Featured Review

Central retinal artery occlusion

Sohan Singh Hayreh

The pathogeneses, clinical features, and management of central retinal artery occlusion (CRAO) are discussed. CRAO consists of the following four distinct clinical entities: non-arteritic CRAO (NA-CRAO), transient NA-CRAO, NA-CRAO with cilioretinal artery sparing, and arteritic CRAO. Clinical characteristics, visual outcome, and management very much depend upon the type of CRAO. Contrary to the prevalent belief, spontaneous improvement in both visual acuity and visual fields does occur, mainly during the first 7 days. The incidence of spontaneous visual acuity improvement during the first 7 days differs significantly ($P < 0.001$) among the four types of CRAO; among them, in eyes with initial visual acuity of counting finger or worse, visual acuity improved, remained stable, or deteriorated in NA-CRAO in 22%, 66%, and 12%, respectively; in NA-CRAO with cilioretinal artery sparing in 67%, 33%, and none, respectively; and in transient NA-CRAO in 82%, 18%, and none, respectively. Arteritic CRAO shows no change. Recent studies have shown that administration of local intra-arterial thrombolytic agent not only has no beneficial effect but also can be harmful. Investigations to find the cause and to prevent or reduce the risk of any further visual problems are discussed. Prevalent multiple misconceptions on CRAO are discussed.

Key words: Central retinal artery occlusion, retinal artery occlusion, retinal arteries, retinal vessels

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Central retinal artery occlusion (CRAO) has been known as a clinical entity since 1859, when von Graefe[1] first described CRAO due to embolism. After that, Schweigger[2] in 1864 described it on ophthalmoscopy. It is an ophthalmic emergency because of instant, massive visual loss. A voluminous literature has accumulated on its various aspects, riddled with serious controversies and misconceptions, particularly about its management.

Since 1955, I have investigated various aspects of CRAO comprehensively, by anatomical studies on the central retinal artery (CRA),[3,4] experimental studies,[5-10] and multiple clinical studies[11-23] on its different features. Recently, I discussed in detail my findings on CRAO, along with a detailed review of the literature on CRAO, in my book, entitled "Ocular Vascular Occlusive Disorders."[23] Following is a very brief account of various clinical aspects of CRAO.

Classification of CRAO

CRAO has always been considered as one disease. However, my prospective study of 244 consecutive patients (260 eyes) with CRAO showed that in fact it consists of the following four distinct clinical entities:[14]

(1) ***Non-arteritic CRAO***: This shows the classical clinical picture of permanent CRAO with retinal infarction, cherry red spot and retinal arterial changes [Fig. 1], absent or poor residual retinal circulation on fluorescein fundus angiography, and no evidence of giant cell arteritis

(2) ***Non-arteritic CRAO with cilioretinal artery sparing***: This has the classical clinical picture of permanent non-arteritic CRAO (NA-CRAO), except for the presence of a patent cilioretinal artery [Fig. 1], which can have a marked influence on the visual outcome and retinal circulation

(3) ***Transient NA-CRAO***: In this, occlusion of the CRA may vary from several minutes to many hours, depending upon the cause of occlusion [Fig. 2]. The visual outcome in this type of CRAO can be totally different from any of the other types, and it depends entirely upon the duration of transient CRAO

(4) ***Arteritic CRAO***: In this condition, giant cell arteritis is the cause of development of permanent CRAO [Fig. 3]. My studies on giant cell arteritis have shown that these eyes almost invariably have associated arteritic anterior ischemic optic neuropathy.[24,25] Clinically, these eyes have the classical fundus findings of CRAO, except for associated optic disk edema due to arteritic anterior ischemic optic neuropathy.

In my study of 260 eyes with CRAO,[14] 67% had NA-CRAO, 16% transient NA-CRAO, 14% NA-CRAO with cilioretinal artery sparing, and 4% arteritic CRAO.

It is important to note that clinical characteristics, visual outcome, and management very much depend upon the type of CRAO.

Demographic characteristics of various types of CRAO

In my study of 244 patients,[14] the mean (range) was: In NA-CRAO mean 68 (26–90) years, in transient NA-CRAO mean

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63 (20–89), in NA-CRAO with cilioretinal artery sparing mean 67 (39–87) years, and in arteritic CRAO mean 74 (62–87). This shows that although CRAO usually develops in older persons, it does occur in children and young persons also.[23] There is no evidence that race or any other demographic parameter make any difference in CRAO development.

Causes of Various Types of CRAO

1. Classical NA-CRAO is most common due to permanent occlusion of the CRA, caused by an impacted embolus at the narrowest part of the CRA, where it enters the sheath of the optic nerve [Figs. 4 and 5][3,4] (not at the lamina cribrosa, as is often erroneously described). The emboli originate from plaques in the carotid artery or the heart[19,20] [Table 1]; rarely, CRAO is due to vasculitis, chronic systemic autoimmune diseases, or thrombophilia.[23]
2. Transient NA-CRAO is most often caused by a migrating embolus, and sometime by a transient marked fall of perfusion pressure in CRAO,[14] or high rise of intraocular pressure.
3. Arteritic CRAO is due to thrombosis of the common trunk of the posterior ciliary artery and CRA arising from the ophthalmic artery[24] [Fig. 6], caused by giant cell arteritis, not of CRA *per se*.

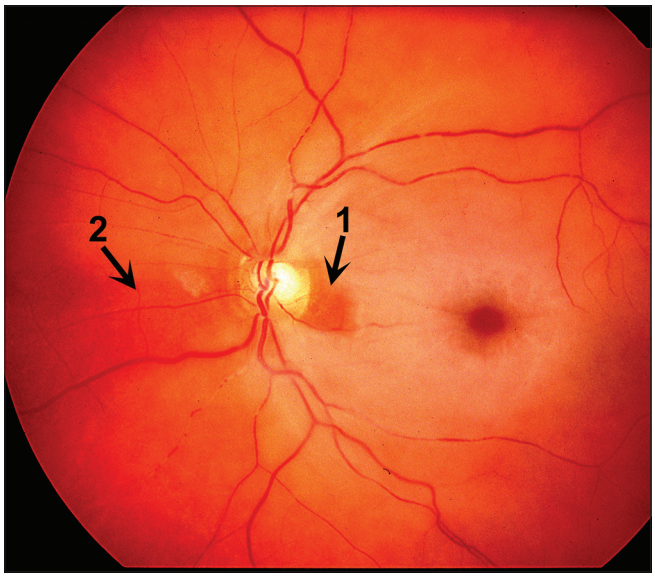

Figure 1: Fundus photograph of the left eye with non-arteritic CRAO (NA-CRAO), and two patent cilioretinal arteries (arrows). It shows cherry-red spot, retinal opacity of posterior fundus – most marked in the macular region, cattle-trucking in the retinal vessels

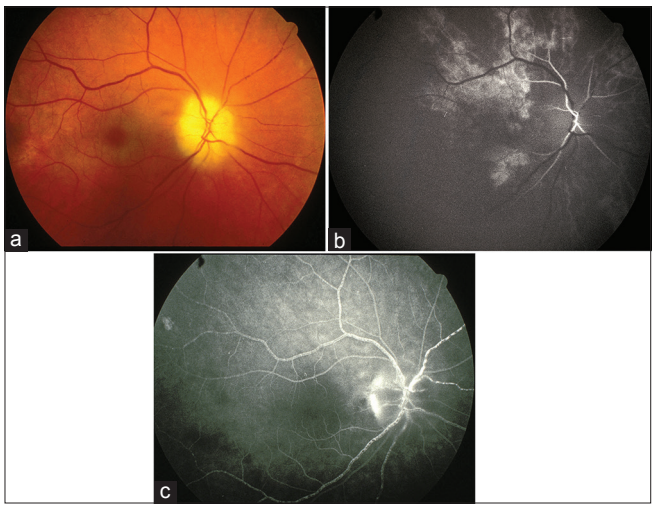

Figure 3: Right eye with arteritic CRAO and arteritic anterior ischemic optic neuropathy. (a) Fundus photograph shows chalky-white optic disk edema, some mild cattle-trucking in the retinal vessels, and cherry red spot with perifoveolar retinal opacity.(b) Fluorescein fundus angiogram, during the early phase, shows posterior ciliary artery occlusion with a few small patches of choroidal filling, and early filling of the central retinal artery.(c) Fluorescein fundus angiogram during the late phase shows cattle-trucking in the retinal vessels, with almost no disk staining

Systemic Conditions Playing a Role in Development of CRAO

These systemic conditions include the following:

1. High cholesterol (particularly low-density lipoproteins – "bad cholesterol") leads to the build-up of plaques on the walls of carotid arteries, which are the common source of embolism causing CRAO

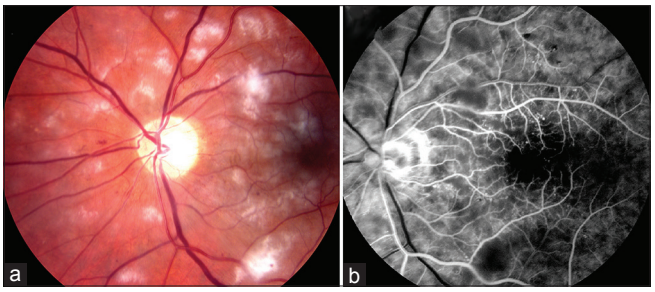

Figure 2: Fundus photograph and fluorescein fundus angiogram of left eye with transient NA-CRAO.(a) Fundus photograph shows large number of cotton wool spots, maximum in the macular region. (b) Fluorescein angiogram, during retinal arterial phase, shows almost normal but slightly sluggish retinal circulation, except for the absence of filling in the foveal region, and cotton wool spots at places mask the background choroidal fluorescence

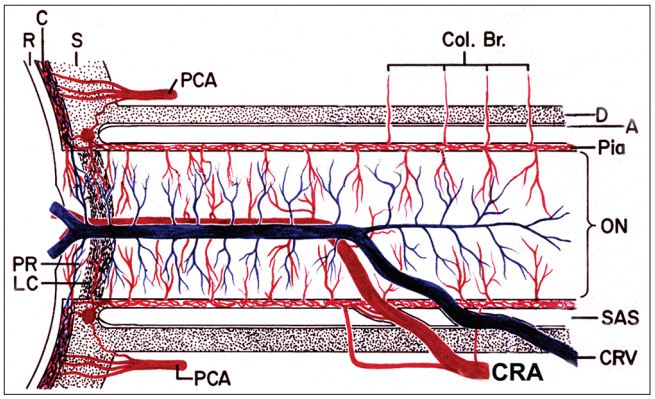

Figure 4: Schematic representation, showing the course of central retinal artery and its branches and anastomoses. A = Arachnoid; C = choroid; CRA = central retinal artery; Col. Br. = Collateral branches; CRV = central retinal vein; D = dura; LC = lamina cribrosa; ON = optic nerve; PCA = posterior ciliary artery; PR = prelaminar region; R = retina; S = sclera; SAS = subarachnoid space

Table 1: Carotid Doppler/Angiography and echocardiogram findings on the side with central retinal artery occlusion[19]

Test finding	Non-arteritic central retinal artery occlusion
Patent foramen ovale	(*n*=234)
	6 (2%)
Carotid Doppler/angiography:	(*n*=199)
Occlusion	
0-15%	109 (55%)
16-49%	23 (12%)
50-79%	32 (16%)
80-99%	13 (7%)
100%	22 (11%)
Carotid Doppler/Angiography	(*n*=187)
Plaque present	133 (71%)
Echocardiogram	(*n*=131)
Normal	39 (30%)
Abnormal, no embolic source	24 (18%)
Abnormal, with embolic source	68 (52%)
Echocardiogram:	(of *n*=68 with embolic source)
Abnormal embolic source	
Mitral valve	18 (26%)
Aortic valve	26 (38%)
Mitral and aortic valves	24 (36%)
Echocardiogram:	(of *n*=42 with mitral valve as
Mitral valve lesion types	embolic source)
Calcified valve	24 (57%)
Mitral valve prolapse	7 (17%)
Other types of lesions	11 (26%)
Echocardiogram:	(of *n*=50 with aortic valve as embolic source)
Aortic valve lesion types	
Calcified valve	39 (78%)
Other types of lesions	11 (22%)

2. Carotid artery disease can produce CRAO by the following three mechanisms:
   (a) Embolism, which is by far the most common cause of CRAO[19]
   (b) A significant stenosis (about 70% or more) or complete occlusion of the internal carotid artery, by markedly reducing the ocular blood flow, can result in development of CRAO. In my study,[19] >80% stenosis of the internal carotid artery was seen in 18% of CRAO cases [Table 1]
   (c) Our study on atherosclerotic monkeys showed that serotonin, a powerful vasoconstrictor, released by platelet aggregation on atherosclerotic plaques in the carotid artery, produces a transient spasm, which can cause transient, complete occlusion, or impaired blood flow in the CRA[26] [Fig. 7]
3. The association of diabetes and arterial hypertension with CRAO has been reported by a large number of studies[23]
4. A variety of cardiac conditions can produce CRAO due to embolism from the heart[19] [Table 1]. In addition, there are reports of development of CRAO following invasive cardiovascular procedures[23]
5. CRAO associated with vasculitis, giant cell arteritis, and chronic systemic autoimmune diseases has been reported[23]

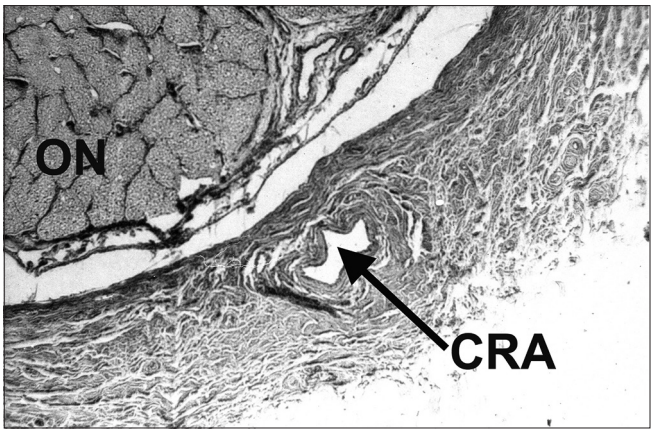

Figure 5: A transverse section of the human optic nerve, showing the central retinal artery (CRA) inferiorly lying within the substance of dural sheath of the optic nerve (ON)

6. There are several controversial reports suggesting that thrombophilia plays a role in the development of CRAO[23]
7. Rarely, CRAO has been seen in association with hematological disorders, for example, sickle cell hemoglobinopathies, leukemia, systemic non-Hodgkin's lymphoma, and orbital lymphoma[23]
8. CRAO has also been reported perioperatively following a variety of surgical procedures, for example, following orbital, eye or head injuries, facial and retrobulbar injections, peribulbar anesthesia, and intraocular gas injection used as tamponade for rhegmatogenous retinal detachment[23]
9. CRAO following hemodialysis is known. It is well known that during hemodialysis, there is often a marked fall of blood pressure. Moreover, these patients almost invariably have marked vasculopathy[23]
10. Other rare miscellaneous conditions associated with CRAO include Fabry's disease, incontinentia pigmenti, oral contraceptives, usage of cocaine, snake bite,[18] migraine, Marfan's syndrome, nephrotic syndrome, and others.[23]

I have discussed all these conditions and reviewed literature at length, elsewhere.[23]

Clinical Features

Symptoms

Typically, there is a sudden, massive loss of vision in the involved eye. It can occur at any time of the day. In my study of 260 eyes with CRAO,[14] visual loss was discovered on waking up in the morning in 35% in NA-CRAO, in 29% in NA-CRAO with cilioretinal artery sparing, in 39% in transient CRAO, and in 30% in arteritic CRAO. When the visual loss is discovered on waking up in the morning, it may be due to embolism, thrombosis, or due to transient CRAO from a fall of perfusion pressure during sleep caused by nocturnal arterial hypotension[14] [Fig. 8]. The visual loss may be preceded by history of amaurosis fugax, caused by transient migrating embolism or giant cell arteritis.[25] I found a history of amaurosis fugax before development of CRAO in 12% in NA-CRAO, in 20% in NA-CRAO with cilioretinal artery sparing, in 30% in arteritic CRAO, and in 13% in transient CRAO.[14] In patients aged 50 years or older with a history of amaurosis fugax,[25] the first essential is to rule out giant cell arteritis, which is an

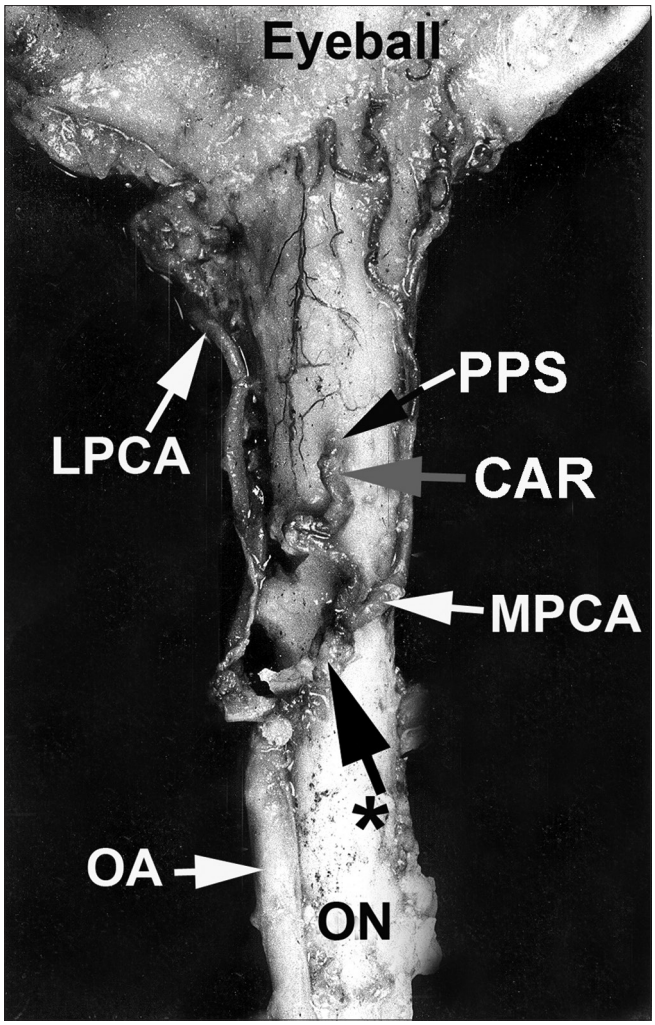

Figure 6: An example of a common trunk of origin of central artery of the retina and posterior ciliary arteries arising from the ophthalmic artery, as seen from below. CAR = Central artery of the retina, LPCA = lateral posterior ciliary artery, MPCA = medical posterior ciliary artery, OA = ophthalmic artery, ON = optic nerve. PPS = point of penetration into the sheath by the central retinal artery.*Common trunk of origin of CAR and MPCA

ophthalmic emergency, because if it is not treated immediately, it can result in massive visual loss which can involve both eyes. Some patients complain of a purplish hue to the blur, which is highly suggestive of retinal ischemia. Hallucinations have been reported with severe vision loss associated with CRAO.[23] Simultaneous onset of CRAO in both eyes does not normally occur; it happens rarely, when there is compression of both eyes during a prolonged surgical procedure or during hemodialysis.

Visual Function in CRAO

The devastating visual loss and its management is a major topic in CRAO. Therefore, from the functional point of view, the most important consideration, both for the patient and the ophthalmologist, is the visual outcome and natural history. In view of that, it requires a detailed discussion of various aspects of visual function in CRAO. My prospective study[14] in 260 CRAO eyes provided this information for the first time.

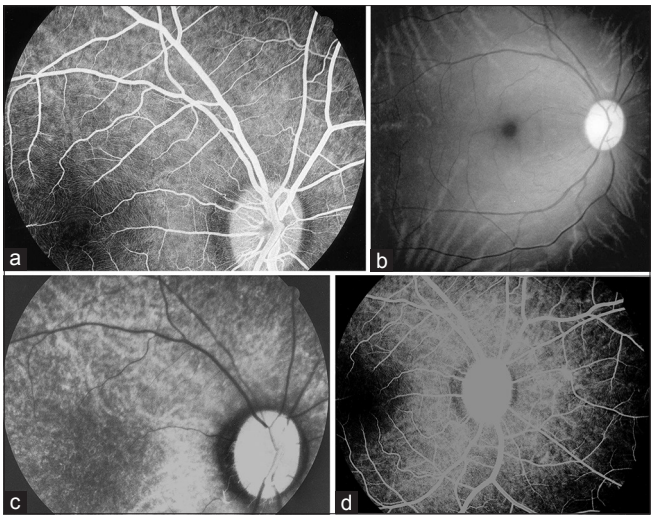

Figure 7: Fluorescein fundus angiograms (a, c, d) and a fundus photograph (b) of right eye of an atherosclerotic monkey before and after intravenous infusion of serotonin.(a) Baseline angiogram during retinal arteriovenous phase, showing normal filling of the central retinal artery, the retinal vasculature, and the choroid, one week before (b, c). (b, c) During infusion of serotonin (b) is a black and white fundus photograph about 2 min after the start of serotonin infusion, showing evidence of CRAO, including pale optic disk, retinal opacity, and cherry red spot at fovea. (c) An angiogram about 4 min, after the start of serotonin infusion, shows normal filling of the choroidal circulation but complete occlusion of the central retinal artery. (d) An angiogram during regression phase shows once again normal filling of the central retinal artery and the choroid

Initial visual acuity

Initially, visual acuity in NA-CRAO was 20/200–20/400 in 7% and counting fingers or worse in 93%. In transient NA-CRAO, it depended upon the duration of CRAO, and in NA-CRAO with cilioretinal artery sparing upon the area of distribution of the patient cilioretinal artery – in both, it varied from 20/40 or better to counting fingers or worse; in arteritic CRAO, it varied from 20/200 to counting fingers or worse.[14]

Initial visual field defects

Visual acuity essentially represents the function of the foveal region and not of the rest of the retina; only visual fields plotted with a Goldmann perimeter provide full information about the function of the entire retina – after all, CRAO involves the entire retina, not only the fovea. Unfortunately, there has been little information on the visual field defects in CRAO in the literature. My study[14] was the first to evaluate visual fields in 145 CRAO eyes, where it was possible to plot them. It provided invaluable information on visual function in CRAO. Initially, there was a complete loss of the central 30° visual field (producing central scotoma) in NA-CRAO in 48%, in NA-CRAO with cilioretinal sparing in 22%, and with transient NA-CRAO in 4% only. Initially, peripheral fields were normal in 22% with NA-CRAO [Fig. 9] and in 63% with transient CRAO.

Natural history of visual loss in CRAO

I investigated the natural history of visual outcome in CRAO in this group of patients.[14] It is widely believed that CRAO results in permanent visual loss, with no chance of any spontaneous visual improvement. But my study showed that not to be true, as is evident from the following.

Visual Acuity Improvement: Table 2 gives detailed information about the initial and final visual acuities in various types of CRAO. In eyes seen within 7 days and with counting fingers visual acuity, it improved by 22% in NA-CRAO, by 67% in NA-CRAO with cilioretinal artery sparing, and by 82% in transient NA-CRAO, but in none in arteritic CRAO.

Visual Field Improvement: Central visual field improved in 39% of transient NA-CRAO, 25% of NA-CRAO with cilioretinal artery sparing, and 21% with NA-CRAO. The peripheral visual field improved in NA-CRAO in 39%; in transient NA-CRAO in 39%, and in NA-CRAO with cilioretinal artery sparing in 25%. Interestingly, in transient NA-CRAO with initial central and peripheral visual fields field defects, those recovered to normal in 26% and 30%, respectively. In addition, in NA-CRAO, peripheral visual fields initially were normal in 22%, and on follow-up, these improved in 39% of the remaining eyes. In other words, 61% of eyes with NA-CRAO finally had normal to good peripheral visual fields, which is of great importance in visual function, as discussed below.

Importance of peripheral visual fields for visual function

Central visual field loss results in impaired central vision, while the peripheral visual field is essential for day-to-day living and navigation; therefore, a person with central visual loss but with good peripheral visual fields [Fig. 9], as in age-related macular degeneration, can lead a reasonably satisfactory functional life although unable to read or do fine work. Unfortunately, the common use of automated static threshold perimetry nowadays, rather than manual kinetic perimetry performed with a Goldmann perimeter, does not provide full information about the peripheral visual fields, because automated perimetry does not provide information beyond the central 30° or less of the field, whereas kinetic perimetry covers the peripheral visual field up to about 90°.

In conclusion, (i) the initial and final visual acuities and visual field defects differ significantly ($P < 0.001$) among the four types of CRAO, (ii) significant improvement can occur in visual acuity and visual field without treatment, and (iii) classification of CRAO is crucial for understanding differences in visual outcome.

Factors play crucial roles in determining the visual outcome in CRAO

Understanding the fundamental facts behind the factors that play a crucial role in determining the visual outcome in CRAO is essential. These include the following:

1. *Duration of acute retinal ischemia*: This is by far the most important factor. My experimental study[9] of

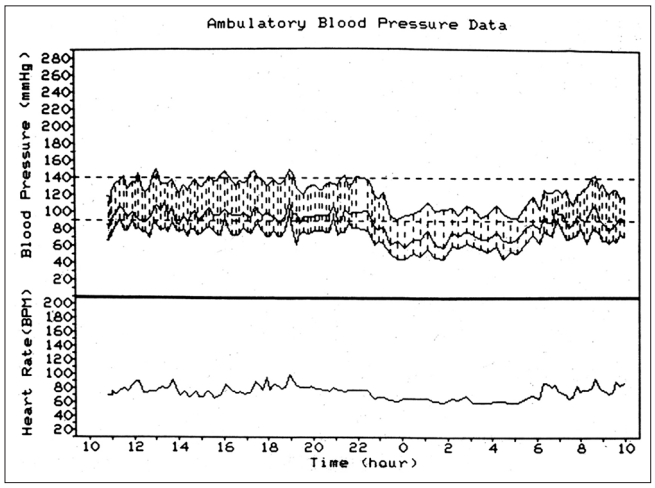

Figure 8: A 24-h ambulatory blood pressure recording in a woman, starting at about 11:00 a.m. and ending at about 10:00 a.m. next day. Note that during the waking hours the blood pressure is perfectly normal but shows a marked drop during the sleeping hours (*nocturnal arterial hypotension*)

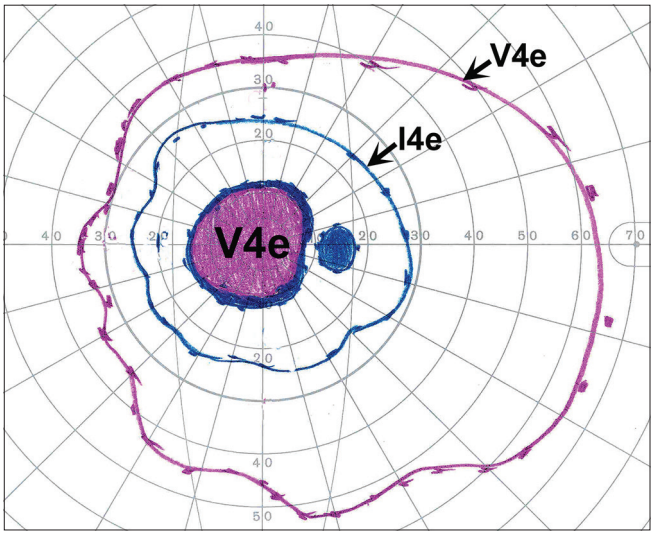

Figure 9: Visual fields of right eye with NA-CRAO, plotted with a Goldmann perimeter, show a large absolute central scotoma, with almost normal peripheral visual field with I-4e and V-4e

Table 2: Initial and final visual acuity by CRAO type

Type of CRAO	Visual acuity	20/15	20/20	20/25	20/30	20/40	20/60	20/70	20/80	20/100	20/200	20/400	CF	HM	LP	NLP	Total*
Non-arteritic CRAO	Initial				1			1			6	13	66	44	28	12	171
	Final			1		1					9	14	43	23	19	12	122
Non-arteritic CRAO with cilioretinal artery sparing	Initial	1	4	2	3		3	1		1	2			9	2		35
	Final		2		2	3	3				6	2	4	6		1	29
Arteritic CRAO	Initial								1			1	2	2		7	13
	Final										1	1		1		8	11
Transient Non- arteritic CRAO	Initial	2	9	4	2		2	2		1	3	2	10	4			41
	Final	3	8	4	5	3	2	1	1		3	3	5				38

*The differences in the total number of eyes for initial and final visual acuity are due to some patients having only one visit

CRAO in 38 elderly, atherosclerotic, hypertensive rhesus monkeys (similar to most patients with CRAO) showed that the retina suffers no detectable damage with temporary CRAO if the circulation is restored within 97 min, but, after that, the longer the ischemia lasts, the more extensive is the permanent damage. CRAO lasting for about 240 min results in massive, irreversible retinal damage. In eyes where the retinal circulation was restored to normal after CRAO of more than 2 but less than 4 h duration, retinal function did not show signs of major improvement until many hours or even a day after restoration of circulation – the longer the ischemia, the longer the lag before any improvement of function started. This is a key finding clinically, because it has unfortunately fostered the mistaken notion that visual recovery can occur in eyes with CRAO lasting for much longer than 4 h or even for days

2. *Type of CRAO*: As shown above, this plays an important role
3. *The cause of CRAO*: This can also play a role. Although embolism is a far more common cause of CRAO than thrombosis,[19,20] rarely, when CRAO is caused by giant cell arteritis, vasculitis, trauma, or other conditions causing thrombosis of CRA, there is poor visual outcome
4. *Site of occlusion in the CRA*: As mentioned above, it is generally believed that the site of occlusion in CRAO is at the level of the lamina cribrosa (as revealed by histopathologic studies of enucleated eyes). Since the narrowest lumen of the artery is where it pierces the dura mater of the optic nerve sheath[3,4] [Figs. 4 and 5], in cases of CRAO due to embolism, the chances of an embolus getting impacted at this site are much higher than at any other site in the artery. In contrast to that, the site of occlusion in thrombosis of the CRA is at the lamina cribrosa, as shown by the histopathological studies. The site of occlusion is an important factor in determining the amount of available anastomoses by the CAR [Fig. 4] and residual retinal circulation in CRAO
5. *Residual retinal circulation*: Fluorescein angiography almost always shows this in fresh CRAO.[5,14,20] That has erroneously been claimed as a sign of only partial occlusion of the CRA and used as a justification for claims of visual improvement for many advocated therapies, even when therapy is instituted many hours or even days after the onset of CRAO. I specifically investigated this issue experimentally in 101 eyes of rhesus monkeys.[5,9] In these experimental studies, the CRA was cut, but there was still residual retinal circulation, which clearly showed that there was no partial occlusion of CRA; there was no correlation between the residual retinal circulation and recovery of visual function.[20] My studies showed that the duration of CRAO is almost always the principal determining factor in the production of irreversible retinal damage, that is, the longer the ischemia, the more marked the retinal damage.[9] The only exception is when there is a large patent cilioretinal artery, which seems to have some protective effect, particularly in the macular retina
6. *Presence and area of supply by a patent cilioretinal artery*: This can have a major impact on the visual outcome in CRAO, as shown above. Importantly, in CRAO when the supply by the cilioretinal artery just touches the foveola [Fig. 10], initially there is a marked decline in visual acuity, but within 2–3 weeks, the visual acuity improves markedly, spontaneously (to almost 6/6) which may erroneously be attributed to whatever treatment is being administered.[15]

In conclusion, all these factors play important roles in the visual outcome of CRAO and require evaluation. Therefore, it is essential to classify CRAO into its different types to make scientifically accurate observations about the visual outcome, which, as shown above, can be very different in the various types.

Misconceptions prevalent about the visual outcome in CRAO

There are several misconceptions about it; they are discussed at length elsewhere.[15] These include the following.

1. There is an almost universal impression that CRAO causes marked, generalized loss of vision and that CRAO cannot produce central scotoma only, with intact peripheral visual fields. As discussed above, although central scotoma is the most common visual field defect in CRAO, the eye with CRAO can still have fairly normal peripheral visual fields [Fig. 9].
2. There is no chance of an eye with CRAO having spontaneous visual improvement. My study findings (above) showed that this is not true
3. That visual acuity testing gives required information about the visual outcome and function in CRAO. As mentioned above, visual acuity essentially represents the function of the foveal region and not the rest of the retina. By contrast, visual fields plotted with a Goldmann perimeter provide information about the function of the entire retina. For day-to-day living and navigation, peripheral visual fields provide the essential information
4. When evaluating visual acuity improvement, one has to keep in mind that apparent visual acuity improvement may simply be due to eccentric fixation, because patients with a central scotoma often learn with experience to fixate eccentrically, resulting in an apparent visual acuity improvement, which does not represent a genuine improvement in the retinal function. Obviously, this important artifact can lead to a mistaken claim of visual improvement following a therapy. Therefore, for genuine visual acuity improvement, there must be simultaneous improvement in both the central scotoma and visual acuity.

Anterior Segment of the Eye

In the anterior segment of the eye, there is usually no specific abnormality related to the CRAO. Initially, the intraocular pressure often tends to be slightly lower than in the fellow normal eye, similar to what is seen with retinal vein occlusion,[27] but, unlike in the latter, the lower pressure does not last long. When CRAO is due to ocular ischemic syndrome, the eye may develop iris and angle neovascularization;[12,13] Otherwise, CRAO eyes do not develop any kind of neovascularization.

There is a prevalent belief that CRAO can cause anterior segment neovascularization and neovascular glaucoma, similar to that seen following ischemic central retinal vein occlusion.[15] It is wrong to consider ischemic central retinal vein occlusion and CRAO as being similar in nature, as far as the development of neovascular glaucoma is concerned. My large studies[12,13] on CRAO have shown no cause-and-effect relationship between CRA and neovascular glaucoma, thereby contradicting claims that CRAO results in development of neovascular glaucoma.

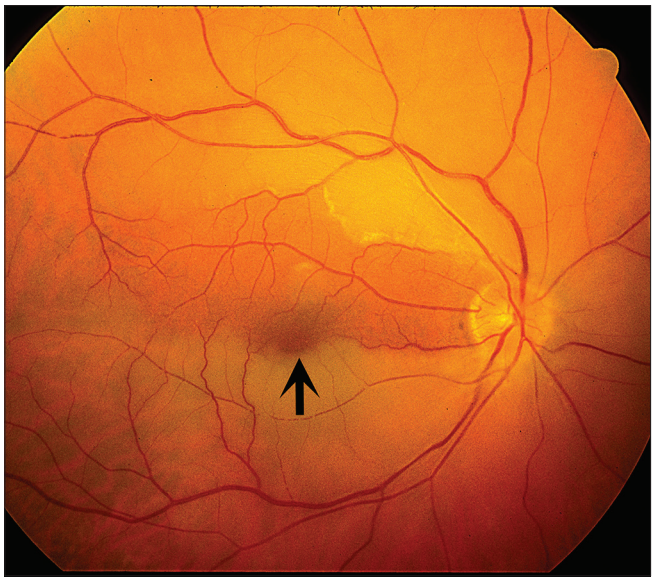

Figure 10: Fundus photograph of the right eye with NA-CRAO, and a patent cilioretinal artery in the macular region. The retinal supply by the patent cilioretinal artery passes through the foveal region (arrow)

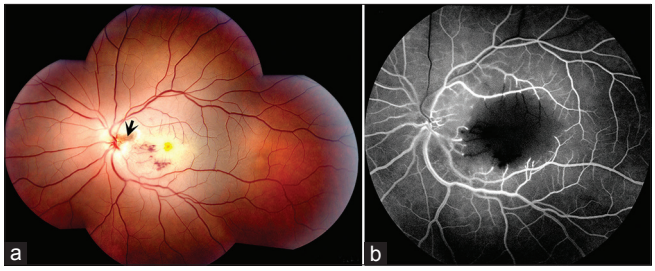

Figure 11: Fundus photograph and fluorescein fundus angiogram of left eye four day after the onset of transient NA-CRAO. (a) Fundus photograph shows retinal opacity of posterior fundus – most marked in the macular region, a small cherry red spot, a few retinal hemorrhages a small patent cilioretinal artery (arrow), and normal-looking peripheral retina.(b) Fluorescein fundus angiogram, during the retinal arteriovenous phase, shows slightly delayed filling of the retinal arteries and veins, with central macular region showing no retinal capillary filling due to no-reflow phenomenon caused by thick ischemic retina in that region

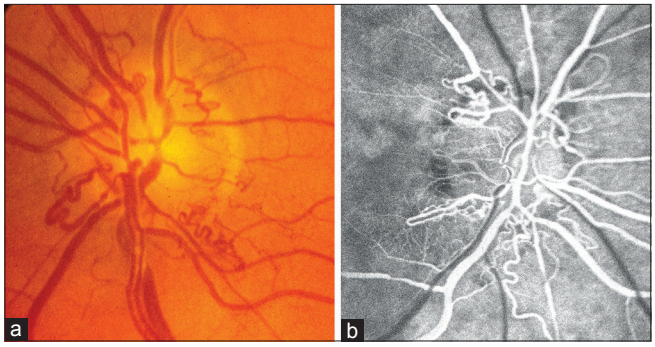

Figure 12: (a) Fundus photograph of the left eye with multiple cilioretinal collaterals on and around the optic disk in an eye with old NA-CRAO. (b) Fluorescein fundus angiogram of the right eye, during retinal arterial phase, with multiple cilioretinal collaterals on and around the optic disk in an eye with old NA-CRAO. Note that, unlike neovascularization, the collateral shows no fluorescein leak

Posterior Segment of the Eye

Ophthalmoscopic findings in CRAO

Nettleship[28] in 1891 published a detailed and comprehensive description of the acute ophthalmoscopic appearance of CRAO in the English literature. He stated: "The classical dense, white haze of the central region of the retina with a well-marked clear patch ('cherry red spot') at the yellow-spot was very well shown; there were no hemorrhages; the arteries and veins were of about the normal size, but no pulsation could be produced in any of them by pressure with the finger upon the globe." He went on to describe the appearance of the blood vessels: "The second feature of interest … is the stagnation of the arterial blood stream without diminution in the size of the arterial column … the large size of the vessels appeared to be inconsistent with the conclusion that their supply was cut off. This phenomenon is by no means uncommon in recent cases of embolism or thrombosis of the arteria centralis, and,… is quite compatible with almost, if not quite complete extinction of sight; on the other hand in some cases the arteries are, as is well known, found to be extremely shrunken from the first." He also gave an excellent diagram of cilioretinal collaterals on the surface of the optic disk seen in a patient 12 months after development of CRAO.

I investigated prospectively the incidence, pattern, and evolution of fundus changes in 248 consecutive eyes with CRAO,[16] as well as experimentally induced CRAO in 101 eyes in rhesus monkeys.[5,6,9]

There is a misunderstanding that retinal whitening, due to infraction of the inner retinal layers, must involve the entire retina to justify the diagnosis of CRAO. In fact, it is mostly located in the posterior pole, maximum within the temporal arcades, with normal-looking peripheral fundus [Fig. 11a]. There is a widespread impression that the "cherry red spot" is due to the red color of the normal underlying choroidal blood. That is not true. The color of the normal fundus is due to the color of the retinal pigment epithelium, not the blood in the choroid. Fundus in black people is gray, but they do not have black blood! The retinal opacity usually starts to resolve in about a week and generally resolves completely within about a month or so, and the retina regains its transparency.

There is no universally consistent pattern of retinal vessels changes. During the initial stages of CRAO, their appearance varies markedly, being extremely attenuated to normal-looking. Cattle-trucking is seen in both retinal arteries and veins during the first week after onset of CRAO [Fig. 1].

Initially, the optic disk may show pale or hyperemic edema, and later on, there is optic atrophy. Cilioretinal optic disk collaterals [Fig. 12] may develop in 18% within 3 months or later, and they may be misdiagnosed as disk neovascularization. Because of this erroneous impression, some authors have claimed that CRAO results in optic disk neovascularization, but my detailed studies[12,16] clearly demonstrated that there is no such cause-and-effect relationship.

Fluorescein fundus angiographic findings in CRAO

It must be performed in all CRAO eyes, because it helps to distinguish various types of CRAO and determine the extent of fundus circulatory abnormalities. NA-CRAO eyes almost

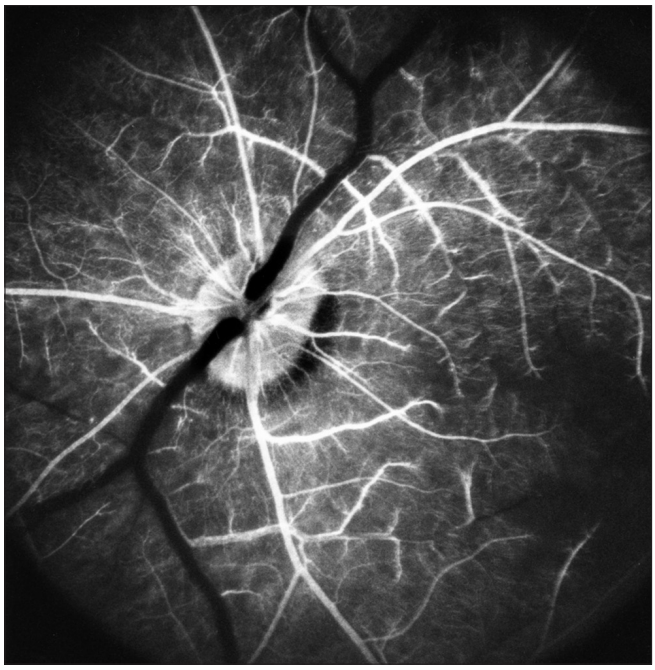

Figure 13: Fluorescein fundus angiogram of the left eye of a rhesus monkey, immediately after experimentally cutting of the central retinal artery at its site of entry into the optic nerve. It shows slow filling of the central retinal artery and the retinal vascular bed, in spite of cutting of the central retinal artery

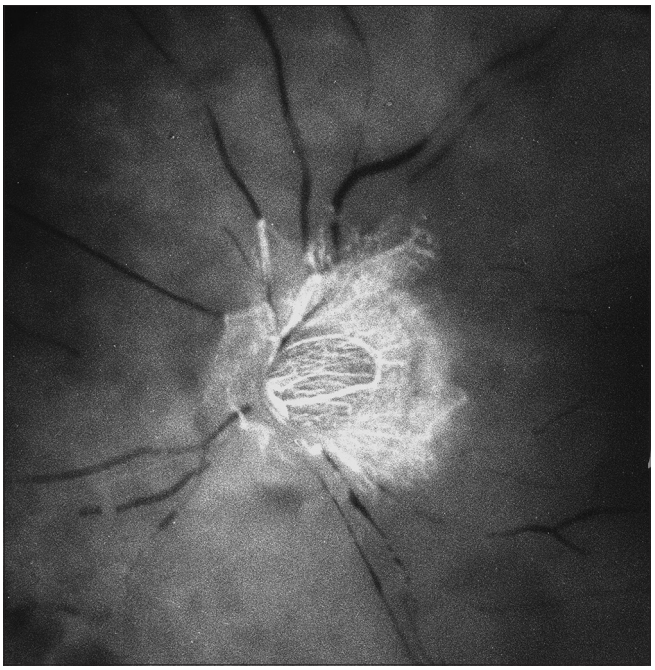

Figure 14: Fluorescein fundus angiogram of the left eye of a patient with NA-CRAO, 29 s after injection of the dye, shows normal filling of the choroid and optic disk vessels (supplied by the posterior ciliary artery circulation), but no filling of the central retinal artery at all as yet. The retinal vessels show typical "cattle-trucking"

always show sluggish filling of the retinal vasculature, and a variable amount of residual retinal circulation [Fig. 13], and it is rare to see complete absence of retinal vascular filling in these eyes [Fig. 14]. I have discussed the mechanism of that residual filling elsewhere.[15,20] The presence of a variable amount of residual retinal circulation has resulted in a mistaken belief among a majority of ophthalmologists that the CRA is not completely occluded in CRAO. Transient CRAO shows normal or almost normal retinal circulation [Figs. 2b and 11b]. In CRAO with cilioretinal artery sparing, fluorescein angiography is the only way to definitely outline the region supplied by the patent cilioretinal artery [Fig. 15], and that is important for determining the visual outcome. In arteritic CRAO, the key diagnostic feature is the presence of associated posterior ciliary artery occlusion[24] [Fig. 3b] because, as discussed above, giant cell arteritis causes thrombosis of the common trunk of posterior ciliary artery and CRA arising from the ophthalmic artery [Fig. 6]. Missing a diagnosis of arteritic CRAO and consequently of giant cell arteritis can result in catastrophic visual loss in both eyes; thus, fluorescein angiography plays a crucial role in the diagnosis of arteritic CRAO and giant cell arteritis. It must, therefore, be performed in all CRAO patients 50 years and older.

During the acute phase of CRAO, my experimental[5,9] and clinical CRAO studies have shown that ischemic retinal whitish opacity and swelling in CRAO are essentially located in the macular region – maximum in the perifoveolar region [Figs. 1, 3a, and 11a]. If there is restoration of circulation in the CRA, the retinal capillaries in the central, thickest part of the macular region do not refill [Figs. 2b and 11b], because of compression of retinal capillaries by the surrounding swollen superficial retinal tissue, resulting in the "no re-flow phenomenon"[9] and consequently in permanent ganglion cell death in the nonperfused retina; the area of central retinal capillary non-filing may vary from eye to eye [Figs. 2b and 11b], depending upon the severity of retinal swelling in the macular region. This results in the variable size of the permanent central scotoma.

There is marked improvement in retinal circulation filling in CRAO eyes with time – the time taken and the extent of this restoration vary markedly from eye to eye, depending upon the site of occlusion and availability and number of CRA anastomoses [Fig. 4].[3,4]

Combined CRAO and Central Retinal Vein Occlusion

There are several reports of this in the literature. The basic question to ask is: Is the simultaneous development of these two very different clinical entities purely coincidental or do they represent one disease? CRAO is usually embolic in origin, while central retinal vein occlusion is always a thrombotic disorder; therefore, there is no reason why two very different processes should occur simultaneously. My clinical, basic, and experimental studies on central retinal vein occlusion have provided an explanation for this clinical entity. They have shown that central retinal vein occlusion is usually due to occlusion of the central retinal vein in the optic nerve, at variable distance posterior to the lamina cribrosa. However, when the central retinal vein is occluded at the lamina cribrosa, it completely blocks retinal circulation, because the central retinal vein has no means to establish collateral circulation soon [Fig. 4] and that converts the retinal circulation into a closed loop – if the blood cannot get out, the blood cannot

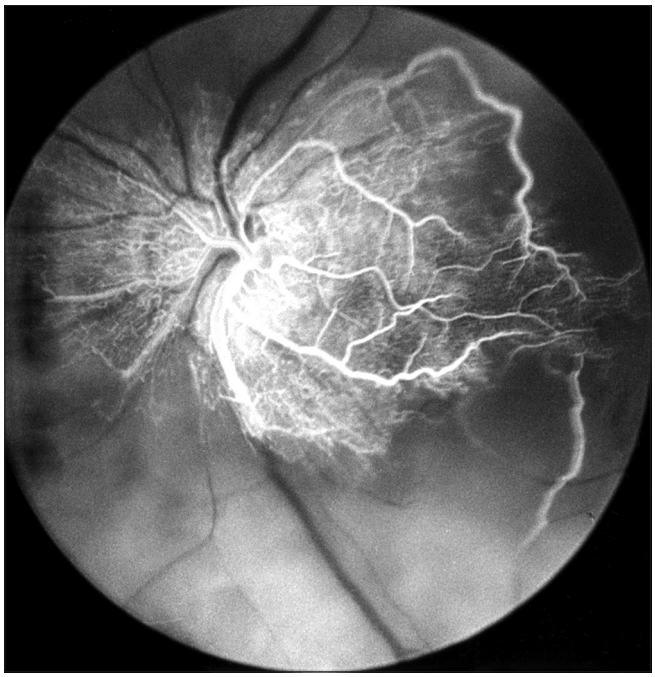

Figure 15: Fluorescein fundus angiogram of the left eye with NA-CRAO with cilioretinal retinal sparing. It shows the area supplied by the cilioretinal artery and retrograde filling the adjacent retinal circulation

get in. This must result in complete stoppage of the retinal circulation; consequently, that results in secondary CRAO. Therefore, when CRAO is associated with central retinal vein occlusion, it constitutes a hemodynamic blockage in the CRA and is not due to actual thrombosis or embolism in the CRA. Thus, simultaneous development of central retinal vein occlusion and CRAO represents one disease entity.

Management of CRAO

There has been a great interest and controversy in its management ever since CRAO has been known. Usually, one or a combination of the following conventional modes of treatments has been advocated in acute CRAO and has claimed success. These[20,23] include (i) ocular massage, in an effort to dislodge the embolus in the CRA; (ii) a reduction of IOP by paracentesis, massage of the eyeball, administration of acetazolamide, and so on to improve blood flow; (iii) vasodilation of the CRA; (iv) inhalations of 95% oxygen and 5% carbon dioxide; (v) rebreathing of expired CO_2 in a bag; and (vi) retrobulbar vasodilators. Except for ocular massage, which occasionally dislodging the embolus, there is no evidence that the rest show any benefit.

Other advocated treatments included (i) thrombolysis by administering a thrombolytic agent, (ii) isovolumic hemodilution, (iii) hyperbaric oxygen, (iv) reduction of red blood cell rigidity by giving pentoxifylline, (v) systemic steroids intravenously to reduce vascular endothelial edema following CRAO, (vi) neodymium: yttrium aluminum garnet laser arteriotomy and embolectomy, (vii) cannulation of the supraorbital artery and retrograde injection of antispasmodic papaverine, (viii) direct massage of the CRA, and (ix) glutamate receptor antagonists.

I have discussed in detail each of these treatments elsewhere.[20,23] To discuss at length, each and every mode of treatment advocated for CRAO would involve writing along, detailed description, which is not desirable in such a review. The two cited references[20,23] give detailed discussion about the various advocated treatments; anyone interested to get more detailed information can consult those references. I have been told that in India, most vitreoretinal surgeons are advocating immediate vitrectomy with low pressure settings in eyes with CRAO irrespective of length of CRAO. Any claim that vitrectomy dislodges emboli has no scientific validity at all, and I have discussed that in my publications on that topic. I am aware that a paper on this method was published from China,[29] based on 10 patients where this procedure was done 24 h to 6 days after the onset of CRAO. There are three major problems with their conclusion. (i) Retinal circulation was said to be restored to normal in four cases, but visual acuity was said to have improved in six cases; that means visual acuity improved in two eyes even when there was no restoration of retinal circulation. (ii) Most importantly, as discussed above, the retina suffers irreversible ischemic damage within 4 h of the onset of CRAO.[9] Therefore, performing this surgical procedure 24 h to 6 days after the onset of CRAO cannot restore function in the irreversibly damaged retina. (iii) As shown above, spontaneous visual improvement does occur as a part of natural history that then is used as evidence for advocating a mode of treatment. These problems invalidate the claim that their surgical procedure helped to improve visual acuity. I consider such practice based on ignorance. It is unfortunate that such scientifically misleading papers get published; it is even more unfortunate that such financially rewarding procedures get perpetuated by vitreoretinal surgeons, at no benefit at all to the poor patient.

Of these therapies, local intra-arterial thrombolysis is currently the most popular. In this mode of treatment, intra-arterial fibrinolysis is delivered directly into the ophthalmic artery by super-selective administration of thrombolytic agent. Almost all the studies are based on retrospective review of charts. Reputable studies by Beatty and Au Eong,[30] Fraser and Siriwardena,[31] Noble *et al*.,[32] Framme *et al*.,[33] and Schumacher *et al*.[34] conclusively showed that local intra-arterial fibrinolysis not only has no beneficial effect, but also can be associated with serious systemic complications. For example, Framme *et al*.[33] in a study of 62 patients compared visual recovery after intra-arterial fibrinolysis to conventional treatment. They concluded that there was no difference between the two modes of treatment in the improvement of visual acuity; additionally, there is an increased risk of a stroke from intra-arterial fibrinolysis. Schumacher *et al*.[34] conducted a prospective, randomized, multicenter clinical trial study in 84 CRAO patients, of whom 40 received conventional treatment and 44 local intra-arterial fibrinolysis. The mean best corrected visual acuity showed no significant differences ($P = 0.69$) between the two groups. Adverse reactions of therapy were seen in 37.1% in the local intra-arterial fibrinolysis group. They concluded that in light of these two therapies' similar outcomes and the higher rate of adverse reactions associated with local intra-arterial fibrinolysis, they could not recommend local intra-arterial fibrinolysis for the management of acute CRAO. I feel that should settle the issue of the role of thrombolytic therapy. This is not surprising, because, as discussed elsewhere,[14,15,23] thrombolysis therapy has little scientific rationale in CRAO and is not entirely safe. However, more recently, Johns Hopkins Hospital study[35] in 42 patients, half

treated by local intra-arterial t-PA study (LIF) and the rest no therapy, claimed that LIF administered in aliquots is associated with an improvement in visual acuity compared with standard therapy and has few side effects. But that study presents problems: (a) the treatment was given 15 h after the onset of CRAO, but my experimental study[9] showed that CRAO lasting for 4 h results in irreversible ischemic retinal damage. (b) My natural history study[14] in 260 eyes showed that the visual outcome very much depends upon the type of CRAO, and their sample size of 21 was far too small to rule that out.

The groundless claims of benefits for various modes of treatments are due to the following two factors:

1. The visual improvement as a part of the natural history of visual outcome[14] has been mistaken for a beneficial effect of treatment
2. My study[9] showed that if the retinal circulation is restored within an hour, there is no irreversible retinal damage with return of normal vision.

Most importantly, when discussing any therapy for CRAO, the first essential is, does a therapy have a scientific rationale? Without it, any treatment must eventually prove useless or even harmful.

Investigations in Patients with CRAO

From the discussion above, it is evident that patients with CRAO should have the following investigations to find the cause and to prevent or reduce the risk of any further visual problems or stroke. Contrary to the practice often advocated, they do not need urgent neurological evaluation, unless they have neurological symptoms, as discussed elsewhere.[22]

1. In all patients 50 years and older with CRAO, it is absolutely critical to rule out giant cell arteritis because that is an important ophthalmic emergency; if it is missed, that can result in catastrophic visual loss in both eyes, which is preventable by immediate diagnosis and aggressive management with corticosteroid therapy.[36-38] This fact has medicolegal implications, apart from the human tragedy involved. All these patients must have immediate evaluation of erythrocyte sedimentation rate and C-reactive protein levels estimated – of the two, the latter is more reliable.[38] Systemic symptoms of giant cell arteritis,[38] when present, can be helpful. All these patients must also have fluorescein angiography because the presence of associated posterior ciliary artery occlusion is diagnostic in these cases [Figs. 3 and 6]
2. Since embolism is the most common cause of CRAO, all patients with CRAO *must* have urgently a complete evaluation to find the source of embolism. As discussed above, the most common sources of emboli are the carotid artery and the heart [Table 1]. In the carotid artery, the most common source of embolus is a plaque, so it is essential to find out if there are any plaques; unfortunately, I have found that evaluation is usually primarily focused on whether there is hemodynamically significant carotid artery stenosis, without paying attention to the presence of plaques. That can miss the actual source of emboli
3. Cardiac evaluation is equally essential, even if the carotid artery shows lesions, because I have found that at times a patient can have lesions in both places, and either of them can be the source of emboli. My study[19] showed that the most common source of emboli in the heart is the valves, although other lesions can also be responsible [Table 1]. Transesophageal echocardiography is the best way to evaluate heart lesions
4. Atherosclerosis is a common cause of lesions in the carotid artery, so it is essential to do their lipid evaluation. I have found that invariably physicians tend to look only at the total cholesterol level. I have seen many patients with perfectly normal total cholesterol levels but with high low-density lipoproteins, which is the most important parameter. The current guideline is to have low-density lipoproteins not more than 70 mg/dL. Similarly, triglycerides should also be in normal limits
5. As discussed above, there are many rare causes of CRAO. In difficult cases, one has to keep those in mind. In my studies, I have not found thrombophilia evaluation fruitful in CRAO
6. In eyes with CRAO, optical coherence tomography (OCT) and OCT angiography do not provide any more worthwhile information than that provided by fundus ophthalmoscopic evaluation, color fundus photography, and ordinary fluorescein fundus angiography; other than it unnecessarily adds to the cost of medical care, which is unfair to the poor patient. I have found that in CRAO, these two new methods of testing are not necessary.

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Conflicts of interest

There are no conflicts of interest.

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