

Central Retinal Artery Occlusion – Retinal stroke: Role of Hyperbaric Oxygen Therapy

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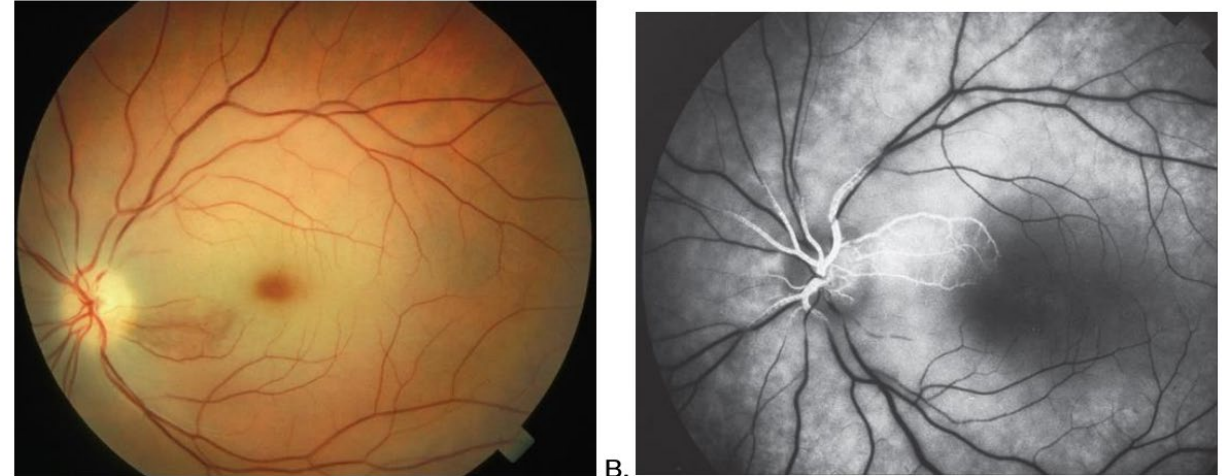
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Outline

- Central Retinal Artery Occlusion (CRAO)
- Current Practice
- Management challenges
- Role of Hyperbaric Oxygen (HBO₂) in CRAO
- Research opportunities to improve CRAO management

Central Retinal Artery Occlusion (CRAO)

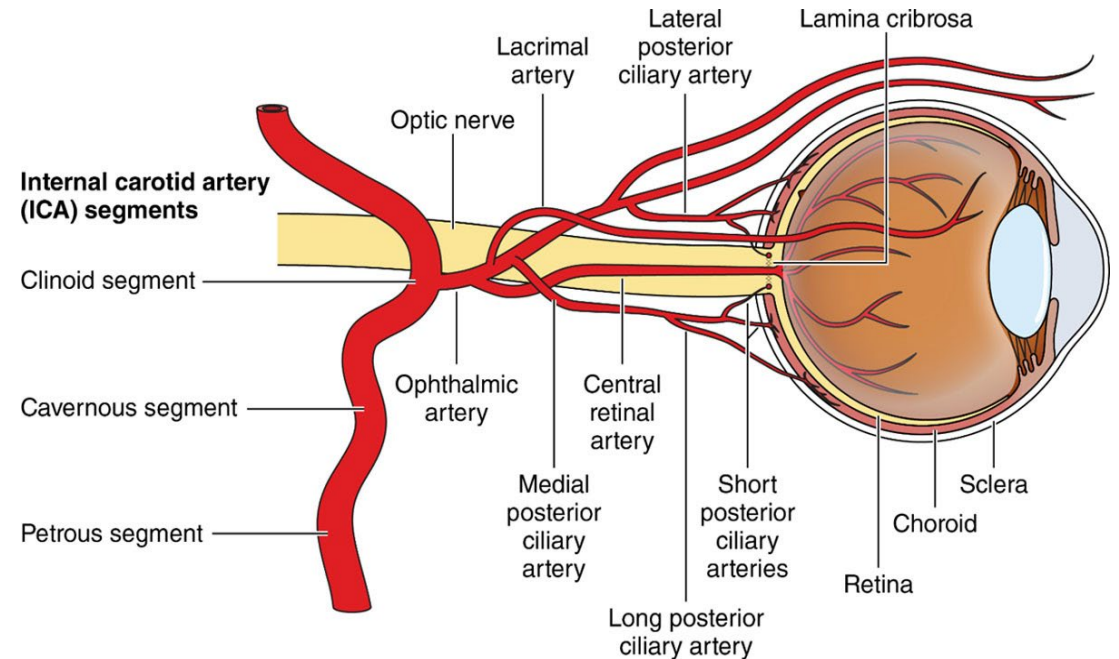
- Ocular form of acute ischemic stroke
- 1 to 2 per 100,000 person-years
- Acute retinal hypoperfusion to inner retinal layer
- Ophthalmic emergency, time is tissue
- Arteritic (5%) and Non-arteritic (95%)



A. B.
FIGURE 1. Central retinal artery occlusion (CRAO). A. Fundus photograph shows superficial macular opacification and a cherry-red spot in the foveola. B. Angiography image reveals preservation of a sector of superonasal macula related to cilioretinal vessels perfused in this image. The patient had hands motions visual acuity. (Courtesy of Hermann D. Schubert, MD. Adapted with permission from the American Academy of Ophthalmology Basic and Clinical Science Course Subcommittee. Basic and Clinical Science Course. Retina and Vitreous: Section 12, 2018-2019. San Francisco, CA: American Academy of Ophthalmology; 2018)

Pathophysiology

- Inner and outer retinal layers have different circulation intertwined by collateralization and passive diffusion
- 15 - 30% of population have a cilioretinal artery → fovea
- Acute retinal hypoperfusion → ischemia → retinal necrosis
- Atherosclerotic hypertensive elderly Rhesus monkeys had irreversible retinal damage when CRAO was > 240 minutes



Brian Mac Grory. Stroke. Management of Central Retinal Artery Occlusion: A Scientific Statement From the American Heart Association, Volume: 52, Issue: 6, Pages: e282-e294, DOI: (10.1161/STR.0000000000000366)

Current Practice: from Presentation to Treatment

Clinical Presentation

- Sudden painless monocular vision loss
- Visual acuity: Counting Fingers or less
- Relative afferent pupillary defect
- Intact retina

Fundoscopy Findings

- Retinal whitening
- Cherry red spot
- Box - carring

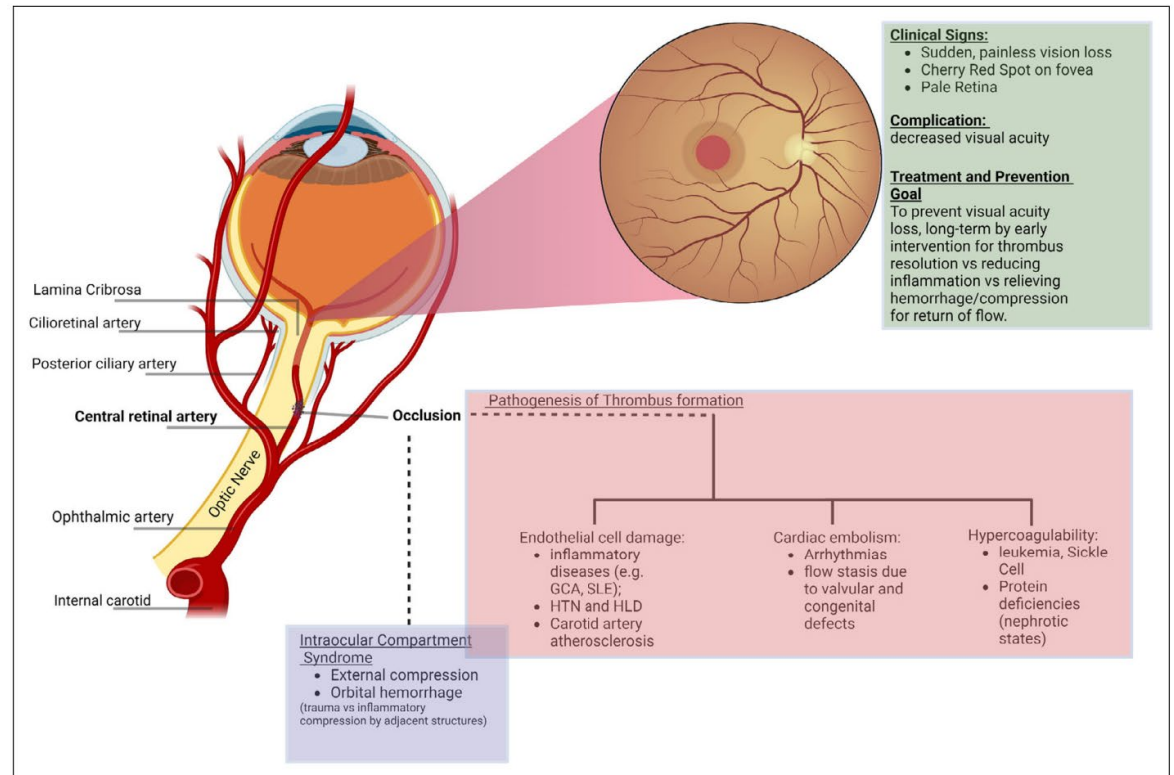
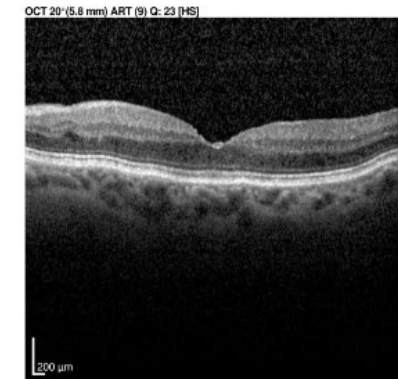
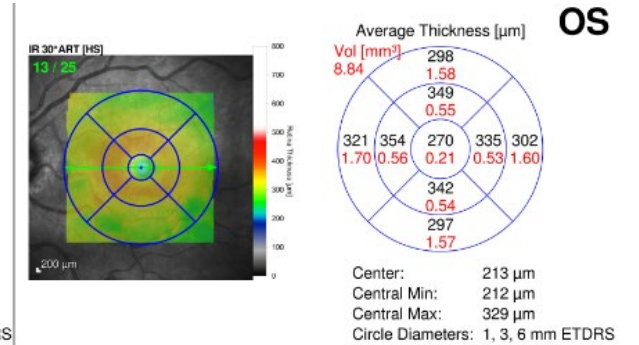
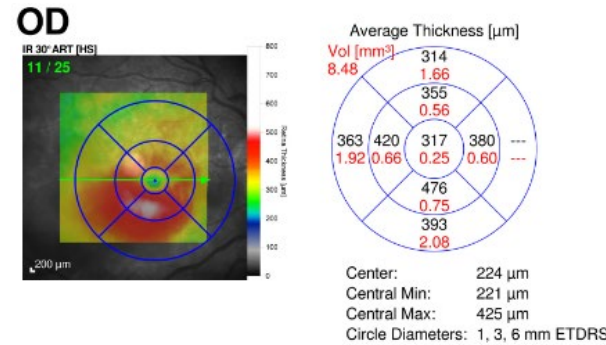


Figure 1. A summary of vascular supply to the retina and central retinal artery occlusion pathophysiological features.¹⁸ GCA indicates giant cell arteritis; HLD, Hyperlipidemia; HTN, hypertension; and SLE, systemic lupus erythematosus.

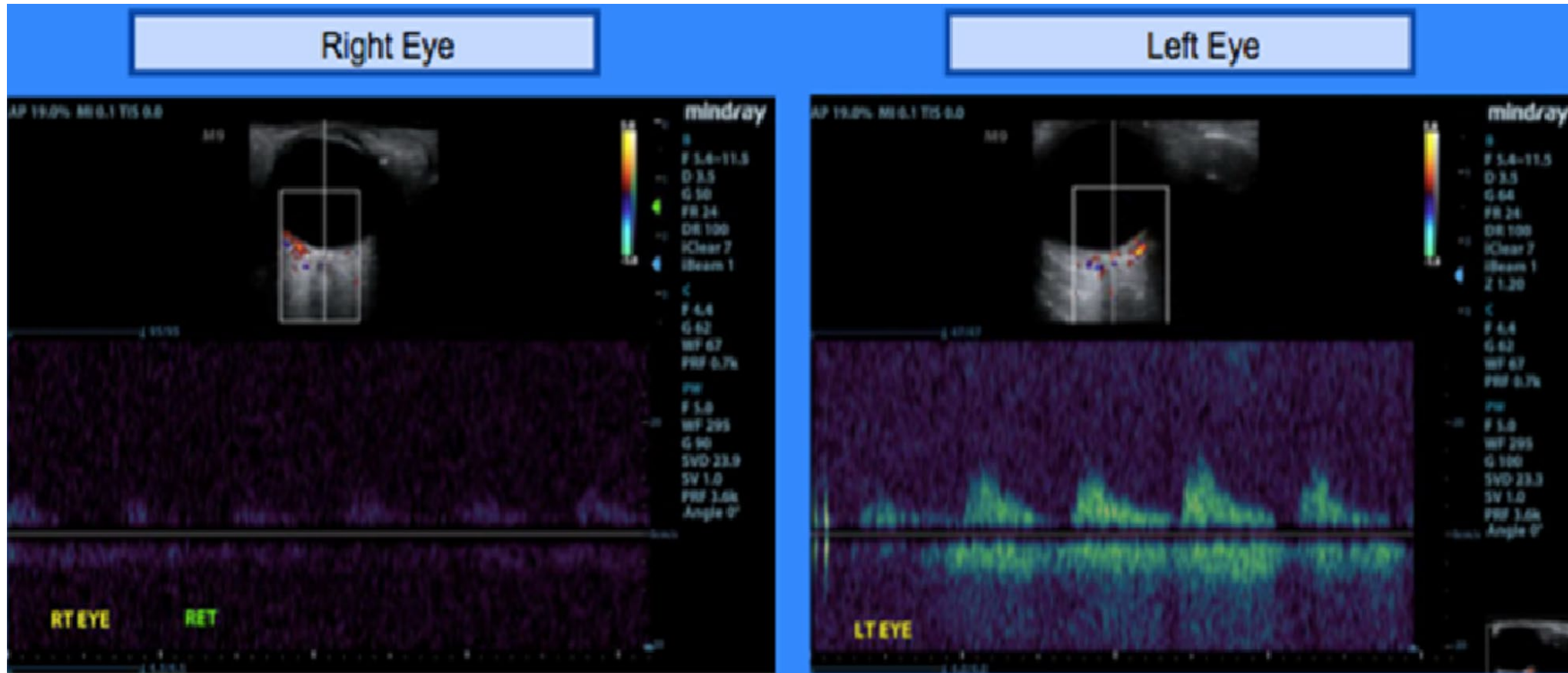
Investigations

Is it CRAO?

- Ocular Coherence Tomography
 - Retinal edema
- Fluorescein Angiography
 - Retinal arterial filling
- Ocular ultrasound
 - Point of care test
 - Arterial and venous flow rate
 - Retrobulbar spot sign
- ESR, CRP, Stroke work-up



Point of Care Ocular Ultrasound

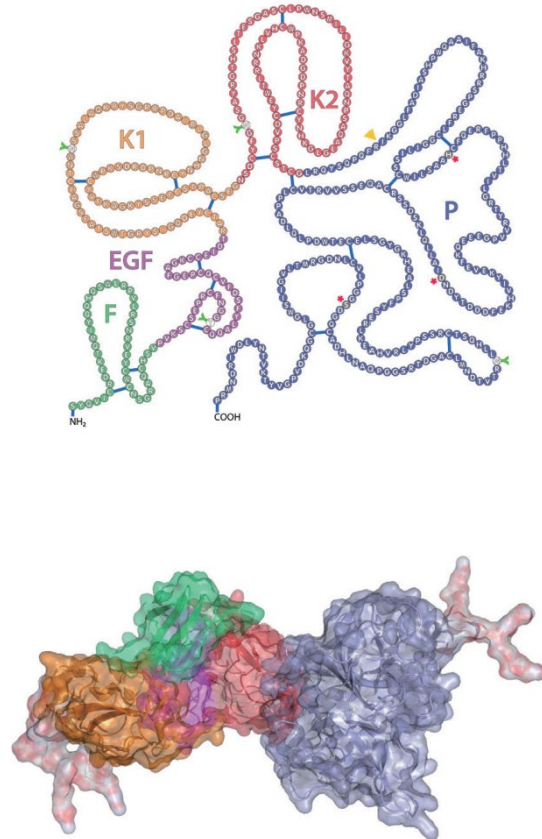


Acute Treatment – Less than 4.5 hours

Intravenous tPA

- Different agents e.g., Alteplase
- No randomized trial (pending RCTs)
- Used in 5.8% of CRAO cases in the United States
- 50% rate of clinical recovery, number needed to treat was 4
- Efficacy beyond 4.5 hours from symptom onset is unknown
- Contra-indication limits its use

Molecular Structure of tPA



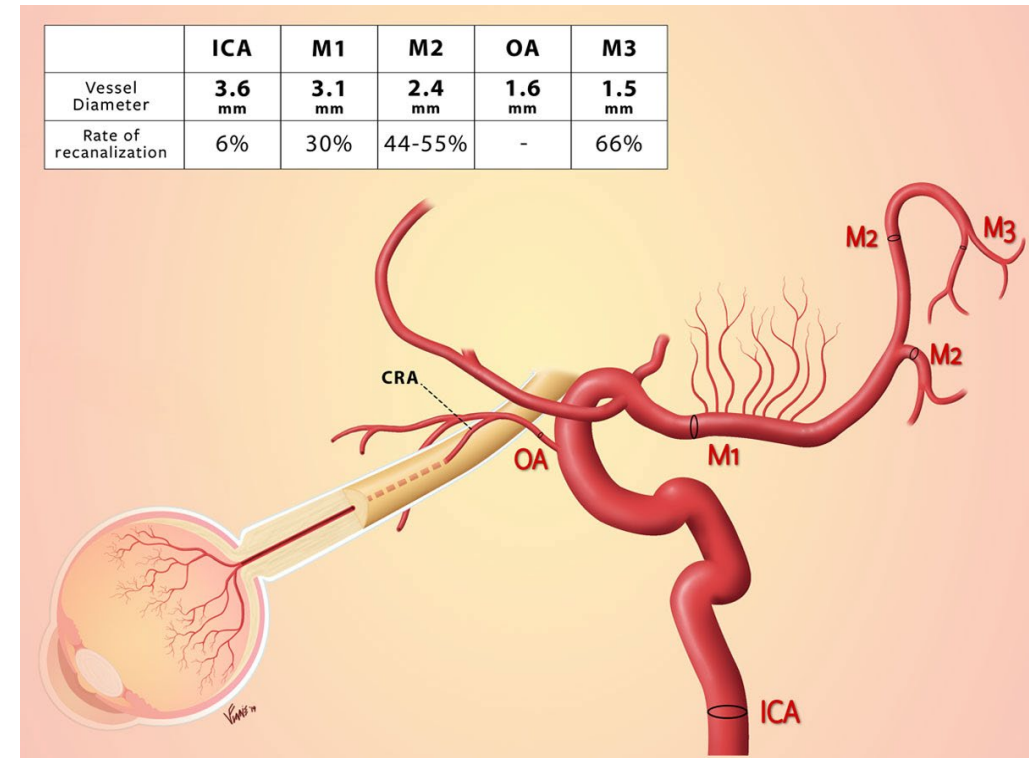
Schorr EM, Rossi KC, Stein LK, Park BL, Tuhim S, Dhamoon MS. Characteristics and Outcomes of Retinal Artery Occlusion: Nationally Representative Data. *Stroke*. 2020;51(3):800-807. doi:10.1161/STROKEAHA.119.027034
Schrug M, Youn T, Schindler J, Kirshner H, Greer D. Intravenous Fibrinolytic Therapy in Central Retinal Artery Occlusion: A Patient-Level Meta-analysis. *JAMA Neurol*. 2015;72(10):1148-1154. doi:10.1001/jamaneurol.2015.1578

Nikitin D, Choi S, Mican J, et al. Development and Testing of Thrombolytics in Stroke. *J Stroke*. 2021;23(1):12-36. doi:10.5853/jos.2020.03349

Acute Treatment: <6 hours

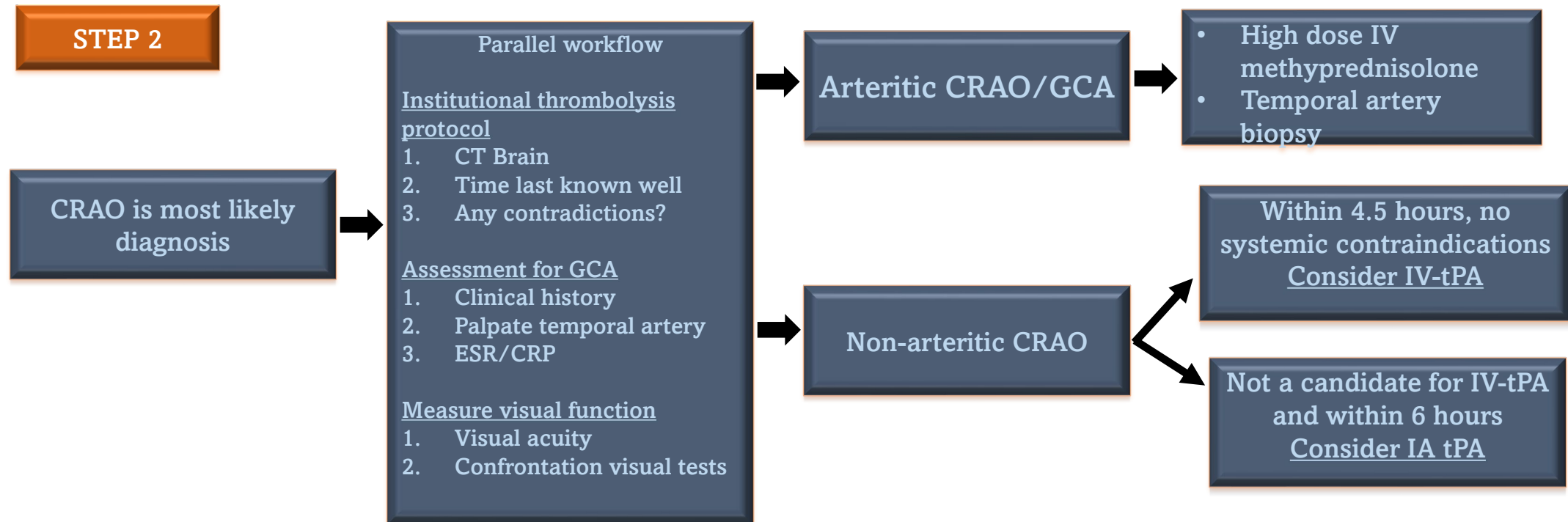
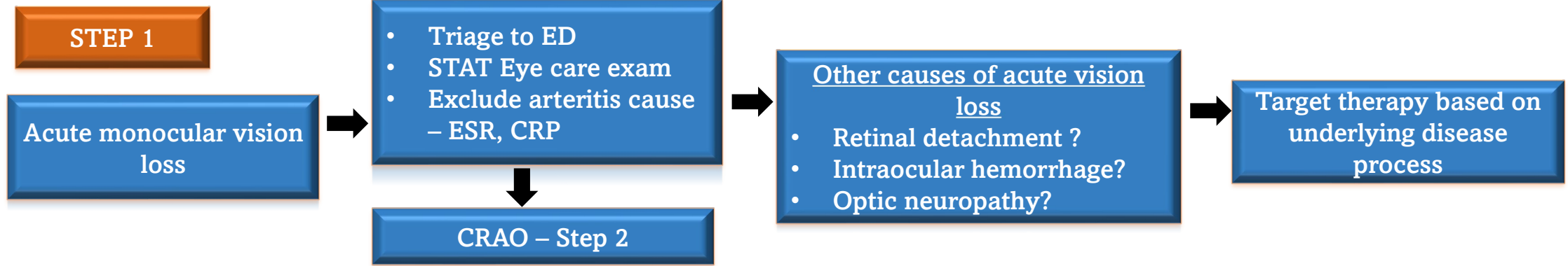
Intra-Arterial tPA

- Direct administering of lower dose tPA into the ophthalmic circulation
- Super-selective microcatheterization
- Single negative randomized study (EAGLE study) – no patient presented within 4.5 hours
- Logistic and procedural challenge
- Risk of arterial dissection and thromboembolic events



Relative diameter of major vessels of the anterior circulation. ICA indicates internal carotid artery; M1, M2, M3, subdivisions of the middle cerebral artery; and OA, ophthalmic artery.

Treatment Protocol for CRAO



Management Challenges

Management Challenges

- Within 4.5 hours and contraindications to IV tPA and IA tPA
- Presentation between 4.5 hours and 6 hours & no IA tPA capabilities
- Presentation between 6 hours and 18 hours
- Provider awareness of treatment options
- Medical practice inertia and resistance to change

Conservative Treatments Options for CRAO

- Ocular Massage
- Anterior Chamber Paracentesis
- Pentoxifylline
- Carbogen (95% O₂ + 5% CO₂)
- Glycerin
- Acetazolamide
- Topical Agents to Lower IOP
- Enhanced External Counter-pulsation
- Anticoagulation
- Aspirin

Role of HBO₂ In The Management of CRAO

What Is Hyperbaric Oxygen?

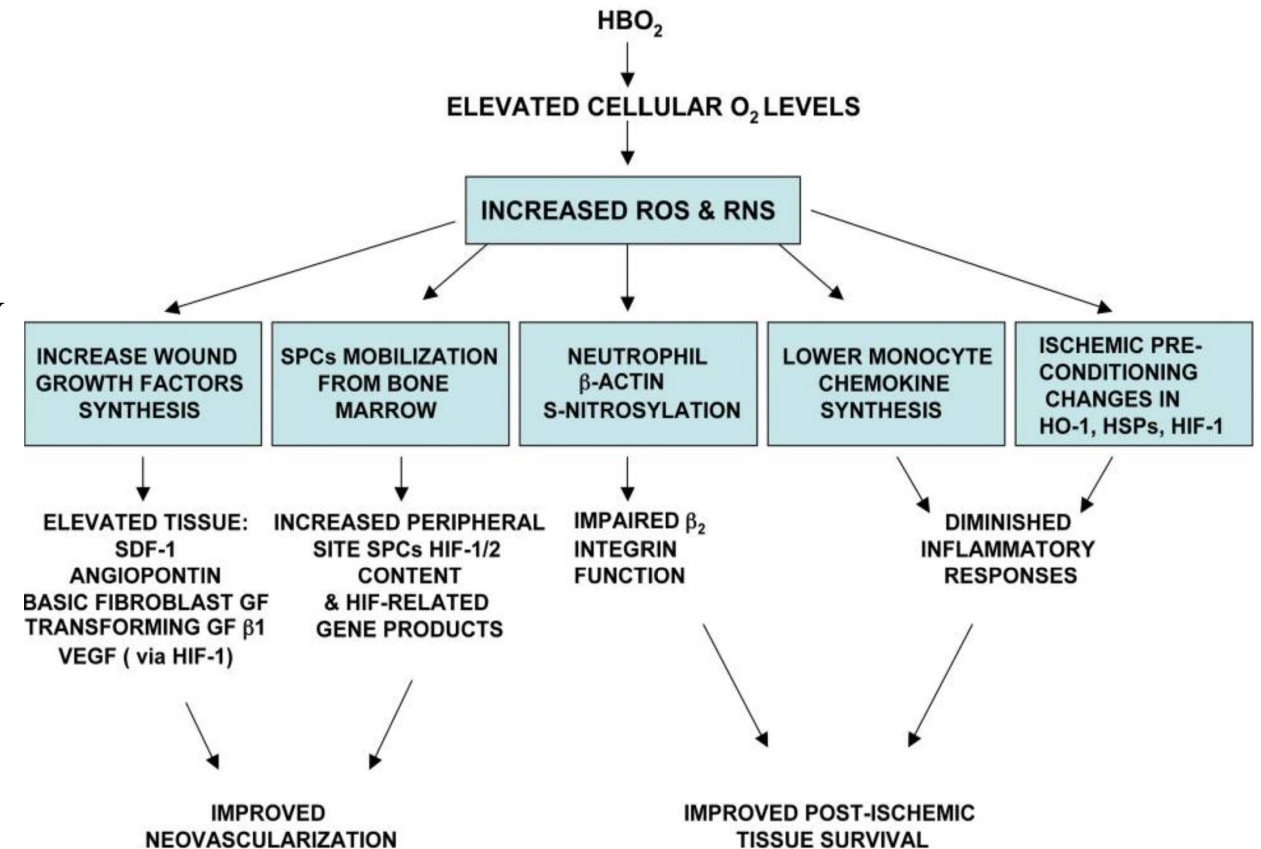
- Intra-nasal delivery of 100% oxygen to patients at higher-than-atmospheric pressure (>1.4 atmosphere absolute)
- Oxygen + Pressure = HBO₂
- Considered as a drug
 - Different diseases require different doses of oxygen
- Can be used for elective or emergent cases



Role of HBO₂ in the management of CRAO

- 10 to 15-fold increase in plasma O₂
- 2 to 4-fold increase in O₂ diffusion capacity from capillaries
- Under normo-baric oxygen conditions, choroid/posterior ciliary artery provides < 60% supply to the retina
- Under HBO₂ conditions, the choroid is capable of supplying 100% of the retina's need via diffusion to inner retinal layer

Overview of Therapeutic mechanism of HBO₂



Why is HBO₂ successful: Mechanism of Action

- Diffusion from a choroidal circulation with increased dissolved plasma oxygen
- Reverses the oxygen debt accumulated during the ischemic period – normal retinal oxygen consumption is 13 ml/100g/min^{1,2}
- Reduces ischemia-reperfusion injury by decreasing β -2 Integrin mediated neutrophil adherence³
- Reduces retinal edema
- Reduces apoptosis and lipid peroxidation in ischemic tissue³
- HBO₂ – **Bridging O₂ until recanalization (usually 72 hours)**

¹Duker JS, Brown GC. Recovery following acute obstruction of the retinal and choroidal circulations. *Retina*. 1988;8(4):257-260

²Hertzog LM, Meyer GW, Carson S, Strauss MB, Hart GB. Central retinal artery occlusion treated with hyperbaric oxygen. *J Hyperbaric Medicine*. 1992;7:33-42

³Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg*. 2011;127 Suppl 1(Suppl 1):131S-141S. doi:10.1097/PRS.0b013e3181fbc2bf

Role of HBO₂ in the management of CRAO

- 0.03 logMAR worse for each hour of delay¹
- No other alternatives with similar outcomes, no evidence of harm, hopeless when left untreated
- Survey found only 7% of U.S. centers with vascular neurology and retinal specialist and/or neuro-ophthalmology offer HBOT²
- Overall, **66%** cases of CRAO have shown improvement with HBO₂³

¹Hadanny A, Maliar A, Fishlev G, et al. Reversibility of retinal ischemia due to central retinal artery occlusion by hyperbaric oxygen. *Clin Ophthalmol.* 2016;11:115-125. Published 2016 Dec 29. doi:10.2147/OPTH.S121307

²Youn TS, Lavin P, Patrylo M, et al. Current treatment of central retinal artery occlusion: a national survey. *J Neurol.* 2018;265(2):330-335. doi:10.1007/s00415-017-8702-x

³Murphy-Lavoie H, Butler F, Hagan C. Chapter 2A. Arterial Insufficiency Central Retinal Artery Occlusion. In: Moon R. eds. Undersea and Hyperbaric Medicine Society Hyperbaric Oxygen Therapy INDICATIONS 14th Edition. Best Publishing Company; 2019: 22 - 25

Overall Goal

To maintain an oxygen concentration
high enough to adequately perfuse
the retinal choroidal circulation and
maintain viability until natural
recanalization and reperfusion occurs

U.S. FDA Regulatory Approval

The U.S. Food and Drug Administration

Undersea and Hyperbaric Medical Society

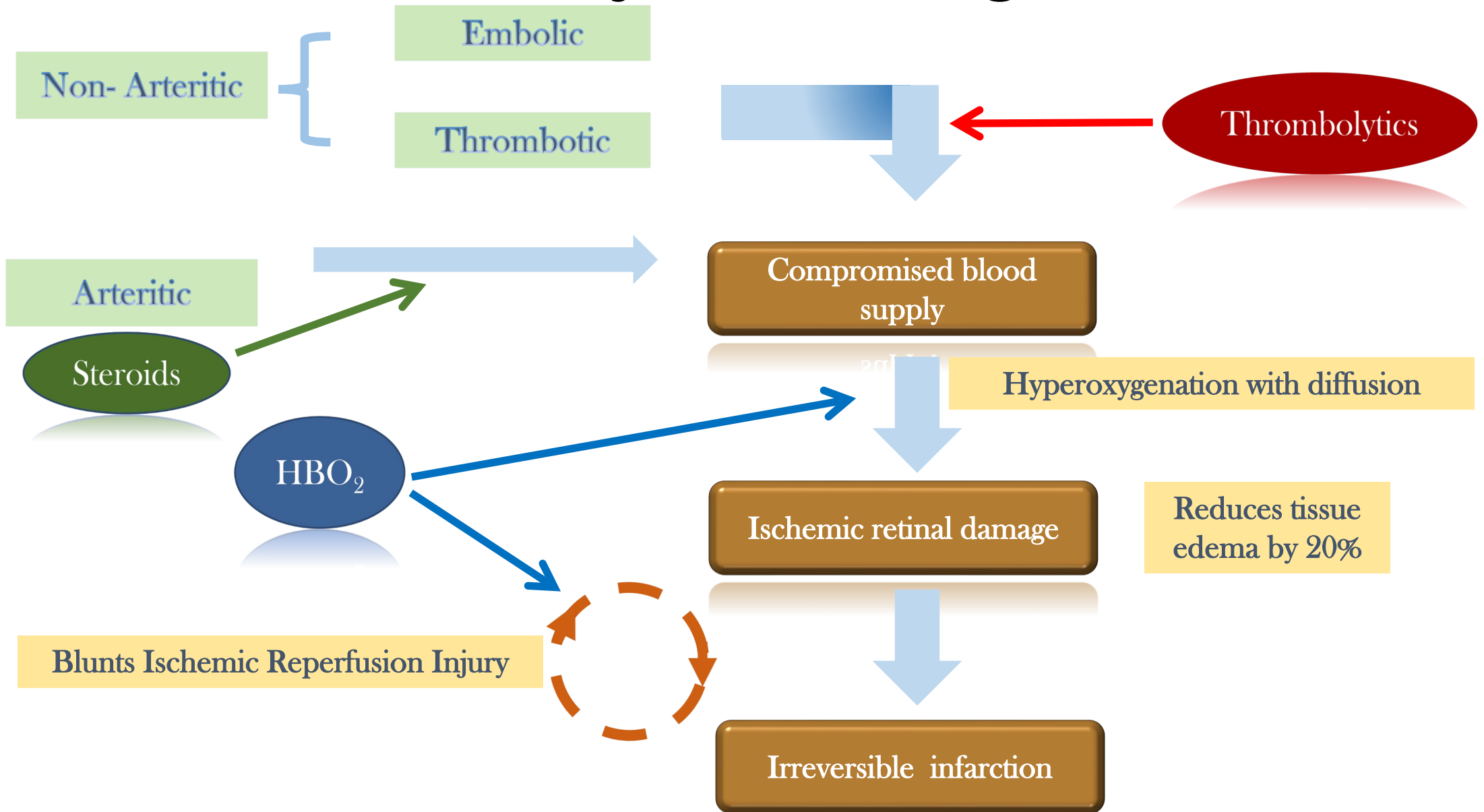
Hyperbaric Oxygen Therapy: Get the Facts. U.S. Food and Drug Administration. Updated July 26, 2021. Accessed August 5, 2023. <https://www.fda.gov/consumers/consumer-updates/hyperbaric-oxygen-therapy-get-facts>

Conditions for which hyperbaric chambers are cleared for marketing by the FDA

FDA clearance of a medical device includes a determination that the device has the same intended use as, and is as safe and effective as, another legally U.S.-marketed device of that type. As of July 2021, the FDA has cleared hyperbaric chambers for the following disorders:

- Air and gas bubbles in blood vessels
- Anemia (severe anemia when blood transfusions cannot be used)
- Burns (severe and large burns treated at a specialized burn center)
- Carbon monoxide poisoning
- Crush injury
- Decompression sickness (diving risk)
- Gas gangrene
- Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
- Infection of the skin and bone (severe)
- Radiation injury
- Skin graft flap at risk of tissue death
- Vision loss (when sudden and painless in one eye due to blockage of blood flow)
- Wounds (non-healing, diabetic foot ulcers)

Where Do they Act? : Target sites



Treatment Protocol in a Facility with HBO₂

STEP 1

Acute monocular vision loss

- Triage to ED
- STAT Eye care exam
- Exclude arteritis cause – ESR, CRP

CRAO – Step 2

Other causes of acute vision loss

- Retinal detachment ?
- Intraocular hemorrhage?
- Optic neuropathy?

Target therapy based on underlying disease process

STEP 2

CRAO is most likely diagnosis

Parallel workflow

Institutional thrombolysis protocol

1. CT Brain
2. Time last known well
3. Any contradictions?

Assessment for GCA

1. Clinical history
2. Palpate temporal artery
3. ESR/CRP

Measure visual function

1. Visual acuity
2. Confrontation visual tests

Arteritic CRAO/GCA

- High dose IV methylprednisolone
- Temporal artery biopsy

Non-arteritic CRAO

Within 4.5 hours, no systemic contraindications
Consider IV-tPA

Not a candidate for IV-tPA and within 6 hours
Consider IA tPA

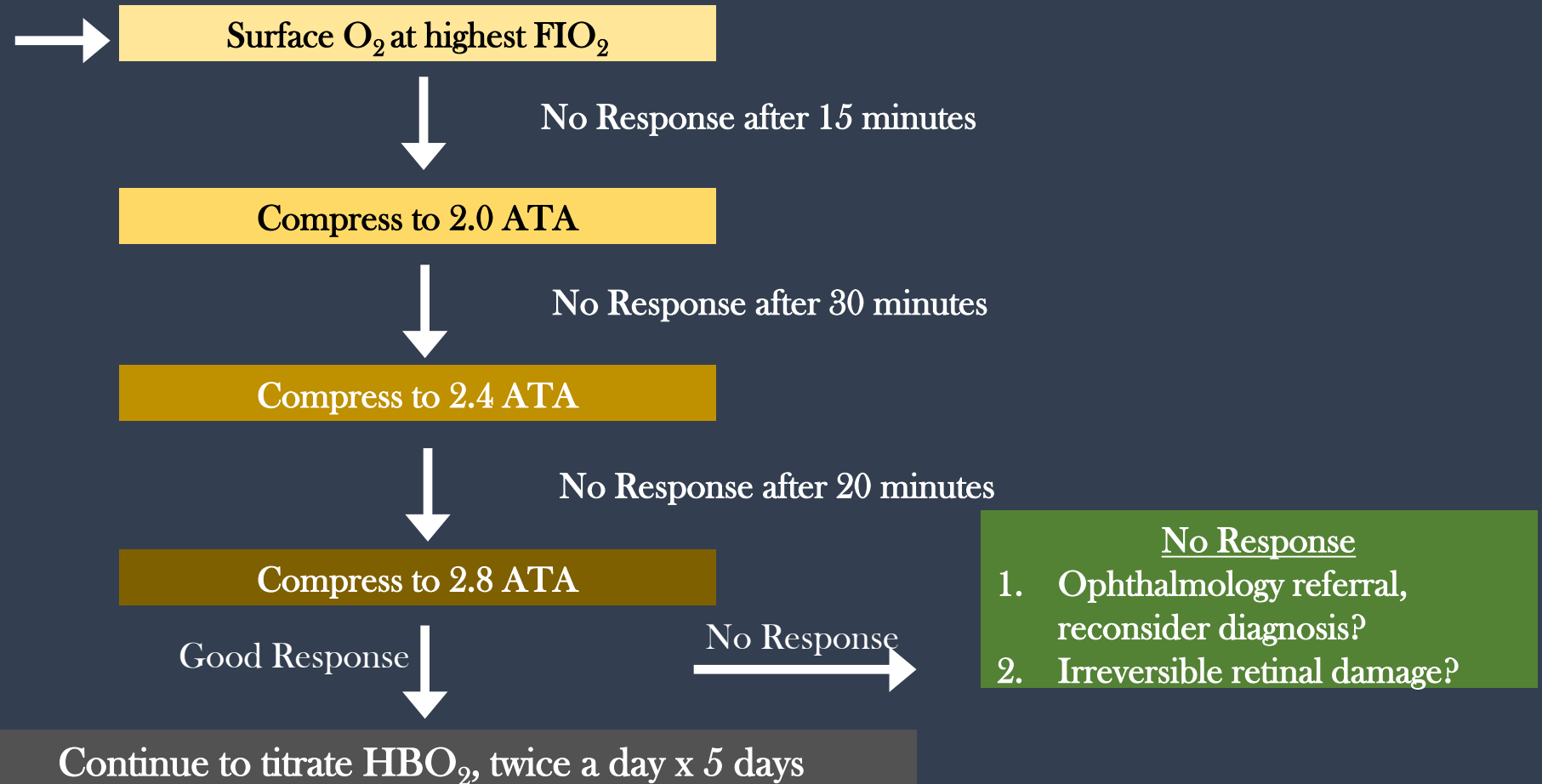
Consider HBO₂

1. Within 4.5 hours but IV tPA & IA tPA are contraindicated
2. Between 6 – 18 hours
3. Between 4.5 – 6 hours but IA tPA is unavailable
4. 2 hours after IV tPA administration with unchanged visual acuity
5. No contraindications to HBO₂

HBO₂ Treatment Protocol for CRAO

Murphy-Lavoie H, et al. Moon R. Hyperbaric Oxygen Therapy INDICATIONS 2019

- Consider HBO₂
1. Within 4.5 hours but IV tPA & IA tPA are contraindicated
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 5. No contraindications to HBO₂



Effectiveness of Presented Therapies

Therapy	Effectiveness	Citation
IV Tissue plasminogen activator	47.0%	Huang L et al. (2022). A systematic review and meta-analysis.
Intra-arterial plasminogen activator	50.4%	Page PS et al. (2018). A Systematic Review and Meta-Analysis.
Hyperbaric oxygen treatment	66%	Murphy-Lavoie H et al (2019). Treatment of Retinal Artery Occlusions: Literature Summary

Huang L, Wang Y, Zhang R. Intravenous thrombolysis in patients with central retinal artery occlusion: a systematic review and meta-analysis. *J Neurol*. 2022;269(4):1825-1833. doi:10.1007/s00415-021-10838-6

Page PS, Khattar NK, White AC, et al. Intra-Arterial Thrombolysis for Acute Central Retinal Artery Occlusion: A Systematic Review and Meta-Analysis. *Front Neurol*. 2018;9:76. Published 2018 Feb 21. doi:10.3389/fneur.2018.00076

Murphy-Lavoie H, Butler F, Hagan C. Chapter 2A. Arterial Insufficiency Central Retinal Artery Occlusion. In: Moon R. eds. Undersea and Hyperbaric Medicine Society Hyperbaric Oxygen Therapy INDICATIONS 14th Edition. Best Publishing Company; 2019: 22 - 25

Deep Dive into Negative Studies

Therapy	Study / Article	Keynote
IA tPA	Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial (EAGLE) - Schumacher M, et al. <i>Ophthalmology</i> . 2010	<ul style="list-style-type: none"> • Mean time between symptom onset and treatment was 13 hours • No patient was treated within 4.5 hours • 4 of 41 (9.7%) patients were treated between 4.5 – 6 hours from symptom onset
HBO ₂	The Effects of Hyperbaric Oxygen Therapy in Patients with Central Retinal Artery Occlusion: A Retrospective Study, Systematic Review, and Meta-analysis - Rosignoli L, et al. <i>Korean J Ophthalmology</i> . 2022	<ul style="list-style-type: none"> • HBO₂ protocol cited is not backed up by the Undersea and Hyperbaric Medicine Society (UHMS) – stopping treatment if no response after 1st treatment • Mean time between symptom onset and treatment was 18.27 hours

Schumacher M, Schmidt D, Jurklics B, et al. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. *Ophthalmology*. 2010;117(7):1367-75.e1. doi:10.1016/j.ophtha.2010.03.061

Rosignoli L, Chu ER, Carter JE, Johnson DA, Sohn JH, Bahadorani S. The Effects of Hyperbaric Oxygen Therapy in Patients with Central Retinal Artery Occlusion: A Retrospective Study, Systematic Review, and Meta-analysis. *Korean J Ophthalmol*. 2022;36(2):108-113. doi:10.3341/kjo.2021.0130

Research Opportunities

Research Opportunities

- Randomized controlled trial comparing tPA with placebo and/or HBO₂
- Compare single therapy (such as tPA) with tPA + HBO₂
- Investigate barriers to early presentation and provide targeted options
- Explore early biomarkers or imaging techniques of retinal viability