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An Explanation for Terson Syndrome at last: the Glymphatic Reflux theory

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Abstract:	Terson Syndrome (TS) describes the presence of intraocular hemorrhage in patients with intracranial hemorrhage, typically subarachnoid hemorrhage. Despite TS being a well-defined and frequently occurring phenomenon, its pathophysiology remains controversial. This review will present the current understanding of TS, with view to describing a contemporary and more plausible pathomechanism of TS, given recent advances in ophthalmic science and neurobiology. Previously proposed theories include a sudden rise in intracranial pressure (ICP) transmitted to the optic nerve sheath leading to rupture of retinal vessels; or intracranial blood extending to the orbit via the optic nerve sheath. The origin of blood in TS is uncertain, but retinal vessels appear to be an unlikely source. In addition, an anatomical pathway for blood to enter the eye from the intracranial space remains poorly defined. An ocular glymphatic system has recently been described, drainage of which from the globe into intracranial glymphatics is reliant on the pressure gradient between intraocular pressure and intracranial pressure. The glymphatic pathway is the only extravascular anatomical conduit between the subarachnoid space and the retina. We propose that subarachnoid blood in skull base cisterns near the optic nerve is the substrate of blood in TS. Raised ICP causes it to be refluxed through glymphatic channels into the globe, resulting in intraocular hemorrhage. We herewith present glymphatic reflux as an alternative theory to explain the phenomenon of Terson Syndrome.
Response to Reviewers:	Many thanks, please see the attached Word document which contains all responses to reviewer and editor comments in red. These are copied below as well.

	Reviewer #1: Review: An explanation for Terson syndrome at last: the glymphatic reflux theory. Terson syndrome is the occurrence of intraocular hemorrhage in the course of a subarachnoidal hemorrhage (SAH). The cause of this is not yet clear. In this paper, the authors discuss the hypothetic explanation of this syndrome due to a glymphatic pathway from the subarachnoidal space to the intraocular compartment. Normally the pressure gradient and therefore the fluid flow is from the eye towards the subarachnoidal space and in the case of a SAH the increased intracranial pressure causes a change in the pressure gradient towards the eye. The paper discusses an interesting hypothesis. In my experience, Terson syndrome is much less frequent than the 24% mentioned by the authors. In this context, it would be also nice to give some estimation about the prevalence after traumatic brain injury and other hemorrhages. Response: Thank you very much for your comments. The manuscript has now been updated with this information. Reviewer #2: In this manuscript the authors forward a hypothesis that the pathophysiology of Terson syndrome is related to an ocular "glymphatic reflux" secondary to subarachnoidal blood in the basal cisterns. To underline their hypothesis they cite various references and discuss different findings from both experimental and clinical studies. This manuscript would be better placed in a journal on medical hypotheses. There is little information on how the relevant literature was screened and a more systematic approach certainly would be appropriate. Also the data which was collected should be set in better perspective. E.g. information gained from one case report certainly has less weight than conclusions coming from well designed studies. Response: We agree and have included a section to outline how the literature was searched and screened. Although Terson syndrome has been well described, there is relative paucity in terms of the amount of published literature. Few well designed studies are available and even those are vague on the exact pathophysiology. There are many imprecisions throughout the manuscript, e.g. when referring to "certain neurological disorders" or "certain dementias" instead of exactly naming the diseases. Response: We agree and have updated the manuscript accordingly. Although the subject by itself is of interest the conclusions made by the authors are not justified by the data which is presented. Unfortunately, also, the authors do not show any of their own work related to the subject under question. Much of the discussion is speculative, and I do not understand why there is even additional speculation on CNS lymphomas which clearly is out of context. Response: The discussion regarding CNS lymphoma has been placed in better context in the updated manuscript. Not unlike Terson syndrome, a satisfactory explanation for the frequent co-existence of lymphoma in brain and eye is lacking. An anatomical explanation, such as the one we propose here, is a possibility. As blood cells spread along perivascular glymphatic channels, so could lymphoma cells. The description of glymphatic circulation as a conduit for tumor cell spread within the CNS was suggested in another paper of ours which is cited (Reference 81). Further, we have another case report which is nearing submission and therefore not citable at present. Glymphatic biology, pathophysiology and applications are still in their infancy and we hope to further explore these going forwards. Once again, we thank the reviewers for their time and constructive feedback.
Author Comments:	Dear Dr Barker, Prof Dr Filippi and Prof Dr Strupp,

	We wish to submit an original article titled “An Explanation for Terson Syndrome at last: the Glymphatic Reflux theory”. We herewith present a novel mechanism to explain the phenomenon of Terson syndrome, whose pathophysiology has remained elusive. As Terson syndrome is a frequently occurring contributor to the morbidity of intracranial haemorrhage, this paper is likely to be of interest to the readership of the Journal of Neurology. This manuscript is an original work – no part of this work has been published or presented, nor has it been submitted for consideration elsewhere. We report no conflicting interests. Thank you for your consideration. Kind regards, Ashwin, on behalf of the co-authors

Reviewer #1: Review: An explanation for Terson syndrome at last: the glymphatic reflux theory.

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Glymphatic biology, pathophysiology and applications are still in their infancy and we hope to further explore these going forwards.

Once again, we thank the reviewers for their time and constructive feedback.

AN EXPLANATION FOR TERSON SYNDROME AT LAST: THE GLYMPHATIC REFLUX THEORY

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Keywords:

Terson syndrome, subarachnoid hemorrhage, intraocular hemorrhage, glymphatic system

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Abstract:

Terson Syndrome (TS) describes the presence of intraocular hemorrhage in patients with intracranial hemorrhage, typically subarachnoid hemorrhage. Despite TS being a well-defined and frequently occurring phenomenon, its pathophysiology remains controversial. This review will present the current understanding of TS, with view to describing a contemporary and more plausible pathomechanism of TS, given recent advances in ophthalmic science and neurobiology.

Previously proposed theories include a sudden rise in intracranial pressure (ICP) transmitted to the optic nerve sheath leading to rupture of retinal vessels; or intracranial blood extending to the orbit via the optic nerve sheath. The origin of blood in TS is uncertain, but retinal vessels appear to be an unlikely source. In addition, an anatomical pathway for blood to enter the eye from the intracranial space remains poorly defined.

An ocular glymphatic system has recently been described, drainage of which from the globe into intracranial glymphatics is reliant on the pressure gradient between intraocular pressure and intracranial pressure. The glymphatic pathway is the only extravascular anatomical conduit between the subarachnoid space and the retina. We propose that subarachnoid blood in skull base cisterns near the optic nerve is the substrate of blood in TS. Raised ICP causes it to be refluxed through glymphatic channels into the globe, resulting in intraocular hemorrhage.

We herewith present glymphatic reflux as an alternative theory to explain the phenomenon of Terson Syndrome.

Introduction:

Terson syndrome (TS) describes the presence of intraocular hemorrhage (including vitreous, subhyaloid, preretinal, intraretinal or subretinal bleeding) in patients with intracranial hemorrhage or traumatic brain injury. Although it was originally described as vitreous bleeding following aneurysmal subarachnoid hemorrhage (SAH) by Moritz Litten in 1881, its eponymous title comes from the French ophthalmologist Albert Terson (1,2). Terson Syndrome is most commonly observed in aneurysmal SAH, occurring in up to 24% of patients (3,4). However, TS has also been described in the context of intracerebral hemorrhages and traumatic brain injury, where blood extends to the basal subarachnoid space (5,6). The reported incidence of TS in traumatic brain injury and intraparenchymal hemorrhage is 3% and 9% respectively (5). Although it can occur in children, TS is usually seen in adults (6-8).

The gold standard for diagnosis of TS is fundoscopy. However, when the view of the fundus is obscured, B-scan ocular ultrasound can be used to confirm vitreous haemorrhage (9). CT and MRI may also demonstrate ocular blood layering (10,11).

The risk of developing TS correlates with increasing clinical and radiological severity of aneurysmal SAH, being associated with a low Glasgow Coma Scale, high Hunt and Hess grade, and high Fisher grade (5,12). The higher the ICP, the higher the risk of developing TS (3,13). Given that patients most at risk of TS are least likely to communicate visual symptoms due to their neurological morbidity, the incidence of TS is probably higher than reported (14). Ophthalmological outcomes are usually favourable with conservative management, although some patients may require vitrectomy for non-clearing vitreous hemorrhage (15-18). Neurological outcomes are worse in SAH if complicated by TS (19-22).

Despite the known observations outlined above, the pathophysiology of TS remains unclear (23,24). The purpose of this paper is to examine existing theories and to propose an alternative pathomechanism of Terson Syndrome.

Existing theories and their flaws:

Two theories have been put forward to explain the source of intraocular hemorrhage in TS (23,24). One suggests that bleeding arises from the rupture of retinal vessels that follows a sudden surge in ICP (25-27). Another suggests that blood originates intracranially with TS representing an extension of subarachnoid blood into the vitreous humor (28). Neither theory has been substantiated further since their original description.

In fact, there is no defined conduit between the subarachnoid space and the vitreous humor (23). A pathway for subarachnoid blood to extend through the optic nerve or in continuity with it, as originally proposed (28), has not been anatomically identified or described thus far.

If TS results from retinal vessel rupture following an acute surge in ICP, it should also be found in other non-hemorrhagic pathologies associated with acutely raised ICP (e.g. acute hydrocephalus, non-hemorrhagic meningoencephalitis or malignant MCA infarction), which is not the case. Furthermore, ICP would be expected to be raised globally and therefore affect both eyes equally. However, TS can present with both unilateral and bilateral ocular involvement (6-8).

Regarding the timing of events: if retinal hemorrhages were caused by raised ICP, TS would manifest immediately at the time of the ICP crescendo, akin to Valsalva retinopathy (29-31). In fact, the onset of TS can often be delayed by up to several days or even weeks post SAH ictus (32). To this end, frustration has been expressed with subacute clinical manifestation of TS and subsequent delayed referral (33). Although the (usually pre-) retinal bleeding seen in Valsalva retinopathy can sometimes mimic TS, patient history helps distinguish one from the other (Figure 1). While Valsalva retinopathy follows a sudden increase in intrathoracic or intraabdominal pressure (e.g. with severe coughing, vomiting or straining), the intraocular bleeding of TS is only seen in the context of intracranial hemorrhage.

A variation of the aforementioned is that venous return from the eye decreases due to raised ICP, resulting in retinal venous stasis and intraocular hemorrhage (34,35). However, given that venous stasis is causal to hemorrhages in central retinal vein occlusion (CRVO), the clinical picture and pathophysiology of which significantly differ from TS, this theory also

falls short (36). CRVO is characterized by venous tortuosity and dilatation, cotton-wool spots, disc and/or macular edema, and most importantly flame-shaped intraretinal hemorrhages throughout all quadrants involving the far periphery (Figure 1(c)). In contrast, TS typically features dome-shaped pre-retinal or subhyaloid hemorrhages at the posterior pole (Figure 1(a)). Moreover, while early vitreous hemorrhage from rupture of the posterior hyaloid face is a hallmark feature of TS, CRVO is generally only associated with vitreous hemorrhage when complicated by retinal neovascularization later on (36,37). Taken together, intraocular blood in TS does not appear to be of retinal origin.

Although TS can occur both in intracerebral hemorrhage and traumatic brain injury, it is typically seen in the context of subarachnoid bleeding (3,5). Of note, TS has never been described in the context of hemorrhagic intracranial mass lesions which do not extend into subarachnoid or intraventricular spaces, such as hemorrhagic metastatic or primary brain tumors or hemorrhagic abscesses, despite ICP being acutely raised in these conditions. In other words, a causal role of isolated raised ICP in the pathogenesis of TS cannot be ascribed. Instead, it appears that SAH, or blood extending into basal subarachnoid spaces, is strongly associated with this clinical entity (14).

We considered whether or not aneurysm site/location could influence development of TS, but data are conflicting. Two studies reported TS being more common in anterior circulation aneurysm rupture as opposed to posterior lesions (4,12). Anterior communicating artery aneurysms were particularly linked with TS in three reports (13,25,38). Other studies have shown no association between aneurysm location and TS rate (5). One study showed an association between vertebral artery dissecting aneurysms and TS (39). Notwithstanding, the common denominator in cases of TS is the presence of blood in the subarachnoid space, as opposed to a particular anatomical propensity.

Similarly, TS has been described in spontaneous thoracic spinal SAH, presenting as a typical coup de poignard of Michon (40) and following spinal blood patch injection (41). Here TS is likely to have occurred due to blood extending into CSF and the subarachnoid space.

One case report and a small case series deserve special mention. In the former, following vitrectomy for a dense vitreous hemorrhage, fluorescein angiography revealed a leakage site

at the nasal disc margin (42). The leakage site corresponded with the demarcation between the inner limiting membrane of the retina and the inner limiting membrane of Elschnig (believed to be the basal lamina of the astroglia in the optic nerve head) (42-44). It was speculated that damage to peripapillary tissues was probably induced by raised ICP transmitted through the optic nerve sheath (42). By way of critique, the SAH experienced by the patient above happened three months prior to the time that fluorescein extravasation was noted. In addition, the finding may simply have been related to the vitrectomy procedure itself, perhaps following traumatic release of abnormal vitreal traction on the optic nerve head. Similarly, in a case series of patients with TS (n=5) undergoing vitrectomy, scanning laser ophthalmoscopy and intraoperative imaging described blood entering the vitreous space from around the retinal vessels near the optic disc (45). However, due to confounding factors and a delayed/subacute timeline, these reports do not reliably explain the pathophysiology of TS. Nonetheless, we do suggest the possibility of a peripapillary ingress route.

In fact, a recent report supports such a mechanism. Using heavily weighted T2 MRI sequences, it was shown that SAH entered the intervaginal subarachnoid space of the optic nerve and from there infiltrated the intraocular space through the perivascular space around the central retinal vessels within the optic nerve (36). The peripapillary paravascular spaces are analogous to Virchow-Robin spaces surrounding cerebral vessels (46,47).

Blood in the subarachnoid space, in the context of raised ICP, appears to be a key factor in TS. Although the possibility of blood simply tracking down the subarachnoid space within the optic sheath and entering the vitreous cavity through the optic nerve head has been suggested (14), these regions are not in anatomical continuity (23). Despite this, there may yet be a role for a peripapillary paravascular ingress route that communicates with the intracranial space via the optic nerve.

Glymphatic systems:

The glial-lymphatic or glymphatic system is a recently discovered system of perivascular channels formed by astroglia (47,48). These pathways allow the flow of CSF from the subarachnoid space and brain interstitial fluid into dural sinuses and onwards (49,50). Although originally described in animal studies, meningeal lymphatic vessels have been demonstrated in humans on MRI (51). Interestingly, although glymphatic systems have only recently been validated, their existence has long been suspected. Indeed, the earliest description comes from detailed hand drawn depictions prepared by the Italian anatomist Paolo Mascagni over 200 years ago (52, 53). The physiological role of glymphatics is unclear but may include waste clearance, fluid/ionic homeostasis, inflammatory reaction and CNS immune surveillance (49,50,54). Meningeal lymphatic vessels have been shown to drain CSF in the skull base (55). Furthermore, a particular role for paravascular Virchow-Robin spaces in glymphatic physiology has been described (47).

More recently, an ocular glymphatic system has been proposed (56-58). Traditional routes for fluid efflux from the globe have included the trabecular and uveoscleral routes (59), with a fluid efflux system from the vitreous humor and retina being a distinct entity. CSF was demonstrated to be travelling along perivascular spaces under normal physiological conditions (58). Physiological flow of the ocular glymphatics is thought to be reliant on the gradient between intraocular pressure and ICP (60). Indeed, a direct communication between the subarachnoid space and the visual system utilizing ocular and intracranial glymphatic systems has been demonstrated (61). In cadaveric studies, post-mortem instillation of India ink in subarachnoid spaces remote to the optic system resulted in accumulation in perivascular spaces, including those of the optic nerve (62,63). A CSF-instilled, CSF-based contrast agent was found to diffuse freely through extravascular channels through the optic nerve across glymphatic pathways as seen on MRI in human subjects (61). This adds weight to animal studies that have previously demonstrated continuity between ocular glymphatics at the ocular lamina cribrosa and CSF cisterns (58,64).

In summary, paravascular glymphatics represent a conduit between the intracranial and intraocular compartments. In other words, glymphatics connect the subarachnoid space and the visual system.

Hypothesis and discussion:

Our concerns regarding pre-existing mechanistic theories of TS were principally based around the lack of a defined conduit between the subarachnoid space and the visual system. In addition, multiple case reports and imaging findings exist that suggest a peripapillary paravascular ingress route that communicates with the intracranial space via the optic nerve.

We hypothesize that reflux of subarachnoid blood along ocular glymphatic pathways is what ultimately leads to intraocular hemorrhage in TS. The glymphatic pathway is the only extravascular anatomical conduit between the subarachnoid space and the retina. Blood and inflammatory mediators in the subarachnoid space may travel along paravascular spaces to enter the globe via peripapillary paravascular spaces when intracranial pressure exceeds intraocular pressure, causing ocular glymphatics to reflux (Figure 2).

Further studies to explore glymphatic reflux in TS may include imaging studies. Heavily weighted T2 MRI sequences in patients with SAH have already demonstrated blood egress through the lamina cribrosa along paravascular pathways, apparently related to the glymphatic system (36). Dedicated MRI sequences with special tracer /contrast agents more suitable in displaying glymphatic channels have been performed in healthy volunteers and patients with neurological disorders including Alzheimer disease, vascular dementia and normal pressure hydrocephalus (65-67). Application of these MRI protocols and tracers in patients with SAH may help explore the exact role of glymphatics and document the reflux we propose. MRI scanners applying heavy T2 weighting with stronger magnetic fields than are in routine clinical use, for example 7.0 Tesla equipped research scanners, may provide yet more detailed imaging to confirm this mechanism of TS.

According to our model, ICP must exceed intraocular pressure for glymphatic reflux to manifest as TS. Consequently, when the opposite occurs, that is intraocular pressure exceeds ICP, intraocular substrates could migrate intracranially. For instance, intraocular injection of silicone oil for retinal detachment in the context of high intraocular pressure has been known to preferentially migrate into intracranial subarachnoid spaces and cerebral ventricles (68-70). This pattern of intracranial spread is suspicious of silicone having migrated through the glymphatic circulation.

Although TS carries a generally favourable visual prognosis, it is associated with significant neurological morbidity and mortality. Whether or not this is due to global glymphatic dysfunction as a result of brain injury remains unclear.

Further relevance of an ocular-cerebral glymphatic circulation:

The essential role of the glymphatic system in neurological disease has been extensively reviewed elsewhere (49). Research of the role of ocular glymphatic physiology and pathology may be of significant value. A role for glymphatic dysfunction in glaucoma has already been proposed (57,64). Furthermore, glymphatic dysfunction has been implicated in the pathogenesis of idiopathic intracranial hypertension, normal pressure hydrocephalus, Alzheimer disease, vascular dementia, ischemic and hemorrhagic stroke (66,67,71-73). Indeed, there may be a role for pharmacological or immunotherapeutic modulation of the glymphatic system not only in the aforementioned but also other in neurological and ophthalmological conditions.

Building on the theme of the ocular-cerebral glymphatic circulation, we asked what other pathological substrates may exploit this selective pathway between brain and eye. A role in the pathophysiology of lymphomas of the CNS is conceivable. Approximately 20-30% of patients with primary CNS lymphoma (PCNSL) have ophthalmic involvement at the time of diagnosis, often affecting both eyes (74). Likewise, 90% of patients with primary intraocular lymphoma (PIOL) go on to develop PCNSL (75). Akin to TS, there is no anatomical explanation to describe simultaneous cerebral and ophthalmic tumors, particularly as they involve both eyes. Furthermore, it is unclear why PCNSL and PIOL do not disseminate beyond the CNS (76). Chemokine receptor expression patterns and CNS immune privilege only marginally explain this phenomenon and many aspects of PCNSL and PIOL pathogenesis remain unclear (76,77).

PCNSL has a predilection for periventricular regions, is closely related to the subarachnoid space, and is often seen tracking along Virchow-Robin spaces (74,75,78,79). In PIOL or

PCNSL with ocular involvement, perivascular sheathing and vascular staining are found often and this is explained by tumor cell presence in retinal vascular walls (77). Dissemination of PCNSL from brain to spinal cord is thought to be related to tumor spread along Virchow-Robin spaces and subarachnoid spaces (80). A case is hereby made for a glymphatic mechanism as the anatomical conduit by which lymphoma spreads from brain to eye and vice versa. This hypothesis may also explain why PIOL and PCNSL remain confined to the CNS. As blood cells spread along perivascular glymphatic channels in TS, so could lymphoma cells. As hypothesized elsewhere, glymphatic systems may have a role in tumor spread and seeding within the CNS (81). Once again, further research will be of interest to determine a role of glymphatic pathways in brain tumors, as with other pathologies.

In 1925, Cushing described CSF as the third circulation of the brain. More recently, in view of the various nuances and paradoxes in CSF physiology and hydrocephalus, a theoretical concept of the "fourth circulation" was put forth (82). Madsen and colleagues described this as "that the passage of pulsations through the brain constitutes a kind of 'fourth circulation'" (82). Pulsatility of cerebral blood vessels is intimately linked with the propulsion of CSF and is the main driver of glymphatic flow (51). As a physiological system linking CSF to interstitial fluid and vascular pathways, glymphatics fulfil the aforementioned criteria of constituting or contributing to a fourth circulation. Further research is indicated as our understanding of CSF dynamics and the pathophysiology of hydrocephalus in general may benefit from a better appreciation of glymphatic circulation.

Conclusion:

We propose the hypothesis of glymphatic reflux as a novel pathomechanism of TS. The glymphatic system is the only candidate theory that offers a mechanism by which subarachnoid blood may enter the globe via the optic nerve. The wider role of glymphatic pathology in ophthalmological and neurological disorders requires further exploration. Neurosurgically significant pathologies such as hydrocephalus and CNS tumors may be intricately linked with glymphatic circulation and further research is indicated.

Appendix: Search Strategy

The following databases were searched: MEDLINE, PubMed and Web of Science from inception to January 2021. Additional relevant papers were found by hand in trial registers or other grey literature sources. Search terms used included Terson, Terson syndrome and Terson's syndrome; subarachnoid, intracerebral, intraparenchymal and intraventricular h(a)emorrhage; traumatic brain injury, brain trauma, head injury, craniocerebral trauma; intraocular, vitreous, subhyaloid, preretinal, subretinal h(a)emorrhage or bleed(ing).

Based on their titles and abstracts, the articles retrieved were screened independently by three reviewers (AK, AMG and HAI). Eligible studies were further analysed. Any disagreement between the reviewers over the eligibility of studies was resolved through discussion.

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Declarations: Authors report no disclosures relevant to the manuscript

Conflicts of interest: None

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Figure legends:

Figure 1: Fundus photographs of TS, Valsalva retinopathy and CRVO illustrating similarities and differences between pathologies. (a) TS of the right eye in a patient with SAH complicated by multiple preretinal and intraretinal hemorrhages. (b) CRVO of the right eye featuring venous tortuosity, dilatation and widespread flame-shaped intraretinal hemorrhages. (c) A patient with left Valsalva retinopathy featuring a large preretinal hemorrhage at the posterior pole (31).

Image (a) was originally published in the Retina Image Bank. Author: Young-Gyun Kim, Photographer: Shin Ji-Young. Terson Syndrome. Retina Image Bank. 2013;5097. © the American Society of Retina Specialists.

Image (c) from Reference 31 - Cai and Han, 2017. Reprinted from Ophthalmology Retina, 1(5), CX Cai, IC Han, Cough-Induced Valsalva Retinopathy, p427, Copyright 2017, with permission from Elsevier.

Figure 2: Hypothesis to explain glymphatic reflux as the substrate of intraocular hemorrhage in Terson Syndrome. In physiological conditions, ocular glymphatic flow terminates in meningeal lymphatics. When intracranial pressure exceeds intraocular pressure, subarachnoid blood in skull base cisterns enters the lamina cribrosa through paravascular glymphatic channels to cause Terson Syndrome.

Figure 1(a)

Click here to access/download;Figure;Figure 1(a) ASRS-RIB-Image-5097 Terson right eye.jpg

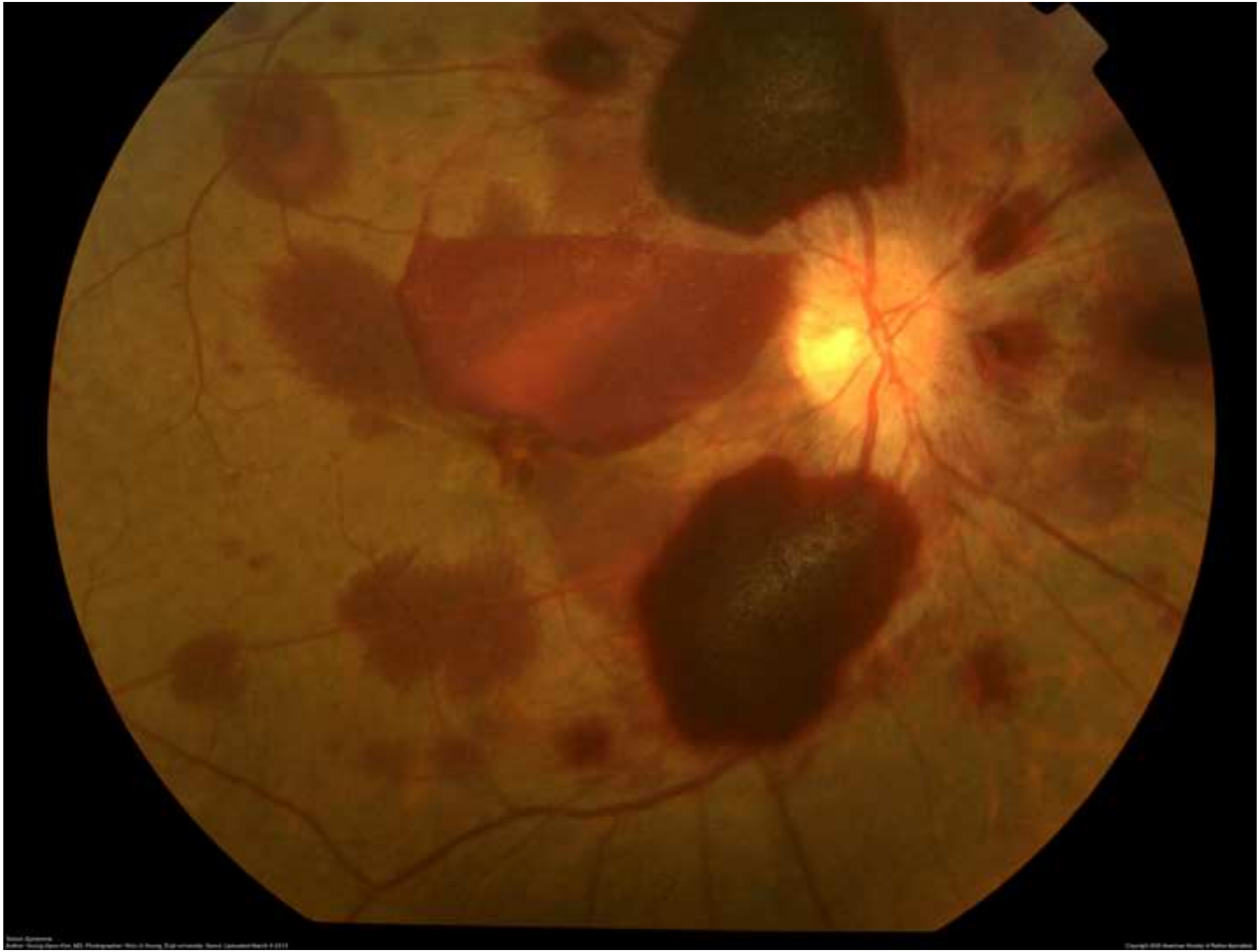


Figure 1(b)

Click here to access/download;Figure;Figure 1(b) CRVO right eye.jpg

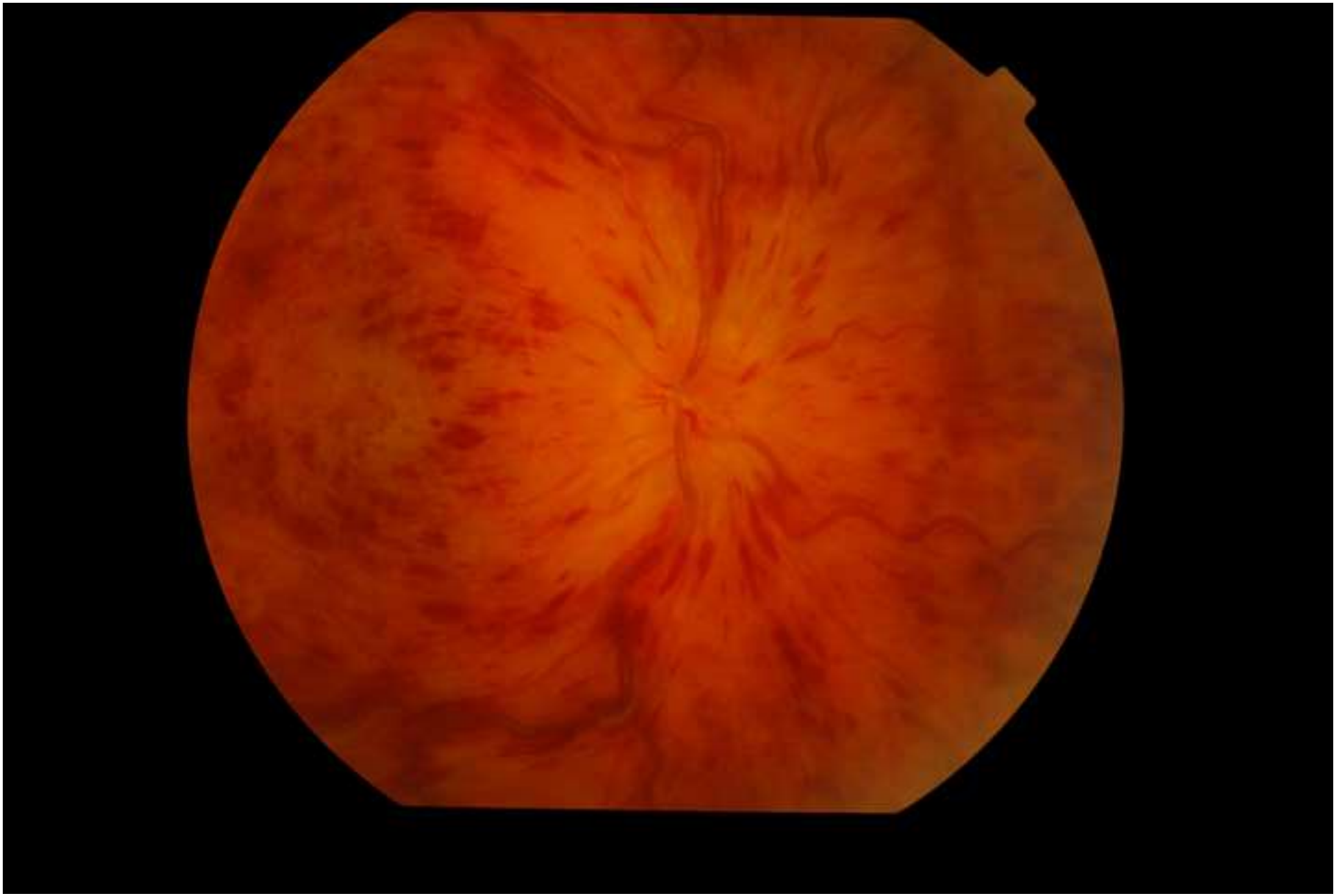


Figure 1(c)

Click here to access/download;Figure;Figure 1(c) Valsalva retinopathy left eye TIFF.tif

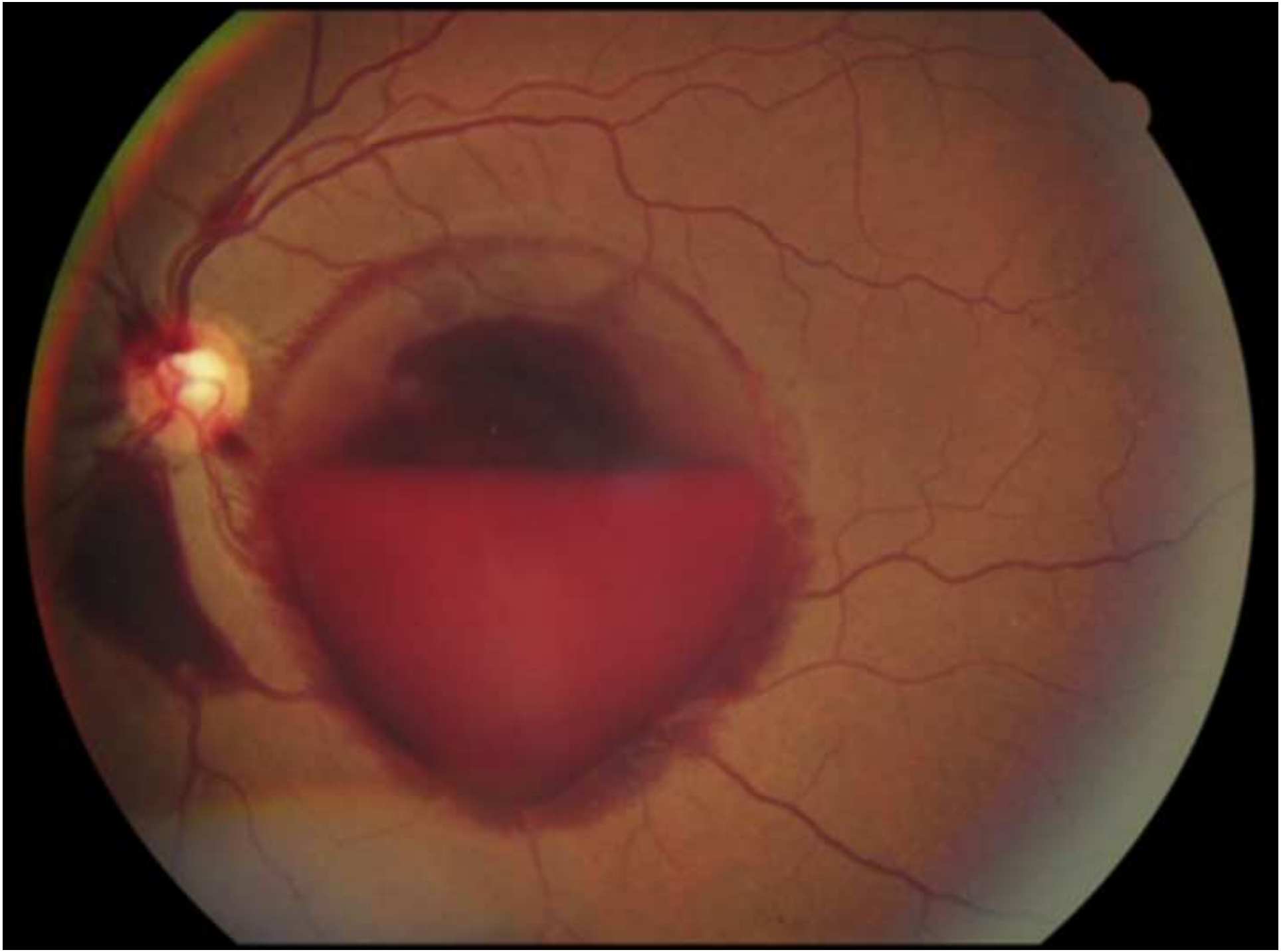
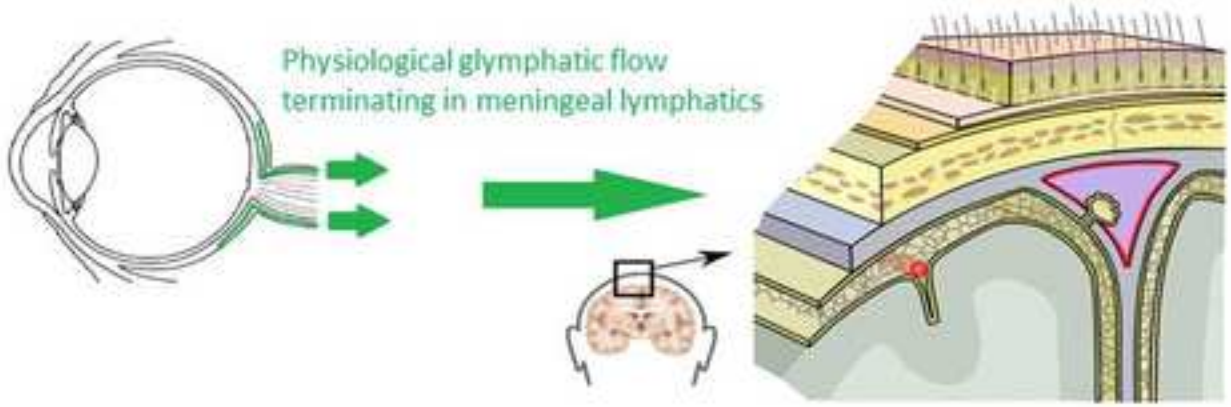


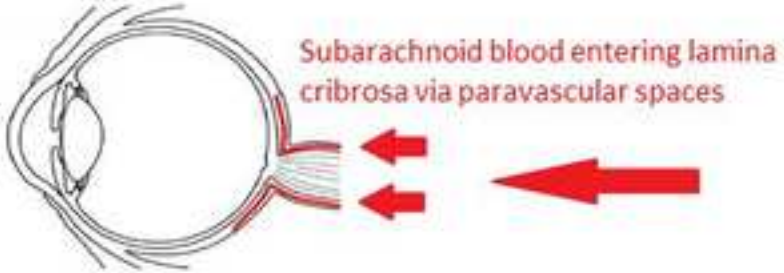
Figure 2

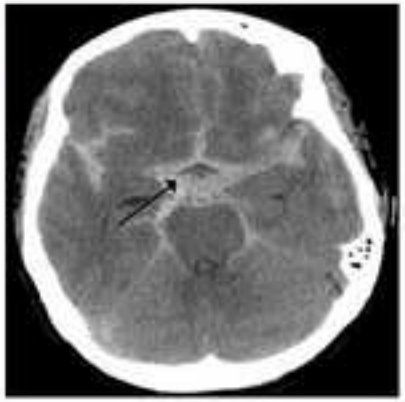


Physiological ocular glymphatic flow

Intraocular pressure > Intracranial pressure

Intracranial pressure > Intraocular pressure





Glymphatic reflux when ICP is raised, causing subarachnoid blood to enter eye

Mechanisms of retinal bleeding:

- Raised pressure
- Bloodborne Inflammatory mediators