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INTEGRATED STUDY MASTER'S THESIS

Management of Acute Central Retinal Artery Occlusion: Neurological Approach

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Abbreviations: CRAO, Central Retinal Artery Occlusion; CRP, C-Reactive Protein; CT, Computed Tomography; DW-MRI, Diffusion-Weighted Magnetic Resonance Imaging; ESR, Erythrocyte Sedimentation Rate; GP, General Practitioner; HBOT, Hyperbaric Oxygen Therapy; IAT, Intraarterial Thrombolysis; IVT, Intravenous Thrombolysis; OCT, Optical Coherence Tomography; OCTA, Optical Coherence Tomography Angiography; TIA, Transient Ischemic Attack.

Summary

The central retinal artery occlusion, or so-called ischemic ocular stroke, is a challenging diagnosis for patients and physicians. The bad outcome that it currently brings along is linked to issues that remind one of the pathways that cerebral ischemic stroke management had to go through over the last decades. Likewise, as with the cerebral ischemic stroke, a neurological approach to central retinal artery occlusion patients is only possible in stroke units, where ophthalmologists are usually not available. Therefore, the diagnostic workup is already challenging. However, even if diagnosed within the debated timeframe, treatment is still without evidence and not to be found in approved stroke guidelines from the American and European stroke associations. Intravenous and intraarterial thrombolysis, according to today's research, are walking a fine line between improved vision and adverse effects. This literature review summarizes the current findings on central retinal artery occlusion management while focusing on the neurologic diagnostic and therapeutic process. It shows the potential for neurologic point-of-care ultrasound in combination with optical coherence tomography and diffusion-weighted magnetic resonance imaging for the improvement of the diagnostic process. Research on therapeutic intravenous thrombolysis on central retinal artery occlusion patients shows promising results. At the same time, conservative methods such as ocular massage, hyperbaric oxygen therapy, and others remain without evidence of effectiveness. Furthermore, not only because of increased rates of ischemic cerebral stroke and neovascular glaucoma in patients with central retinal

artery occlusion, the awareness of the disease, both among medical and non-medical societies, must be raised. An effective interplay among medical specialists remains key for the optimal central retinal artery occlusion management.

Keywords: Central Retinal Artery Occlusion, Neurological Point of Care Ultrasound, Intravenous Thrombolysis, Ocular Stroke, Painless monocular blindness, Neurological Approach

1 Introduction

Central retinal artery occlusion (CRAO) is a vision-threatening disease affecting 1.9 cases per 100.000 inhabitants in the United States (1). The consequential permanent loss of vision is immensely negatively impacting the lives of those affected. Together with the ongoing lack of evidence-based treatment of CRAO and management guidelines, the current state of CRAO workup, with all its uncertainties, reminds the pathway of ischemic cerebral stroke. As so often, a look in the past can teach and give inspiration for the present. Similar to CRAO now, treatment options for ischemic cerebral stroke remained very limited in number and effectiveness until the mid-1990s. The hope for the spontaneous resolution of the thrombi and restoration of function was mostly disappointed. The contribution of the neurologist to its treatment was restricted to a topographic diagnosis, mostly without consequences (2).

The first brain computed tomography (CT) and magnetic resonance imaging (MRI) documented brain damages were usually more precise and reliable, and more importantly, able to exclude a bleeding, which would have contraindicated antithrombotic therapy (3).

The neurologists' tasks on brain strokes were thus quite limited in their effectiveness and treatment options. The Introduction of intravenous lysis in the middle of the 1990s ended the era of the neurologists as, when it came to strokes, therapeutically incapable diagnosticians, and included them among the emergency interventionists. It was clear that the lysis would only help during the first hours following the insult. It is still believed that lysis must happen within the first 4.5 hours. This led to the foundation of the first stroke units, which were unique in their ability to provide the required rapidity. Here, neurologists worked together with radiologists and cardiologists (2).

This was followed by a second revolution in the early 2000s with the thrombectomy for severe ischemic strokes. The first MERCI Retriver was approved in 2004. With a short setback in 2013, the technology of Stent Retriever imposed itself since 2015 after new studies, for limited indications (4).

Even though used more restrictively as the lysis, stent retriever formed the capabilities of stroke units with an even more rapid intervention and more intensive and complex cooperation among neurologists and neuroradiologists. To perform intervention within 4.5 hours or even earlier after symptom onset requires a reliable team and standardized processes. These processes, since then, are getting optimised by improvements in pharmacology and neuroradiological technology. This, in the last ten years, gave the domain of emergency neurology the time to pay its attention to another topic: the stroke of the eye, by an occlusion of the central retinal artery. This, before, has not been given much attention, even though it causes severe and substantially irreversible loss of vision.

Nevertheless, even though acknowledged by patients and primary caregivers, sudden loss of vision is often not identified as an emergency treatment needing disorder (5).
Especially the term of transient ischemic attack (TIA) shows itself to be counterproductive, since it is used as an alibi for the trivialization of such events. Instead of pointing out the imperativeness of immediate intervention, patients are often referred to outpatient ophthalmologist or neurologist consultations (5).
Even though every neurologist is aware of the importance of rapid therapy, it still constitutes a challenge for the chain of care in its entirety. Already, the diagnostic itself is not always simple, and, at least currently, often requires ophthalmologic competence and equipment, which in most cases is not to be found in stroke units (6).
Additionally, there's still dispute concerning the right intervention and its effectiveness, within a time window that almost comes with anachronistic connotations (7).
The interest in this topic anyways increased, according to the rise in publications in the last years.

Even though the eye is principally managed by an ophthalmologist, the neurologist is on the front line in case of vascular events, since emergency management of ischemic events of neurological organs in stroke units is the neurologist's responsibility. Only in stroke units are qualitative and quantitative skills provided adequately to detect and effectively treat these events in the required time frame. Ophthalmologic clinics, in contrast to stroke units, are usually not found outside of cities with university hospitals (6). In cities without an ophthalmologic clinic, private ophthalmologists would have to manage this emergency and send the patient to the next stroke unit. Having the advantage of already covered ophthalmologic differential diagnostics, there is, however, not always an emergency duty by an emergency-experienced ophthalmologist available in every city. Thus, long drives and

multiple hours of waiting time are to be expected. In conclusion, there is no alternative for the CRAO management in stroke units.

Having concluded the jurisdiction of the neurologist as CRAO caregiver, it is left to determine how to manage CRAO as an emergency neurologist. More specifically, this literature review will summarize the current literature on how to diagnose and treat CRAO in an emergency setting, and how much time neurologists and their patients have left after the onset of symptoms.

2 Methodology

A primary literature search was carried out using the PubMed database to search for the terms central retinal artery occlusion, retinal ischemia, eye stroke, orbital ultrasound, intravenous thrombolysis, macular thickness evaluation, optical coherence tomography, and central retinal artery occlusion awareness. The time range for the usable literature was set as the last 10 years. This time range was met with the exception for the latest evaluation of the CRAO incidence in the United States, Minnesota, by Leavitt et al. 2011, and for literature by the Author Sohan Singh Hayreh, whose publications are used in many cases in research as fundamentals. Studies that were not published in English were filtered out. With the kind support of this thesis supervisor, it was possible to include clinical examples of the potential of ultrasound in CRAO diagnostics in the form of orbital and carotid ultrasound images and one clinical case.

3 General Information on CRAO

3.1 Anatomy of the Retina and Retinal Artery Supply

To get a complete understanding of every disease, it is always essential to be fully aware of the anatomy. The ophthalmic artery is the first branch of the internal carotid artery after it emerges from the cavernous sinus and enters the skull. Its origin is in the inferolateral side of the optic nerve. It provides the central retinal artery, which first runs above or below the optic nerve, before continuing within the nerve, shortly before the ocular bulbus.
The retina is supplied by two arterial systems, which both emerge from the ophthalmic artery. The retinal circulation supplies the inner retina. The choroid system, made of arterioles, supplies the outer retina and the choroid (8).

The central retinal artery has three sections. The intraorbital section, from its origin to the emergence through the dural sheath surrounding the optic nerve. The intradural section, between the optic nerve and the dural sheath, and finally the intraneural section, within the optic nerve.
The central retinal artery emerges in the area of the head of the optic nerve and splits into the upper and lower branches, which are subdivided into the nasal and temporal branches. These vessels supply the optic nerve and the inner retina (8).

The central retinal artery is about 160 µm thick and narrows particularly before it enters the optic nerve. This is the most frequent locus of arterial occlusions due to emboli. The ophthalmic artery consists of a close anastomotic network with connections to the arteria maxillaris interna, arteria temporalis anterior, arteria dorsalis nasi, and arteria facialis (8).
In up to 25% of humans, there is an additional cilioretinal artery, which emerges from the posterior ciliary circulation and supplies parts of the retina (9). These individuals typically have less severe presentations and better long-term prognosis (10).

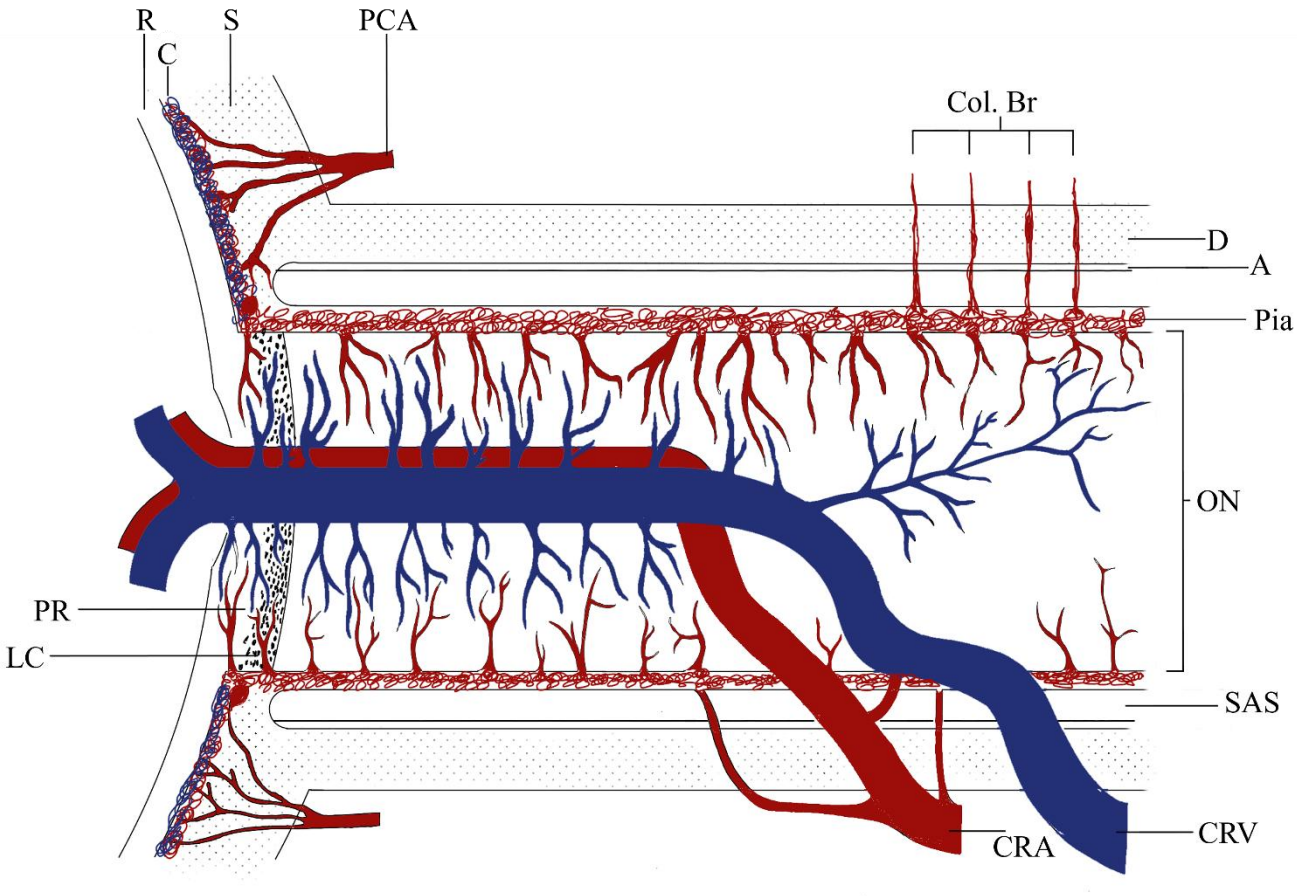

Figure 1: The Anatomy of the Central Retinal Artery
Schematic representation, showing the course of the central retinal artery and its branches and anastomoses. The author re-created this figure using information from (11).

Abbreviations: 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.

3. 2 Tolerance of Retinal Tissue to Ischemia

The cells of the retina have an above-average, highly active metabolism and rely on a continuous supply of substrates for their anaerobic glycolysis, which causes them to be very sensitive in case of ischemia. It is imaginable, however, that older ischemic proven cells resist ischemia for longer. That is what studies on monkeys are indicating (12).
An infarction of the retinal ganglion cells occurs in the setting of a complete CRAO in a time frame that is highly debated. However, some experts have determined this time point to be at 12 to 15 minutes (7).

Studies on monkeys found this timepoint to be at more than 240 minutes (12). There are two particularly interesting studies investigating the retinal survival time to ischemia in monkeys. One was performed in the 1980s on young healthy rhesus monkeys by Hayreh and Weigeist (13). The second one was in the early 2000s by Hayreh and Zimmerman on 38 elderly, atherosclerotic, and hypertensive rhesus monkeys (12). Both studies came to different conclusions.

The first study, which was performed on young healthy rhesus monkeys, revealed irreparable damage to the retina developed after 105 minutes, while the retinal tissue still recovered after 97 minutes of ischemia (13).

The second, more recent study showed that the retinal ischemia in older, atherosclerotic, and hypertensive monkeys did not manifest in any verifiable damage within 97 minutes. When CRAO exceeded this time, the irreversible damage started to accumulate with time. The study concluded that CRAO exceeding 240 minutes leads to severe, irreversible retinal damage in monkeys (12).

Even though it is not entirely transmissible in human settings, it indicates that older cells that were already exposed to ischemia are resisting ischemia for longer. As a possible explanation, Hayreh and Zimmerman suspect the concept of ischemic preconditioning. It has been shown that ischemic preconditioning by short transient ischemic or hypoxic episodes can increase the ischemic tolerance of the myocardium, the brain, and also the retina (12). However, the exact mechanism remains a topic of debate.

Other investigations on monkeys by Hayreh and Weingeist showed that 89% of eyes affected by an occlusion of the central retinal artery had a remaining circulation. This is probably because of cilioretinal capillary anastomoses, pial anastomoses proximally to the loci of occlusion.

The meaning and the function of this network might explain the variety of the pre- and postischemic symptoms, as well as the different postischemic outcomes (14).

3.3 Classification of CRAO

CRAO can be classified into the following subtypes: arteritic CRAO or non-arteritic CRAO (with or without cilioretinal artery sparing), complete or incomplete CRAO, transient monocular blindness (amaurosis fugax), or permanent CRAO. A rapid classification is important, as the recommended therapy and management differ (10,11).
Non-arteritic permanent CRAO accounts for more than two-thirds of all cases (11), and is caused by thrombi composed of platelets and fibrin, and results from atherosclerosis (10).

Non-arteritic transient CRAO, which causes 16% of all CRAOs (11). Patients suffering from this have a 1% risk per year of having a permanent non-arteritic CRAO. Transient vasospasm due to serotonin release from platelets on atherosclerotic plaques is set to be the mechanism in animal models. It has the best visual prognosis (10).
Related to non-arteritic transient CRAO is amaurosis fugax, describing a transient visual loss in an eye, which can occur due to retinal ischemia but also ischemia of the optic nerve head only, as for example in giant cell arteritis. Thus, it can, but not necessarily must be due to a transient CRAO (9).

Non-arteritic CRAO with cilioretinal sparing, present in 14% of CRAOs, describes the preservation of the cilioretinal artery, resulting in preserved perfusion of the macula region (11).

Arteritic CRAO (4% of CRAOs (11)) due to giant cell arteritis seems to be the most common arteritic entity. However, it can also be caused by polyarteritis nodosa, granulomatosis with polyangiitis, Susac syndrome, and systemic lupus erythematosus. It can cause bilateral visual loss. If suspected, it is essential to determine the inflammatory markers and treat immediately with systemic corticosteroids (10).

3.4 Aetiologies and Risk Factors of CRAO

To manage CRAO effectively, diagnostics and awareness are key. For both, education among physicians and patients about predisposition is beneficial. This helps to suspect and detect CRAO on time, and in the best case, even prevent it. Furthermore, the EAGLE study revealed that in 78% of patients who presented with CRAO, a previously undiagnosed risk factor was diagnosed. Many risk factors for the development of CRAO correlate with the predisposing factors for ischemic cerebral stroke (15).

One example is the increased level of cholesterol, especially low-density-lipoprotein, being found to lead to the formation of plaques on the endothelial walls of the carotid arteries, becoming a major source of emboli and thus CRAO (11).

The carotid artery disease can cause CRAO by two mechanisms. By embolism, which is with 61% (16) the most common cause of CRAO and by hemodynamic disturbance (i.e., poor arterial perfusion). This means significant stenosis or a complete obstruction of the internal carotid artery, as well as dissection. This can lead to severely reduced ocular blood flow and thus to the development of CRAO (11).
The EAGLE study showed a stenosis of the internal carotid artery in 40% of cases of CRAO. Of this cohort, only 3% had been previously diagnosed with significant carotid stenosis (15).
Other Studies performed on atherosclerotic monkeys showed that serotonin, a potent vasoconstrictor, is released by thrombocyte aggregation on atherosclerotic plaques in the carotid artery, which might lead to the development of transient spasms. This again can cause the temporary complete occlusion or at least partial obstruction of the central retinal artery's blood flow (17).

The link between diabetes and arterial hypertension with CRAO was described in many studies. Around 19% of CRAO patients simultaneously suffer from diabetes (18). Some even see evidence for a causal relationship between type 2 diabetes and CRAO (19).

Different cardiac conditions can cause CRAO due to emboli. The most common loci of emboli in CRAO are the narrowest part of the central retinal artery, where it emerges into the dural sheath of the optic nerve. Further, there are reports on CRAO events after cardiovascular procedures (11).

Controversial reports are indicating a role of thrombophilia in the development of CRAO. In rare instances, CRAO was linked with haematological disorders such as sickle cell hemoglobinopathies, leukaemia, systemic non-Hodgkin’s lymphoma, and orbital lymphoma. CRAO following haemodialysis is also well documented, since it often comes with a drop in blood pressure. Beyond that, patients usually suffer from pronounced vasculopathy (11).

CRAO has also occurred following surgical interventions of different kinds. For example, after orbital, eye, or head trauma, facial injections, retrobulbar injections, peribulbar anaesthesia, and intraocular gas injection, used as a tamponade in the treatment of rhegmatogenous retinal detachment (10).

Amaurosis Fugax is also found to be an important predictive factor for CRAO. In a study by Hayreh and Zimmerman, a history of amaurosis fugax before the development of CRAO was found in 12% of

non-arteritic CRAO, in 20% of non-arteritic CRAO with cilioretinal artery sparing, in 9% of arteritic CRAO, and 13% of transient CRAO, making it an important risk factor for history taking (9).

Various other disorders are seen to be predispositions of CRAO, including Fabry's disease, oral contraceptive, cocaine consumption, snake bite, migraine, Marfan's syndrome, nephrotic syndrome, incontintia pigmenti, and many more have been described along with CRAO (11).

4 Diagnostic Workup

4.1 Imaging Modalities

For a neurological management of CRAO in stroke units, a neurological or a neuroradiological diagnosis of CRAO is needed. Even though it is unclear whether a neurologist could replace an ophthalmologist in case of CRAO, we know two things for certain. First is that retinal tissue in the majority of cases does not resist ischemia for more than 4.5 hours (12). Thus, a rapid management strategy is important. Second is that most European hospitals (in Germany, 57.45% (6)) are not able to provide an emergency ophthalmologist or ophthalmologic equipment, and certainly do not have the finances to change that soon. Thus, stroke units and their neurologists and neuroradiologists must be able to diagnose CRAO in the existing infrastructure by themselves.
It must be operable by neurologists or neuroradiologists, with, if at all, the simplest possible training. It must be able to diagnose CRAO events within a short time frame with a high sensitivity and specificity, while possibly diagnosing differential diagnoses. And finally, it must be economically viable, and preferably already be found in most emergency centres.
Therefore, there are limited diagnostic techniques that match the criteria for neurological management of CRAO.

Currently, the established diagnostic techniques are focused on an ophthalmologic approach. These include fluorescein angiography, fundus autofluorescence, optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), and electroretinography (20). However, it is hard to imagine that those can be included in stroke units. Additionally, all these require years of ophthalmological training and experience, until they can be used confidently, and their effectiveness is debatable. Fluorescein angiography, for example, the gold standard for diagnosing CRAO, is a time-consuming examination that takes around 20 minutes. Beyond that, a recent study by Abdellah et al.

showed normal fluorescein angiography in 26.67% of CRAO cases, which questions fluorescein as a legitimate CRAO diagnostic standard (21).

When investigating the offer of literature covering diagnostic methods for CRAO, which do not require an ophthalmologist, another challenge for the neurological management of CRAO becomes clear. That is, how to diagnose CRAO in stroke units without an ophthalmologist on site. No wonder that in a survey among emergency-medicine physicians, only 28.9% felt comfortable diagnosing CRAO (22). Concluding my review of the current literature, three imaging modalities met at least partially the criteria and have at least the potential to allow the neurological and neuroradiological workup in stroke units. OCT, POCUS, and DW-MRI. However, none of the imaging modalities bypasses the essentialness of a well-functioning interdisciplinary teamwork to achieve the best outcome.

4.1.1 Optical Coherence Tomography (OCT)

OCT provides a detailed assessment of the retinal microvasculature, while having the advantage compared to other imaging modalities, to detect retinal changes earlier, making it a useful tool for early CRAO diagnosis. It further provides a sensitivity of 100% and a specificity of 94.3% (23). OCT can categorize CRAO as mild, moderate, and severe occlusions. There are specific OCT diagnostic criteria for acute CRAO. These include a hyperreflectivity of the inner retinal layer and shadowing of the outer retinal layer. In chronic CRAO however, retinal thickness is again reduced while stratification is maintained (20).

The possibility of detecting the time of ischemic onset is another advantage that OCT provides. With an unknown time of ischemia onset, patients might not meet the criteria for an effective thrombolytic treatment. Further, after a certain time of ischemia persistence, the risks of thrombolytic treatment might outweigh the unpredictable benefits. A German study revealed the potential of OCT-based retinal thickness analysis as a tool to determine ischaemic onset in CRAO patients. This would allow to asses intravenous thrombolysis (IVT) eligibility even in patients with unknown time of ischemic onset (23).

However, to evaluate the images provided by OCT or OCTA machines, an ophthalmologist is still required. Literature shows two recent creative approaches to potentially solve this problem. The first is a remote ophthalmologic consult. Therefore, a hospital provider placed OCT machines in the stroke

centres of three hospitals. Patients who were suspected of CRAO were evaluated by the stroke neurology service, and OCT was performed. The images were then interpreted remotely by an ophthalmologic professional. Thus, an ophthalmology consult was not required to be present in order to make the final decisions on CRAO diagnostics and treatment (24).

4.1.2 Point of Care Ultrasound, POCUS

POCUS is progressively emerging as a possible solution. Even compared to OCT, it excels by not requiring radiation and further does not require contrast material or sedation. It is economical, in most hospitals already pre-existing, and provides instant hemodynamic data. Several studies confirm Neuro-POCUS to reliably detect CRAO and to differentiate between arteritic and non-arteritic origin (25,26). Thus, Neuro-POCUS is a rapid and efficient method to examine patients with a suspected acute stroke or for stroke prevention. It allows distinction among possible CRAO aetiologies and to detect accompanying diseases. Among which are carotid artery stenosis, carotid artery dissection, or atrial fibrillation. If negative for CRAO, it is possible to search for differential diagnoses, such as anterior ischemic optic neuropathy, retinal detachment, and massive vitreous haemorrhage. Furthermore, it can be used to monitor arterial recanalization during systemic thrombolysis as well as the spontaneous course of the disease (27,28).

Additionally, POCUS brings the advantage of rapid diagnosis in patients where transportation possibilities are limited, due to infections, ongoing interventions, or unstable patient conditions. Neuro-Pocus can answer evolving clinical questions immediately without any delay and dependency on a functioning departmental interplay, while having the advantage of using economically viable devices that are usually preexisting in even rural hospitals. The probes needed are quickly changeable according to the situation's needs. For the ultrasound examination of the eye, colour-coded sonography is recommended. The mechanical index of the high-frequency transducer should be minimized to o ≤ 0.23 and thermal index ≤ 1 (27).

With the proper usage of the Doppler function and B-mode, a hyperechoic structure within the occluded artery, what is known as the spot sign, can be found, minimizing the probability of an atheromatous aetiology. It describes the detection of hyperechogenic material near the end of the optic nerve in orbital ultrasound, indicating a lodged calcified or crystalized cholesterol embolus in the central retinal artery behind the lamina cribrosa and thus serving as a helpful indicator in CRAO-diagnostics. Even though the spot sign eases CRAO-diagnostics by being detected in 31-83% of cases,

they seem to correlate with a worse visual outcome and a less likely but not excluded probability of recanalization (27). An image of a CRAO with positive spot sign ultrasound is provided in Fig. 2.

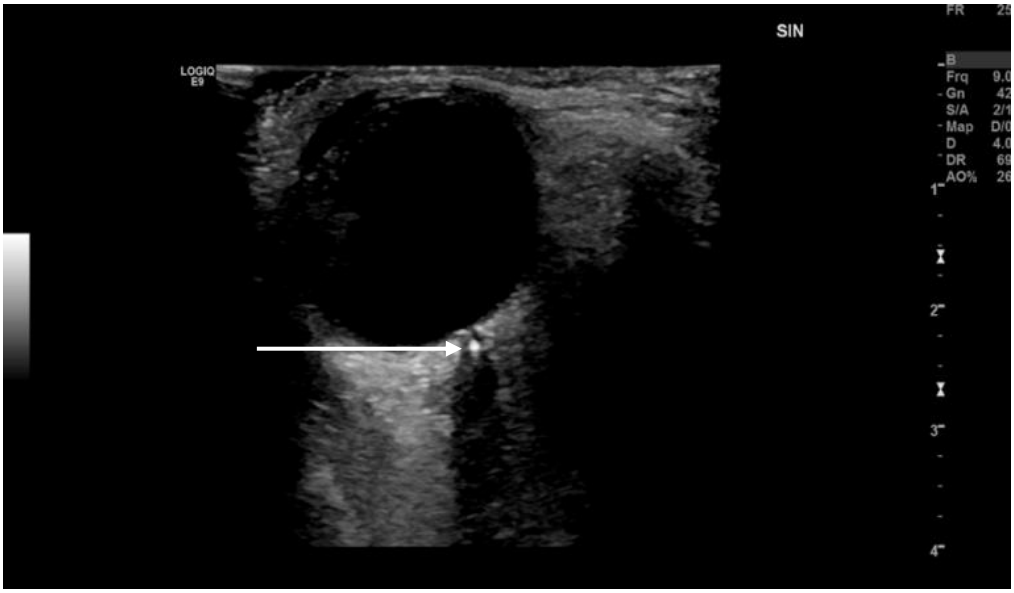

Figure 2: CRAO with Positive Spot Sign on Transorbital Ultrasound

Transorbital ultrasound: the left eye CRAO with positive spot sign in the optic nerve head of the central retinal artery (long arrow). (Image from the personal archive of Jurgita Valaikiene, with permission.)

For further examination of CRAO patients and possible underlying causes and accompanying diseases a medium-frequency (5–12 MHz; optimally 3–15MHz) linear array probe for cervical vessel examination is recommended, as well as a low-frequency (2.5 MHz; optimally broad-band 1–5MHz) phased array for intracranial arteries and parenchymal structures, and a 2-MHz monitoring probe for continuous monitoring of micro-embolic signals and information on cerebral hemodynamics. Additionally, sensitivity and specificity can be enhanced by using an ultrasound echo contrast agent (27). A clinical example of the utility of POCUS in emergency hospital settings is described in Figs. 3 and 4.

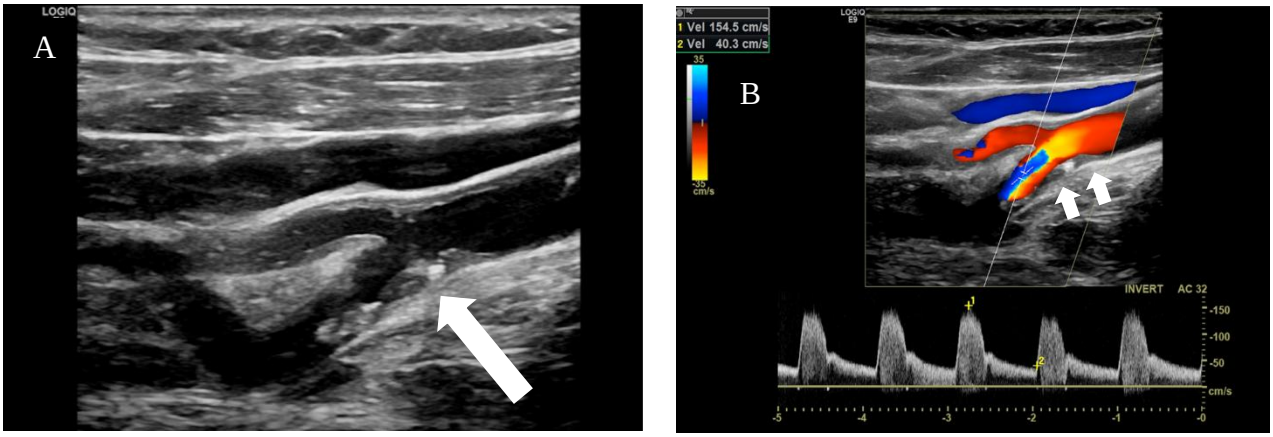

Figure 3: Extracranial Sonography of the Internal Carotid Artery.
Extracranial color-coded duplex sonography: ipsilateral symptomatic moderate grade ICA stenosis with heterogenous atherosclerotic plaques (arrow) in B-mode (A) and elevated velocities in C-mode and PW-mode (arrows), corresponding to 50-69% stenosis according to the NASCET criteria (B). (Images from the personal archive of Jurgita Valaikiene, with permission.)

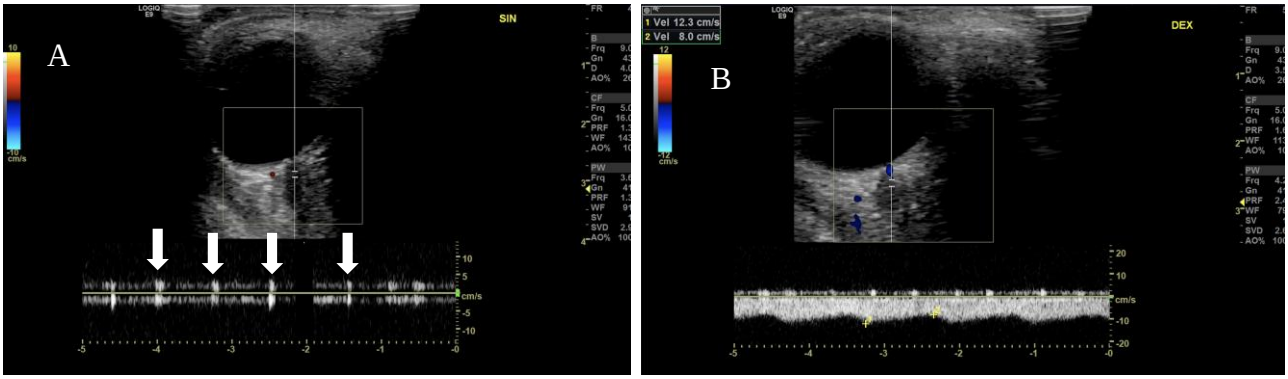

Figure 4: Transorbital color-coded duplex sonography of bilateral CRAOs, confirmed by an ophthalmologist.
A, Left eye CRAO without hyperechoic retrobulbar signal in the optic nerve in a patient with acute painless blindness 3 days ago: the occlusion signals in the central retinal artery (arrows) and the venous flow were registered. B, the right eye CRAO, which was diagnosed 6 months ago: no spot sign in the optical nerve head and no flow in the central retinal artery were detected, and only the venous flow was registered. Additionally, secondary glaucoma of the right eye was diagnosed. Cervical ultrasound showed nonsignificant atherosclerosis of both carotid arteries. Arterial hypertension and dyslipidaemia were diagnosed. No heart rhythm disorders were detected. Optimization of medical treatment was applied, including secondary stroke prevention with antiplatelets.
(Images from the personal archive of Jurgita Valaikiene, with permission.)

Even though literature shows the great potential of POCUS in CRAO diagnostics, almost half of neurologists describe their practical POCUS skills to be poor (18.9%) or very poor (30.9%) (29), while

neuro-POCUS needs skilled practitioners. Considering the lack of literature on large cohort studies on the topic of POCUS usage in CRAO diagnostics, I see POCUS in this context only at the beginning of its potential role in the diagnostic management of CRAO. Virtually all the provided literature on Neurosonology in CRAO diagnostics concludes that more research is needed.

4.1.3 Fundoscopy

A dilated fundoscopic examination, if applied correctly, can reveal CRAO typical findings such as retinal oedema, which becomes apparent as a retinal whitening, slow segmental blood flow in the attenuated retinal arteries, and usually normal-appearing optic disc, as well as a cherry red spot. This cherry red spot mostly appears after several hours of ischemia and usually persists for several days after CRAO (30). One study found the spot sign to be present in 90 % of CRAO (31) eyes, another study found them to be present in 66.7% of CRAO eyes (32). The difference in occurrence might be explained by the different time of presentation after symptom onset, as well as the sparing of the cilioretinal artery. However, no literature can be found on the incidence of the spot sign within the 4.5-hour time frame, in which CRAO needs to be diagnosed and treated.

Fan et al. found reasons for the spot sign to be absent to be leopard print fundus (32.26%), coexistence of retinal vein occlusion (25.81%), inner retinal coagulative necrosis not to be obvious (19.35%), cilioretinal artery sparing (12.9%), and macular oedema (9.68%) (30).

Even though the cherry red spot eases CRAO-diagnostics, they seem to correlate with a worse visual outcome. The absence of the spot sign challenges the diagnostic workup of CRAO by fundoscopy, and the spot sign is not unique to CRAO. It can occur in other diseases leading to retinal ischemia and infarction, as well as the accumulation of different substances in retinal ganglion cells (30). Furthermore, fundoscopic examinations are time-consuming and require ophthalmological expertise, usually not found in stroke units.

4.1.4 Diffusion Weighted Magnetic Resonance Imaging

A retrospective cross-sectional study by Lange et al. was performed to investigate DW-MRI results in early CRAO in 68 Patients within 24 hours after the onset of visual impairment by two blinded neurologists. The detection rate within the first 12 hours was found to be significantly lower (39.3% vs 79.5%) when compared to the detection rate between 12 and 24 hours after symptom onset. Overall RDR detection rates ranged from 52.8% to 62.5%, with false positive rates in 4.2%–8.3% of cases. Also, the share for false positive ratings was highest within the first 6 hours (33).

However, in addition to acute non-arteritic CRAO, up to 30% of patients with acute non-arteritic CRAO show cerebral ischemia within 7 days following CRAO diagnosis (34). Therefore, MRI can detect simultaneously manifesting cerebral ischemia, even if no clinical neurological symptoms are present. Further, MRI can be more exact in the detection of vascular occlusive diseases. Consequently, MRI is usually performed in patients with a sudden loss of vision regardless of a suspicion for CRAO diagnosis. Since MRI is done in these patients anyway, it would be an efficient and time-saving diagnostic approach for CRAO diagnosis. However, more research is needed on the time frame in which DW-MRI restrictions occur in CRAO, as well as on its sensitivity. Furthermore, for clear imaging, a stable eye position without movements is needed, which is hard to perform, especially in emergency settings on usually older patients.

The likelihood of detection of retinal ischemia by DW-MRI most probably goes along with the extent of retinal cell oedema, which develops progressively after interruption of the blood flow. Siebert et al. suggested that a mild retinal oedema in CRAO may not be enough to produce a detectable sign in DW-MRI. Since IVT is a highly time-dependent therapeutic option, it is important to determine the time of CRAO onset (35).
Wenzel et al. found the retinal thickness to increase in a near-linear increase within the first 5 hours, followed by a plateauing of oedema progression 10-20 hours after CRAO onset (23).
Thus, if DW-MRI is not suitable for acute CRAO detection, it might be suitable for determining the time of CRAO onset in patients reporting CRAO symptoms at wake-up. Theoretically, DW- MRI with an absence of restricted retinal diffusion might exclude advanced retinal infarction and thus, spare non-intravenous-thrombolysis-suitable patients from unnecessary risks.

4.2 Further Investigations

Giant cell arteritis needs to be ruled out in patients 50 years and older to prevent and limit the risk of other visual problems or stroke. Therefore, all these patients should undergo an evaluation of erythrocyte sedimentation rate and C-reactive protein (CRP) levels.
With embolism being the most frequent aetiology of CRAO, all CRAO patients should undergo investigations to find the embolic source. Plaques are the most common cause of emboli in the carotid artery. The absence of hemodynamically significant carotid artery stenosis should not distract from

paying attention to the presence of plaques, which can be missed as the actual source of emboli. Furthermore, even if carotid artery lesions are detected, cardiac evaluation is important, since lesions can be present in both places, making both loci as possible embolic sources. Therefore, transoesophageal echocardiography is a reliable diagnostic tool.
For the evaluation of atherosclerosis, as a common cause of carotid artery lesions, lipid evaluation, including both cholesterol levels and low-density lipoproteins, should be performed.
Finally, rare aetiologies, as discussed in more detail above, should always be kept in mind for further investigations (11).

4.3 Differential Diagnosis

Typically, CRAO manifests as a sudden, painless, monocular loss of vision. Central vision can be preserved if cilioretinal artery sparing is present. Therefore, it is recommended to identify atherosclerotic risk factors, as mentioned above. If no atherosclerotic risk factors are present, a variety of differential diagnoses must be considered. These include mostly ophthalmologic diagnoses such as acute-angle-closure glaucoma, anterior ischemic optic neuropathy, globe rupture, retinal detachment, retinal vein occlusion, and vitreous haemorrhage, to name some of the most significant. Since many syndromes can be accompanied by loss of vision, a thorough differentiation of other causes is essential. CRAO can, for example, also be caused by vasospasm of the ophthalmic artery. In this case, however, the CRAO specifying a cherry red spot will be missed during fundoscopy (10).
An acute angle-closure glaucoma can also lead to temporary vision dysfunction. However, it is typically associated with pain and redness of the eye. Orbital tumours, which create pressure on the optic nerve, should also be mentioned, causing loss of vision, however, only occuring when looking in certain directions (10).
Furthermore, the course and the development of the vision disturbance give important hints on its causes. Patients with optic neuropathy can experience a sudden loss of vision that does not persist and does not vary in intensity. A unilateral optic neuropathy can be detected by its relatively afferent pupillary defect. Accompanying swelling or haemorrhage of the optic disc can indicate a non-arteritic ischemic optic neuropathy, giant cell arteritis, or other inflammatory disorders. If, however, a neuropathy without any changes on the optic disc is present, an optic neuritis, neuromyelitis optica, or Leber hereditary optic neuropathy should be considered (10).

Furthermore, leukemic infiltrates in the optic nerve head area can cause CRAO and lead to cherry red spots as well as macular infarction following trauma, retinal vascular occlusion, lupus erythematosus, and sickle cell anaemia, which can lead to similar appearances (10).

Table 1.

Overview of additional Diagnostic Methods after CRAO Diagnosis

Investigation	Rationale
Carotid doppler	Ruling out ipsilateral carotid artery stenosis
Echocardiography	To diagnose valvular heart disease and vegetation of cardiac valves, which act as an embolic source
Complete blood count with peripheral blood smear	To detect blood dyscrasias and hyperviscosity
Erythrocyte sedimentation rate and CRP	To detect temporal giant cell arteritis
Coagulation profile	Ruling out coagulopathies
Glucose levels and lipid profile	Ruling out atherosclerotic diseases
Blood cultures	Ruling out bacterial endocarditis or septic embolus
Serum homocysteine levels	Ruling out hypercoagulable states
Vasculitis profile	Ruling out hypercoagulable states
Serum protein electrophoresis, prothrombin time/activated partial thromboplastin time, antiphospholipid antibodies, fibrinogen, homocysteine levels, prothrombin mutation, factor V Leiden,	Ruling out Coagulopathies
Cranial and cervical MRI angiography or CT angiography	Ruling out vascular occlusive disease

The author re-created the table using information from (20).

5 Treatment

Various treatment methods have been tested with different rates of success. While the state of research quite homogenously agrees on the treatment of arteritic CRAO, the treatment of non-arteritic CRAO is still at the centre of debate in medical research. Even though it has been studied since the 1960s, only 5.8% of patients affected by CRAO receive IVT (36). The lack of clear CRAO-treatment guidelines certainly originates from the lack of randomized controlled trials. The overview of recent studies done

on this issue, however, indicates that lysis of non-arteritic central retinal artery must have a certain therapeutic effect, while it is again unclear in what time frame. This time frame ranges from 12 minutes (7) to 4.5 hours (12) in different studies. Thus, the aspect of treatment of non-arteritic CRAO must be marked with a question mark.
The interplay between the timely window and treatment methods is currently investigated in major European studies, with results expected in early 2026. Promising trials on IVT in CRAO are REVISION (Early Reperfusion Therapy With Intravenous Alteplase for Recovery of VISION in Acute Central Retinal Artery Occlusion), as well as THEIA (THrombolysis (Alteplase) in Patients With acutE Central retInal Artery Occlusion) and TenCRAOS (TENecteplase in Central Retinal Artery Occlusion Study).

5.1 Therapeutic Approach to Arteritic Central Retinal Artery Occlusion:

CRAO that is caused by giant cell arteritis requires immediate and specific treatment as a distinct clinical entity. The goals of the therapy should be the resolution of giant cell arteritis symptoms, the prevention of further loss of vision in the affected eye, as well as the prevention of loss of vision in the spared eye. The risk of bilateral vision loss with delay or stoppage of therapy is found to be within 20-50%. Therefore, in all patients with suspected giant cell arteritis, glucocorticoids should be administered in high doses (80-120 mg per day of oral prednisone). Even though not established as standard care, one can consider a three-day course of IV pulse methylprednisolone (500-1000 mg daily) followed by high-dose prednisolone (37).
The British Society of Rheumatology recommends simultaneous therapy with 75 mg of oral aspirin daily. Within 14 days, a temporal artery biopsy should be performed, without delay of steroid initiation. Individuals with positive temporal artery biopsy should receive a high dose of prednisone for at least four weeks or until the resolution of symptoms and laboratory abnormalities, followed by a gradual tapering over 6-24 months. However, no guideline for tapering these patients can be found (38).
Patients who present with high laboratory and clinical suspicion for giant cell arteritis should be treated as suspected giant cell arteritis, regardless of their biopsy results, as temporal artery biopsy can be negative due to a short biopsy specimen or the presence of skip lesions. Furthermore, temporal artery ultrasound and the evaluation of the “halo sign” may replace a biopsy in patients with a high clinical suspicion for giant cell arteritis who are not surgical candidates. On the other hand, patients with low suspicion for giant cell arteritis and negative biopsy results should be tapered off steroidal treatment

within fourteen days and treated for alternative causes of vision loss. Patients who suffer from a relapse of eye symptoms should be reinitiated on full-dose steroidal therapy. In contrast, patients who suffer from a relapse of headache during their tapering period should be returned to the previous step-off dosing (37).

5.2 Intravenous Thrombolysis in Non-Arteritic Central Retinal Artery Occlusion

IVT within less than 4.5 hours following symptom onset is considered to be the gold standard of acute ischemic cerebral strokes. Since CRAO can be viewed as a subtype of ischemic stroke, one would assume similar guidelines. However, no guidelines exist for IVT in the case of CRAO.

The efficacy of IVT on non-arteritic CRAO patients remains a topic of scientific debate. Even though a lot of studies have been done on this issue, none can provide the outlines to give scientific proof for the efficacy and safety. REVISION, THEIA, and Tencraos will hopefully answer the question on whether IVT is effective on non-arteritic CRAO or not, whether safely applicable or not, and in what timeframe after CRAO onset. Until then, the medical community needs to draw on the so far provided studies, of which I will present, which I consider to be the most relevant within the last decade.

In 2020, Grory et al. published a cohort study including 112 patients, who were presented within 48 hours after symptom onset and with visual acuity of less than 20/200. Of those patients, 25 received IVT, while 44% of this group showed an improvement in vision. Side effects were rare, since only one patient developed an asymptomatic intracerebral haemorrhage. The authors completed their study with an updated meta-analysis of 238 patients. Of these, 67 received IVT within 4.5 hours, while 37.3% experienced visual acuity improvement (39).

In 2022, Schönecker et al. published a pilot study about the efficacy and safety of IVT on patients with retinal infarction. In total, 38 patients were included, of which 19 had CRAO, six had branch retinal artery occlusion, and 13 had transient vision loss. Of the 19 CRAO patients, nine were treated with IVT. In comparison to the patients treated with standard of care, the IVT group showed a significant improvement in the modified ranking scale from the time of patient presentation to patient release. One patient treated with IVT suffered a symptomatic intracerebral haemorrhage (40).

In a retrospective observational study by Raber et al. from 2023, 37 CRAO patients were examined who either received IVT within 4.5 hours or who underwent conservative therapy. The IVT group included 16 patients, and the conservative therapy group 21 patients. In the IVT group, patients received the standard stroke protocol dosage of alteplase. Additionally, alternative therapies were

administered, such as bulbar massage (IVT group 29% vs. conservative group 57%) and intraocular pressure-lowering medications (IVT group 40% vs. conservative group 70%). Of the 16 IVT-patients, three (19%) showed visual improvement. One patient's blindness improved to severe visual impairment, and two patients' blindnesses improved to regaining the ability to read. In the conservative group, no patient showed an improvement in vision (41).

A prospective observational cohort study performed by Bustamante et al. f rom 2018 to 2023, the activation criteria were sudden, painless monocular loss of vision within 6 hours after symptom onset. Criteria-meeting patients underwent IVT within 4.5 hours after symptom onset or IAT within 6 hours after symptom onset. All patients were examined by an ophthalmologist to determine their best-corrected visual acuity. Visual amelioration was defined as improved if gaining one letter in the early treatment diabetic retinopathy study scale from baseline to one week. Of 49 CRAO patients, 12 received IVT and 3 intraarterial thrombolysis (IAT). Results showed better rates of visual amelioration (33% vs 5.9%) without any thrombolysis-related complications (42).

What combines those studies is, first, the lack of randomised controlled trials and the heterogeneity of study designs, outcome measurements, and treatment arms, as well as the low sample sizes. Second, the conclusion is that there is a need for more research on this topic with larger randomised controlled trials. However, all the studies indicate a tendency, even though to a different degree, of improved CRAO outcomes. Even though the time window, rate of improved outcomes, as well as the benefit-to-risk ratio, remain unclear, IVT is currently seen as the most promising emergency therapy for non-arteritic CRAO in stroke units. Despite its potentially best outcomes among potential non-arteritic CRAO therapies, it also brings the advantage that every stroke unit already brings the know-how, infrastructure, and technology for thrombolysis performances, given the fact that it has been used for decades for the treatment of cerebral ischemic strokes.

5.3 Intraarterial Thrombolysis in Non-Arteritic Central Retinal Artery Occlusion

The direct application of tPA into the ophthalmic circulation through superselective microcatheterisation of the ophthalmic artery ostium theoretically brings the advantage of thrombolytic therapy being applied directly at the site of the thrombus, reducing the risk of intracranial and systemic bleeding.

Since the amount of tPA that reaches the systemic circulation is far smaller, this method could be taken

into consideration for patients who, because of systemic contraindications, are not suitable for IVT, for example, after an operation, gastrointestinal bleeding or coagulopathy.
However, this reduction of systemic complications brings other risks, for example, arterial dissection, a catheter-induced spasm, or the distal embolization due to the possible dislodgement of atheromatous plaque in the ophthalmic circulation.
Since the eligible vessels are very small (the ophthalmic artery, for example, has a diameter of only 1.3 mm, the central retinal artery 160 µm), a mechanical removal of the thrombus is not possible with today's technology (43).
In the last 20 years, multiple retrospective studies have investigated this method of treatment. Many of which indicate that IAT could lead to an improvement in vision. However, the only prospective randomised controlled study – the EAGLE study- including patients up to 24 hours after onset of symptoms, was terminated early because IAT did not exceed the results of conservative treatment of CRAO patients. However, the patients who received intra-arterial fibrinolysis had a substantially higher incidence of adverse outcomes, compared to the patients receiving standard medical care (37% compared to 4.3%). On average, patients presented 13 hours after symptom onset. No patient was treated within 4.5 hours, and only 4 out of the included 41 patients received therapy within 6 hours. Thus, there has not been a randomised controlled study about IAT within the 4.5-hour time window on CRAO patients (44).
Even though the concept seems promising, there are multiple technological and logistical issues emerging. Those include the necessity of supplying an endovascular interventional team and a catheterisation laboratory. Furthermore, IAT differs from endovascular thrombectomy of a cerebral stroke, since canulisation of the lesser ophthalmic artery is necessary. The favoured technique of superselective microcatheterisation of the ophthalmic artery includes the placement of a small microcatheter (0.6 nm) into the ostium of the artery. Even though a further catheterisation of the ophthalmic artery is technically possible, it is not recommended due to the risk of arterial dissection and thromboembolic events. The proximal catheterisation of the ophthalmic artery is often performed in intraarterial chemotherapy administration in case of retinoblastoma. However, it becomes more challenging with atherosclerotic patients, to whom most non-arteritic CRAO patients belong (43).
The literature asks for more research to be done on the field of intra-arterial thrombolysis in CRAO.

5.4 Conservative Treatment Approaches on Non-Arteritic Central Retinal Artery Occlusion

There are several conservative treatment approaches for non-arteritic CRAO that are currently applied in some stroke centres. I will present the most prominent ones in more detail. Less commonly applied approaches are listed in Table 1.

5.4.1 Ocular Massage

More experimental therapeutic approaches include Immediate ocular massage, by applying pressure on the orbital bulb, attempting to resolve the thrombus. It attempts to cause fluctuations in the intraocular pressure in order to resolve the embolus. The embolus then can either resolve or migrate into a peripheral part of the retinal perfusion system, in the best case, causing reperfusion. The technique is described as repeated pressure on the ocular bulbus followed by a quick release for 3-10 minutes. However, all studies suggesting this conservative therapy do so as an addition to other therapies (45).

5.4.2 Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) uses the increased oxygen content to diffuse more effectively into the retina from the choroidal circulation. This technically allows the inner retina, which in the case of CRAO does not receive its oxygenation supply through the central retinal artery, to receive enough oxygen through the choroidal vasculature and any remaining retinal artery perfusion. This would ensure the retinas survive until the central retinal artery recanalizes. However, this concept is only applicable as long as the retinal ischemia is still reversible (46).

A retrospective cohort study conducted on 41 CRAO patients in a time frame of 12 years investigated the visual acuity outcome after HBOT. Patients who received HBOT within nine hours after symptom onset regained better visual acuity with a median gain of 5.90 lines compared to 0.00 lines in patients who received HBOT after nine hours. It is also worth noting that patients who received more than five HBOT sessions reported better improvement of visual acuity than those with fewer than five. The study concluded HBOT to be a relatively safe therapy, with only one patient suffering barotrauma (47).

5.4.3 Other Available Treatment Methods

Other available methods of treatment and their mechanism of action for managing acute CRAO are presented in Table 2.

Table 2.

Additional available treatment methods

Treatment	Putative mechanism of action
Anterior chamber paracentesis	Lowering IOP/Increasing retinal artery perfusion
Intravenous, oral, and topical intraocular pressure-lowering agents	Lowering IOP/Increasing retinal artery perfusion
Pentoxifylline	Vasodilation
Carbogen inhalation therapy	Vasodilation
Sublingual isosorbide dinitrate	Vasodilation
Enhanced external counterpulsation	Vasodilation
Neodymium: Yttrium-aluminium garnet laser embolysis	Dislodging the embolus

Other available treatment methods and their mechanism of action for managing acute CRAO. The author created the table using information from (45).

Abbreviations: IOP, intraocular pressure.

6 Visual Outcome

The loss of vision is the centre of the discussion around CRAO. For the patient, the visual outcome is the most important question. For the medical field, the more interesting question is how the visual outcome after therapy differs from the natural history of this disease. Considering that, it requires a detailed discussion of various aspects of the visual function in CRAO.

6.1 Initial Visual Acuity

The research of Hayreh et al. delivers data on the initial visual acuity as a starting point. At the beginning of his study, the visual acuity in non-arteritic CRAO was in seven percent of cases to be at 20/200-20/400, while limited to counting fingers or worse in 93%. In case of transient non-arteritic CRAO, it depended on the duration of CRAO, while in non-arteritic CRAO with cilioretinal artery sparing, it depended on patient-specific cilioretinal perfusion. In both cases, visual acuity was varying between 20/40 or better and counting fingers. In case of arteritic CRAO, it was found to be within 20/200 and finger counting or worse (11).

6.2 Initial Visual Field Defects

However, the visual acuity only represents the function of the foveal region and not the remaining retina. More conclusive information about the function of the entire retina is provided by visual fields. CRAO finally affects the entire retina, not only the fovea.
Hayreh's study investigated the visual fields of 145 eyes with CRAO and thus provides valuable information on the visual function in CRAO patients.
Initially, in 48% of non-arteritic CRAO patients, 22% of cilioretinal sparing non-arteritic CRAO patients and 4% of transient non-arteritic CRAO patients, complete loss of the central 30° visual field occurred, causing central scotoma. 22% of non-arteritic CRAO patients and 63% of transient CRAO patients were initially normal (11).

6.3 Visual Acuity Improvement

In eyes that were examined within seven days and with visual acuity of counting fingers, the visual acuity improved by 22% in non-arteritic CRAO patients, 67% in cilioretinal sparing non-arteritic CRAO patients, and 82% in transient non-arteritic CRAO patients. In arteritic CRAO, no improvement was found (11).

6.4 Visual Field Improvement

The central visual field improved in 39.9% of patients with transient non-arteritic CRAO, 25% of patients with cilioretinal artery sparing non-arteritic CRAO, and 21% of patients with non-arteritic

CRAO, while the peripheral visual field improved in 39% of patients with non-arteritic CRAO, 39% of patients with transient non-arteritic CRAO, and 25% of patients with cilioretinal artery sparing non-arteritic CRAO (11).

In a retrospective study, which was published in Neurology in 2023 by Kang et al., the aetiology of CRAO was classified after symptom onset as either embolic or non-embolic origin. It showed that the presence of an embolic source was unrelated to a clinically significant visual improvement after one month, after covariates, including CRAO-subtypes, had been modified.

Factors that went along with visual improvement following CRAO included incomplete CRAO, the time of retinal artery occlusion, the residual circulation, the site of occlusion, as well as the cilioretinal artery sparing. Interestingly, the presence of an embolic source as well as an incomplete CRAO both independently were an indicator for visual improvement.

A possible explanation is an embolus that occludes an intact vessel, which likely dissolves. Cardio emboli are known for their ability to easily and spontaneously dissolve. Additionally, the distal flow can remain, since the emboli possibly do not fit tightly in the intact artery. Also, Emboli were more frequent in CRAO with an embolic source. This indicates that these emboli possibly were part of an embolus of the central retinal artery, which migrated distally, after the proximal vessel was recanalized, or that they belonged to multiple micro-emboli that occluded the vessel from the beginning. Second, the localisations of the thrombus and embolism are different, which is why collaterals might work differently. Hayreh and Zimmerman suggested that emboli were most likely localised in the dural sheath, the narrowest part of the central retinal artery, while thrombi typically occlude the lamina cribrosa. The first could cause less retinal damage, because more collateral vessels would still be intact (12).

Third, mechanisms that are not originating from emboli could indicate a vasculopathy that affects longer than the retinal survival time. An in-situ vasculitis and thrombosis typically lead to additional thrombogenesis and inflammation in the neighbouring vessels and tissues. Giant cell arteritis, for example, the most common aetiology of arteritic CRAO, is often associated with an anterior ischemic optic neuropathy, which worsens the visual outcomes.

In the study, a significant part (40.4%) showed visual improvement. A worse initial visual acuity was associated with a stronger visual improvement, possibly because of the natural history of acute CRAO. Another study showed that only 8.3% of eyes with initially well visual acuity showed an improvement, compared to 38.4% of eyes with initially worse visual acuity. This implies that a worse initial visual acuity has a greater potential for the rescue of the penumbra by early reperfusion, since the retinal

reperfusion is a precondition for visual improvement. CRAO with an embolic source is more likely to be recanalized than CRAO without an embolic source.
Even though an artery-to-artery embolism or cardioembolic is the most frequent source of CRAO, the aetiology remains unknown in 38%-50% of cases, which is significantly higher than the embolic strokes without known aetiology. This discrepancy could be because of different pathological mechanisms compared to ischemic stroke, including factors such as vasculopathy, clot composition, fragmentation, and migration (48). Small emboli from potentially minor embolic sources, which rarely cause cerebral stroke, as a low left ventricular ejection fraction, calcific aortic valve, or no stenotic carotid atherosclerosis, could also lead to CRAO (48).

7 Central Retinal Artery Occlusion as Precursor of Neovascular Glaucoma and Ischemic Cerebral Stroke

7.1 Neovascular Glaucoma

A causative relation between CRAO and neovascular complications is still a topic of debate. It is believed that retinal tissue after infarct, such as after CRAO, can no longer produce vascular endothelial growth factor, and thus, the development of post-CRAO neovascular glaucoma must always be secondary to chronic ischemic disorders (49).
Hayreh et al. investigated the natural history of 64 eyes with CRAO and found that 11 cases were caused by severe carotid artery stenosis. The authors concluded that there was no link between CRAO and neovascular complications (50).
However, ever since, many reports have been published that indicate signs of ocular neovascularisation, without a chronic ocular ischemic syndrome present.
Deoumois et al. are reporting five cases of neovascular glaucoma following CRAO, in cases in which both the carotid artery and the ophthalmic artery were non-pathological. A major retrospective study on 214 CRAO-eyes showed an incidence of 10.9% iris neovascularisations, while around half of these, the carotid artery was found to be normal. Beyond that, the authors found a significant difference in reperfusion rate and prevalence of diabetes in the group with iris neovascularisation (51).
Hayreh states that even in the case of complete occlusion of the central retinal artery, there still is a certain degree of slower retinal perfusion detectable on fluorescein angiography. This remaining degree of retinal circulation, which might be caused by collateral circulation, cilio-retinal capillary

anastomoses as well as pial and intraneural anastomosis, continues to supply a certain number of retinal cells, and thus protects them from infarction. This would lead to a hypoxic state of the cells, which then would begin to release vascular endothelial factor (52).
The hope for further insights lies in the REVISION trial, which, next to the possible benefits of lysis therapy, also investigates the development of neovascular complications following thrombolysis (53).
Even though there are comprehensive retrospective analyses and prospective studies on the course of CRAO and the development of possible complications, such as ocular neovascularisation, the impact of thrombolysis therapy on the further course of the disease is barely investigated.
In this context, a retrospective analysis of the medical records of six consecutive patients who had undergone intra-arterial thrombolysis after CRAO describes the development of neovascular glaucoma in four of them, four to seven weeks after treatment. In this context, the authors mention six cases of CRAO, which were treated with intra-arterial thrombolysis. Four of them developed an early-onset, aggressive neovascular glaucoma, requiring multiple surgical interventions (49).

7.2 Ischemic Cerebral Stroke

According to a study published in Ophthalmology in 2015, based on a self-controlled case series, patients who suffered from CRAO are at increased risk of stroke or acute myocardial infarction. This was especially found to be the case within the first week after the CRAO event (54).
Similar risk factors, such as carotid disease or radiogenic emboli, could lead to this increased risk of stroke after CRAO, the authors claim. The researchers analysed data from Korean insurance data banks and identified patients with newly developed CRAO between 2009 and 2010. The control periods were set to be 181 to 365 days before the CRAO-event and 181 to 365 days before and after the CRAO-event.
Results showed that out of the 1585 included CRAO-patients, 139 developed ischemic stroke, 13 haemorrhagic stroke, and 15 acute myocardial infarctions within 365 days before or after the CRAO-event. The incidence rate ratios for stroke/acute myocardial infarction in the first 30 days after CRAO-event, as well as in the last 90 days before CRAO-event, were significantly increased, compared to the control periods. Especially interesting was that the incidence rate ratio value was highest within the first week. Additionally, no difference in incidence rate ratios was found among different age groups and genders. When only looking at the risk of
ischemic stroke, this was found to be even higher, especially within the first week after a CRAO event (54).

It is, of course, essential to underline the limitations of this study, especially in its limitation to investigate the impact of the cardiovascular and neurological interventions, as well as the lack of data on potential deaths. However, it clearly shows the increased risk for CRAO accompanying events such as ischemic stroke and myocardial infarction.

Another study on a cohort of 300 patients with CRAO, diagnosed between 2001 and 2016, was performed to contribute additional data to the discussion on the ideal time point for cerebrovascular workup, following CRAO. Of the 300 patients, 5.3 % suffered an ischemic stroke around the time of the CRAO event. 2.3% occurred within 15 days before the event, 1.3% simultaneously with CRAO, and 1.7% within 15 days after CRAO. It showed that most ischemic strokes were associated with CRAO of an embolic cause (55).

Hayreh and Zimmerman performed a retrospective analysis and found a 7% risk for transient ischemic attack or stroke concerning CRAO, while only 1% of events happened within 3 months after CRAO (16).
Even though the most prevalent time point of cerebral ischemic events remains unclear, literature underlines a clear need for secondary stroke prevention following CRAO events. Suppose an examining doctor during an examination or diagnostic workup finds or suspects an embolic cause. In that case, it should therefore raise the Urgency of cerebrovascular workup, not limited to only urgent carotid imaging.

8 Awareness of Central Retinal Artery Occlusion

As we know, the time frame of any therapy, whether it is effective or not, is very limited. Every adjusting factor that can lead to earlier reperfusion of the retina is of immense importance. Thus, public awareness as well as the awareness of medical professionals is crucial. However, the studies that were done to determine the awareness among the population as well as professionals show that there is vast potential for improvement. Within 2019 and 2020, a survey was conducted among patients of a Swiss interdisciplinary outpatient department, asking about the state of awareness of the Swiss population on CRAO symptoms, warning signs, and approach in case of sudden loss of vision. Of those 350 participants, 28.6% recognised acute unilateral loss of vision as a symptom of an ischemia of the eye. 39.5% had already heard of retinal infarction. Almost half (47.7%) stated that they would seek a general practitioner or ophthalmologist consultation. 67.7% recognised temporary loss of vision as

potentially dangerous and would consult a doctor. The majority (60.8%) believed that treatment in case of acute loss of vision should be applied within the first two hours after the onset of symptoms.
In comparison, 89.9% of participants would go to the emergency department of a hospital if they had symptoms of a cerebral stroke. However, only 55.4% of participants stated they would do the same in case of CRAO symptoms.
To investigate the general practitioners' (GP) and ophthalmologists' knowledge, a questionnaire asking about CRAO symptoms, differential diagnosis, aetiology, and management of sudden vision loss, as well as therapy options and time windows, was sent to GPs' offices.
Out of the 102 who answered, all identified CRAO as an emergency, and the vast majority (88.9%) were able to identify sudden unilateral loss of vision as a typical symptom of CRAO. The most frequently stated approach (59.9%) was to send the patient to the most proximal stroke centre. The majority of GPs (53.9%) considered thrombolysis as potentially effective. 51.0% considered Aspirin a valid treatment, while 37.3% would take systemic thrombolysis into consideration.
Among the ophthalmologists, 67 were included in the survey results. Of which 98.5% recognised CRAO as a medical emergency and 64.2% would send their patients to the emergency department of a stroke centre. 76.1% of ophthalmologists considered the symptoms to be reversible in case of therapy within 4 hours after onset. 47.8% considered early treatment with Aspirin as potentially effective. 80.6% stated that they think of conservative therapies (for example, ocular massage, intraocular pressure lowering) as appropriate measurements. However, only 23.9% would administer systemic thrombolysis, and 41.8% IAT (5).
Between January 2016 and August 2020, 101 patients were treated for CRAO in a German hospital. In 2018, that hospital released institutional guidelines for the treatment of CRAO with IVT based on the patient's approval of its off-label usage. Simultaneously, the number of CRAO patients who were administered to the stroke unit increased from 52.2% to 97.4%. The rate of thrombolysis increased from 0% to 14.1%. The by far most common reason why patients were not seeking medical attention in this hospital's emergency department was prehospital delay until presentation (58.8%). 44.4% of these patients had presented themselves primarily at a private-practice ophthalmologist (56).
In July of 2021, all of the then 335 certified stroke units in Germany were invited to participate in an anonymous online survey. The majority (86.7%) of the 135 participating centres stated that patients with unilateral loss of vision were treated as emergencies. However, only in 44.9% of hospitals did specific guidelines for such cases exist. In 62.5% of cases, first assessment was performed by neurologists while in 31.6% of centres this was done by their ophthalmologic colleagues. 51.9% of

participating centres stated that they're not able to perform ophthalmologic expertise. Fundoscopy was the most frequently used diagnostic tool for ophthalmologists in 43.7% of hospitals. In comparison, 86.2% of neurologists performed CT. As a side note, neurologists more frequently ordered ophthalmologic consultation than the other way around (37.8%).

Ocular massage was the most commonly applied ophthalmologic therapy (15.5%), while IVT was performed in 57.4% of cases. IAT was only performed in 4.7% of stroke centres. 94.8% of hospitals stated that CRAO patients are hospitalised routinely or exclusively in stroke units. When the patient was hospitalised, 94.5% of stroke units performed extracranial ultrasound, 93.0% performed transcranial ultrasound, 88.3% were ECG-monitoring their CRAO patients, and transthoracic echocardiography was done by 79.7%. In comparison, transoesophageal echocardiography was done by 53.1% of stroke units (6).

Another example of the delayed medical presentation of patients after the onset of CRAO symptoms is shown by a small study on 260 patients in the University Hospital of Iowa by Hayreh and Zimmerman. It shows that the first visit in the clinic after CRAO onset varied greatly, with 48% of patients seen within 7 days, 51.2% seen within 8 days to more than 6 months after onset (57). The results are nicely illustrated in Fig. 4.

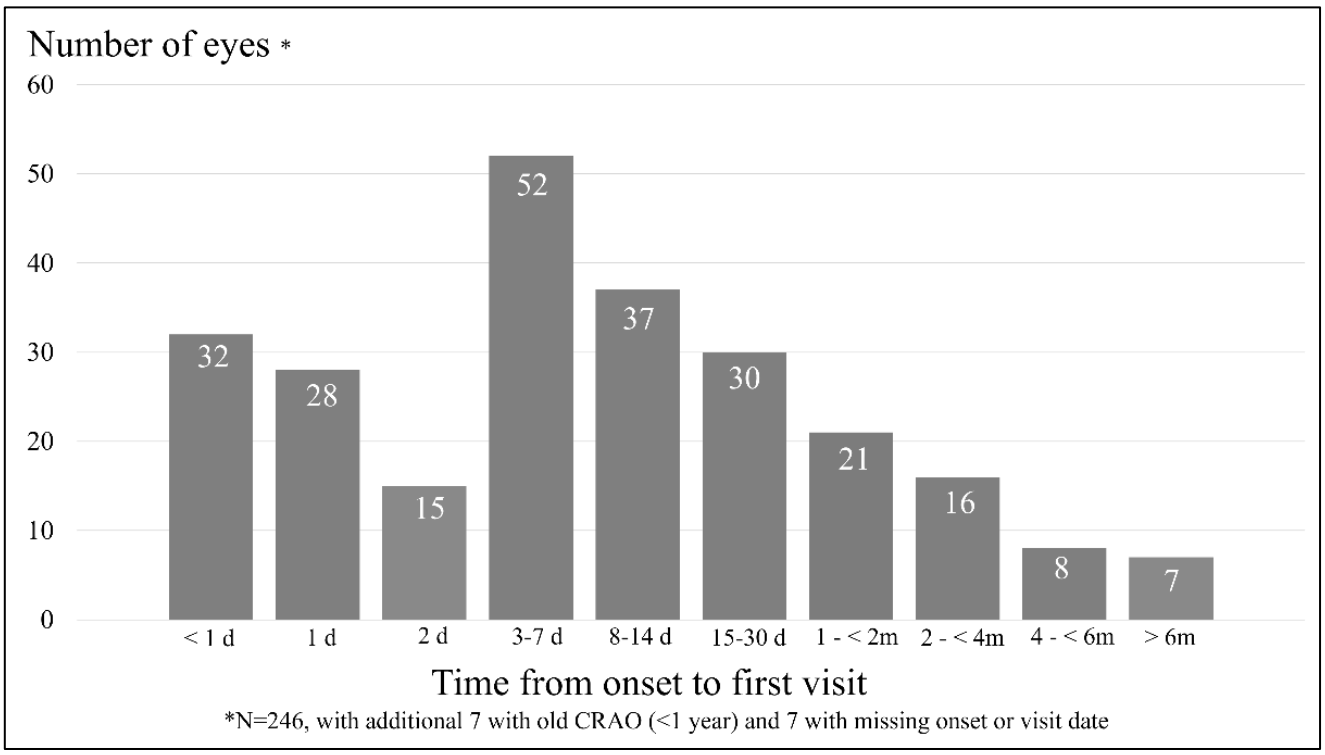

Figure 4: Timely Interval between CRAO Onset and First Clinic Visit

Time interval between the onset of central retinal artery occlusion (CRAO) and the first clinic visit. The graph shows the distribution of the time interval. The author re-created this figure using information from (57)*.*
Abbreviations: d, Day; m, Months; N, Number.

The results show the lack of awareness not only within the general population but also among trained professionals. Another conclusion to be drawn is that the lack of guidelines and clear instructions, based on standardised workup, can not lead to satisfying results. Understandably, since early presentation to a medical professional and rapid diagnosis is not a priority in a disease for which no treatment guidelines exist. It might be more comfortable to tell a patient that he arrived too late for effective treatment than to tell him he arrived on time, but there are no recommendations on how to help him.
In summary, it seems that there is a huge potential benefit in the rise of public awareness, for the correct behaviour and reactions following CRAO events.

Patients should be familiarised with the signs and symptoms of CRAO, especially the sudden, painless loss of vision. The urgency of immediate medical care in case of a sudden loss of vision must be stressed. Beyond that, it might be beneficial for patients with CRAO-risk factors to check their eyesight to rapidly recognise any worsening regularly. Time is crucial for the preservation of eyesight, and any delays can cause irreversible damage. CRAO is a medical emergency, and even though there is no specific evidence-based therapy, an early diagnosis and immediate start of treatment could improve visual outcomes.

Patients with the risk factors of hypertension, diabetes, cardiovascular diseases, and hyperlipidaemia should be encouraged to change their state of risk by lifestyle modifications, giving up smoking, as well as targeted medication.

Regular medical follow-ups are essential to assess visual function, manage risk factors, and address potential complications at an early stage. The emotional impact of a sudden loss of vision should be acknowledged, and support services should be offered to improve coping with it.

9 Conclusions

Considering its aetiologies, non-arteritic central retinal artery occlusion is an analogue of a stroke of the carotid artery circulation, requiring fast diagnostic workup, therapeutic management, and raising awareness. Central retinal artery occlusion management in its parts must be divided among the responsible medical care givers, whether neurologists or ophthalmologists, while maintaining a functioning teamwork. Ophthalmologists are rarely found in hospitals with stroke centres. Even with private on-call ophthalmologists, it is close to impossible to call in an ophthalmologic professional once central retinal artery occlusion suspicion is raised and perform ophthalmologic diagnostic workup within the necessary time frame, may it be longer or shorter than 4.5 hours. Point of care ultrasound, optical coherence tomography, and diffusion-weighted magnetic resonance imaging appear as possible solutions but require more practical research. The current lack of diagnostic research might be because of a lack of therapeutic evidence-based consequences. However, no therapy is applicable if central retinal artery occlusion is not diagnosed on time. I therefore see the next challenge in central retinal artery occlusion management, in its rapid diagnostic approach and the raising of awareness among the population and medical professionals.

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