Retinal Artery Occlusion

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Abstract

Retinal artery occlusions (RAO) are characterized by the sudden obstruction of the arterial blood flow in the retinal circulation with consequent ischemic damage to the retina. RAO can be subdivided into several forms, including central retinal artery occlusion (CRAO) and Branch retinal artery occlusion (BRAO). Patients affected by CRAO experience a sudden, monocular loss of vision. On fundus biomicroscopy, if the retinal obstruction is incomplete a slight gray haze may be visible, but when the flow blockage is complete a progressive whitening and swelling of the inner retina develops. Patients affected by BRAO complain of sudden, partial or complete, visual loss associated with visual field damage. The area concerned by the BRAO shows evidence of acute retinal ischemia corresponding to the distribution of the occluded branch retinal artery. At present, there is no generally agreed treatment regimen for RAO, although a number of therapeutic interventions have been proposed.

Classification

According to the involved vessels, RAO can be subdivided into several forms, including:

- Central retinal artery occlusion (CRAO).
- Branch retinal artery occlusion (BRAO).
- Cilio-retinal artery occlusion.
- CRAO sparing cilio-retinal artery.
- CRAO associated with CRVO.
- Ophthalmic artery occlusion.

The two main forms are central retinal artery occlusion and branch retinal artery occlusion.

Etiology

The etiology of RAO encompasses many conditions, as summarized in table 1.

Table 1. Etiology of RAO

<table>
<thead>
<tr>
<th>Intravascular</th>
<th>Extravascular</th>
<th>Drug effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>Vasospasm</td>
<td>Anti-VEGF (bevacizumab, ranibizumab [2])</td>
</tr>
<tr>
<td>Embolus</td>
<td>External compression</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Decreased flow</td>
<td>Disc anomalies</td>
<td></td>
</tr>
</tbody>
</table>

Retinal Artery Occlusions

Definition

Retinal artery occlusions (RAO) are a group of diseases characterized by the sudden obstruction of the arterial blood flow in the retinal circulation with consequent ischemic damage to the retina [1].
Particular attention has been paid to the embolic obstruction, which can be derived by endogenous or exogenous emboli, as listed in Table 2. It is noteworthy that the potential occludability differs in relation to the nature of the embolus. In particular, calcium emboli cause a severe vascular occlusion with blood flow blockage, whereas platelet emboli may obstruct the flow only occasionally. The emboli are biomicroscopically detectable in 20–40% of eyes [3]. Biomicroscopic examination can allow the identification of the emboli structure because calcium emboli are usually single, solid, whitish, and nonrefractile, and more often are situated near to the optic disc, remaining stable over time. Platelet emboli are dull, gray-white, single or multiple, and are more often lodged at a vessel bifurcation. Cholesterol emboli are often multiple, yellowish and refractile, and may be found in several fundus regions.

The most frequent retinal emboli are represented by cholesterol emboli (74.0%), platelet-fibrin emboli (15.5%), and calcific emboli (10.5%) [4]. Overall, in younger people the emboli are more often derived from heart valves (prolapse of mitral valve, rheumatic fever, congenital anomalies), whereas, in older patients emboli can take origin from ulcerated atheromatous plaques in the carotid artery.

### Central Retinal Artery Occlusion

**Classification**

Central retinal artery occlusion (CRAO) can be classified into distinct categories because the visual outcome can be different in the 2 subtypes according to the long-term visual function conservation: permanent and transient CRAO [5].

<table>
<thead>
<tr>
<th>Embolus type</th>
<th>Biomicroscopy</th>
<th>Occludability</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>yellowish, glistening</td>
<td>occasional</td>
<td>arteriosclerosis carotid-ophthalmic artery</td>
</tr>
<tr>
<td>Platelet</td>
<td>whitish, grayish</td>
<td>rare</td>
<td>arteriosclerosis carotid-ophthalmic artery</td>
</tr>
<tr>
<td>Calcium</td>
<td>chalky-white</td>
<td>common</td>
<td>aortic valve disease, calcified arterial</td>
</tr>
<tr>
<td>Fat</td>
<td>multiple cotton-wool spots</td>
<td>no</td>
<td>fractures, pancreatitis</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Roth's spots</td>
<td>no</td>
<td>subacute bacterial endocarditis</td>
</tr>
<tr>
<td>Parasites</td>
<td>parasites</td>
<td>occasional</td>
<td>systemic disease</td>
</tr>
<tr>
<td>Tumor cells aggregates</td>
<td>yellowish plaques</td>
<td>common</td>
<td>atrial myxoma</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>white-yellowish dots cotton-wool spots</td>
<td>common</td>
<td>amniotic fluid during pregnancy or labor</td>
</tr>
<tr>
<td>Talc</td>
<td>white-yellowish dots cotton-wool spots</td>
<td>occasional</td>
<td>drug addicts</td>
</tr>
<tr>
<td>Air</td>
<td>multiple bubbles</td>
<td>occasional</td>
<td>barometric decompression, surgery or trauma, bronchiectasis</td>
</tr>
<tr>
<td>Glass beads</td>
<td>cherry-red spot</td>
<td>common</td>
<td>glass beads</td>
</tr>
</tbody>
</table>
Permanent CRAO consists of three types:

- **Non-arteritic CRAO**: found in 66% of CRAO, corresponds to eyes with the classic clinical picture of permanent CRAO with retinal infarction, cherry-red spot, and absent or poor residual retinal circulation on fluorescein angiography, but with no evidence of giant cell arteritis.

- **Non-arteritic CRAO with cilio-retinal artery sparing**: accounting for 14% of CRAO cases. In this condition, a central island is spared corresponding to the area of the retina supplied by the patent cilio-retinal artery, whereas the surrounding retina shows the typical ischemic alterations.

- **Arteritic CRAO**: detected in 4% of CRAO cases, in which the cause of development of permanent CRAO is giant cell arteritis, and most invariably associated with arteritic anterior ischemic optic neuropathy [6]. Therefore, the visual loss is the result of acute ischemia, not only of the retina but also of the optic nerve head. Clinically, these eyes have the classic fundus findings of CRAO with or without optic disk edema, but, most importantly, on fluorescein angiography there is evidence of a posterior ciliary artery occlusion in addition to CRAO.

- The fourth category is transient non-arteritic CRAO, corresponding to 16% of the whole CRAO cases. In transient non-arteritic CRAO, the diagnosis is based on a history of marked sudden visual loss and classic fundus findings of CRAO but normal retinal circulation on fluorescein angiography, whereas the visual outcome depends on the duration of transient CRAO, which may vary from several minutes to many hours.

**Symptoms**

Patients affected by CRAO experience a sudden, monocular loss of vision in most of the cases. Vision loss is preceded in up to 25% of cases by amaurosis fugax or transient ischemic attack [4].

Visual acuity is generally compromised at the initial examination visit. Functional values correspond to counting fingers or worse in 74% of the whole CRAO cases, whereas only 11% of cases present a visual acuity of 20/40 or better. Unfortunately, visual prognosis is generally bad, because 61% of eyes will achieve a visual acuity of counting fingers or worse at the final visit, whereas only 16% will have a visual acuity of 20/40 or better [5].

It is noteworthy that visual acuity differs among the 4 CRAO types if seen within 7 days from the CRAO onset, being better in transient non-arteritic CRAO and in CRAO with cilio-arterial artery sparing. Moreover, visual acuity has shown a tendency to improve in the specific subgroup examined within 7 days from the CRAO onset, i.e. the earlier diagnosed CRAO. Overall, visual acuity improves in about 80% in transient non-arteritic CRAO and in 22% of non-arteritic CRAO [5]. Thus, visual acuity improvement essentially occurs during the first 7 days, with minimal chance of any appreciable improvement thereafter. The patients may also complain of dark areas in the visual field corresponding to scotomata of various shape and size on visual field examination.

**Clinical Picture**

If the retinal obstruction is incomplete, a slight gray haze may be visible, but when the flow blockage is complete a progressive whitening and swelling of the inner retina develops. These changes are due to the denaturation of the intracellular protein, together with the increased intracellular water content, and finally the complete cellular necrosis.

Overall, on initial ophthalmic evaluation, there is more often evidence of acute retinal ischemia, as demonstrated by the identification of retinal infarction with cherry-red spot or, in eyes with transient CRAO, by the recognition of multiple scattered patches of retinal infarction all over the posterior pole with or without intervening retina showing whitening or even a faint cherry-red spot. Moreover, the presence of box-carring (cattle trucking) of a blood column in the retinal vessels, except in cases affected by transient CRAO, may be detected. Fluorescein fundus angiography
performed soon after the onset, discloses the absence, or at least the marked stasis of retinal arterial circulation, except in eyes with transient CRAO, where the flow may be normal.

Nevertheless, the clinical picture may change according to the time of the diagnosis. A study by Hayreh and Zimmerman [7] revealed that even the most pathognomonic aspect for CRAO, which is the detection of the cherry-red spot is detectable in 90% of permanent CRAO and only within 7 days from onset, reducing to 15% after 1 month from onset. The complete data are listed in Table 3.

Retinal Tolerance Time to Acute Retinal Ischemia

Hayreh’s studies of experimental CRAO in elderly atherosclerotic and hypertensive rhesus monkeys have showed that retina suffers from almost no detectable damages up to 97 min. After that time, the longer the CRAO, the more extensive the retinal damage. In particular, CRAO lasting for about 4 h results in massive and irreversible ischemic retinal degeneration. Thus, no treatment instituted much longer than 4 h after loss of vision can logically hope to restore vision [7].
Branch Retinal Artery Occlusion

Classification
Branch retinal artery occlusion (BRAO) is a relatively common relatively retinal vascular disorder characterized by the occurrence of an obstruction along the course of a retinal branch. BRAO can be classified into three main subtypes, including [9]:
- Permanent BRAO: detectable in 63% of BRAO, in which the vessel occlusion is stable with no reperfusion.
- Transient BRAO: characterized by temporary blood flow obstruction, and detectable in 9% of BRAO cases.
- Cilio-retinal artery occlusion (CLRAO): this is a distinct clinical entity different from the usual type of BRAO, because the cilio-retinal artery arises from the posterior ciliary artery, instead of the central retinal artery. It can be visible in 28% of BRAO cases and comprises 3 distinct etiological types, including:
  - Non-arteritic cilio-retinal artery occlusion.
  - Arteritic cilio-retinal artery occlusion, associated with giant cell arteritis.
  - Cilio-retinal artery occlusion associated with central retinal vein occlusion/hemi-central retinal vein occlusion, which is a distinct clinical entity, due to transient hemodynamic blockage of the cilio-retinal artery, caused by a sudden rise in intraluminal pressure in the retinal capillary bed (owing to central retinal vein occlusion) above the level of that in the cilio-retinal artery, and where, unlike regular, non-arteritic form, there is no thrombotic or embolic occlusion of the artery.

Symptoms
In general, patients affected by BRAO complain of sudden, partial or complete, visual loss associated with visual field damage. Visual acuity impairment can be variable [9]. At the moment of the diagnosis, a visual acuity value of at least 20/40 can be seen in 74% of permanent BRAO, 94% of transient BRAO, 73% of Non-arteritic CLRAO, and 36% of arteritic CLRAO. Visual acuity improvement may occur over time, with a value of at least 20/40 seen in 89% of permanent BRAO, 100% of transient BRAO, and 100% of non-arteritic CLRAO at the end of the follow-up. Visual acuity recovery in BRAO essentially may depend on two main features. First of all, the junction between the normal and infarcted retina in BRAO: when the border passes through the fovea the visual acuity may suddenly deteriorate initially, but a spontaneous and significant improvement can occur within several days or weeks, from ≤20/200 up to 20/20. Moreover, the retina can recover/improve function only so long it is not irreversibly damaged by acute ischemia, bearing in mind that hypoxia lasting more 240 min results in massive, irreversible retinal damage [8].

Clinical Picture
Aspect and extension of the retinal areas involved may differ on the basis of the arterial vessel implicated. Overall, on initial ophthalmic evaluation, the area concerned by the BRAO shows evidence of acute retinal ischemia corresponding to the distribution of the occluded branch retinal artery. Fluorescein fundus angiography, if performed soon after the onset, reveals the absence or marked stasis of circulation in the involved branch retinal artery, except in eyes with transient BRAO.

Many types of central and peripheral visual field defects can be registered, including central and peripheral scotomata.

Ocular Neovascularizations in RAO

Ocular neovascularizations (NV) can also occur in ROA [6, 10]. In general, ocular NV are visible after CRAO of permanent type. More specifically Iris NV can be detected in 18%, angle NV in 15%, and optic disc NV in 0.2% of CRAO cases. Neovascular glaucoma has been described in up to 15% of CRAO. BRAO in general does not result in ocular NV. It is believed that the pathogenic mechanisms leading to the development of
Ocular NV are related to the underlying ocular ischemic syndrome rather than the RAO.

**Treatment**

Treatment options should be different according to the origin of RAO.

In non-arteritic RAO we may consider:

- Conservative treatment.
- Invasive treatment.
- Ophthalmic artery catheterization + thrombotic agent injection.
- Surgical treatment.
- Vitrectomy + CRA cannulation, Nd:YAG-laser, surgery.

In arteritic RAO, it is mandatory to advise systemic steroid therapy, which should be modulated and eventually tapered over the follow-up with the support of an internal medicine specialist.

Conservative treatments in non-arteritic RAO is still controversial and may include:

- Ocular massage.
- Anterior chamber paracentesis.
- Vasodilators (isosorbide dinitrate, tolazoline).
- Carbonic anydrase inhibitors (acetazolamide).
- Hyperosmotic agents (glycerol, mannitol).
- Thrombolitics (streptokinase, urokinase).
- Corticosteroids (methylprednisolone).

At present there is no generally agreed treatment regimen for RAO, although a number of therapeutic interventions have been proposed. Indeed, no reliable randomized clinical trial (RCT) exists to support a therapeutic choice. Only small RCTs from single centers have reported limited beneficial results with the use of pentoxifylline (three 600 mg tablets daily) [11], and enhanced external counterpulsation (EECP) combined with hemodilution [12].

The aggressive systematic treatment of RAO, proposed by Rumelt et al. [13] required two separate steps, first with ocular massage with a 3-mirror contact lens (10 s pression/5 sec release) for 20 min + sublingual isosorbide dinitrate 10 mg + intravenous acetazolamide 500 mg + intravenous mannitol 1 mg/kg. In the case of no reversion of the clinical picture, the second step included: anterior chamber paracentesis + intravenous methylprednisolone 500 mg + streptokinase 750,000 iu + retrobulbar tolazoline 50 mg. Overall, the results of this approach have been controversial.

Intra-arterial thrombolysis is based on the use of catheter-assisted super-selective intra-arterial thrombolysis. Even though a precise evaluation of this approach is difficult, several non-randomized, case series and cohort studies have reported some benefit compared with conventional conservative therapies [14].

A surgical removal of intra-arterial embolus has been proposed by Garcia-Arrumi and coworkers, obtaining a successful removal of the embolus in 6 of 7 patients, with a visual acuity improvement from a median value of 20/400 to 20/40 [15]. Nevertheless, therapy for CRA is still disappointing. The Cochrane review regarding RAO treatment options reports that ‘There is currently not enough evidence to decide which, if any, interventions for acute non-arteritic CRAO would result in any beneficial or harmful effect. . . ’ and that ‘ . . . .Large, well-designed RCTs are still required to establish the most effective treatment for acute CRAO’ [16].

**References**


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