and history of transient ischemic attacks or cerebrovascular events

showed that the use of LIF was the principal determinant for achieving a good visual outcome, and individuals who received LIF were 13 times more likely to achieve an improvement in visual acuity of three lines or more on a Snellen chart than were those who did not (odds ratio 13, 95% CI 1.2–145.0; $P=0.03$).

Although this study was nonrandomized, the point estimates of the improvement in visual acuity for the standard therapy group mirror those of the spontaneous improvement of visual acuity found in studies of the natural course of CRAO. In addition, the LIF group showed an improvement in visual acuity consistent with that seen in previous studies employing thrombolytic therapy, and this improvement exceeded that found in studies of standard therapy. Owing to the nonrandomized nature of this and previous studies, however, LIF cannot yet be considered to be standard therapy, and it should be used only within the confines of an approved clinical trial. Nevertheless, these studies provide sufficient equipoise for a multicenter randomized controlled study of LIF to be conducted that, in the event of a positive outcome, would represent a major step forward in the treatment of CRAO.⁶⁰

CONCLUSIONS

In summary, all current acute management strategies for CRAO have limited efficacy, the evidence for which is based on data from nonrandomized studies. Of all the treatments to date, thrombolysis, especially LIF,¹⁸ shows the most promise. A randomized controlled trial is required, however, before this approach can be recommended for use in daily clinical practice.

KEY POINTS

- Central retinal artery occlusion (CRAO) is considered to be an acute stroke of the eye that involves hypoperfusion to the retina and optic nerve head and leads to a reduction in visual function
- CRAO has a poor spontaneous recovery rate
- Current standard therapies for CRAO have not conclusively been shown to change the natural course of the disease
- Local intra-arterial fibrinolysis shows promise in nonrandomized studies for the treatment of CRAO, but a randomized controlled trial will be required to demonstrate efficacy before this treatment can be considered for use in standard clinical practice

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Competing interests

The authors declared no competing interests.