Special Original Article - A Tribute to Prof Sohan Singh Hayreh

Pathogenesis of Terson syndrome

Sohan S Hayreh

Purpose: The aim of this experimental study was to investigate the pathogenesis of Terson syndrome (TS), which currently is controversial. **Methods:** The central retinal artery (in 39 orbits), posterior ciliary arteries (in 8 orbits), and central retinal vein (CRV in 21 orbits) were occluded in rhesus monkeys by exposing them to lateral orbitotomy. Fundus examination and fluorescein fundus angiography were performed before and immediately after cutting the vessels and serially thereafter during the follow-up period. The rationale of the experimental study design is discussed. **Results:** In eyes with central retinal artery occlusion, retinal hemorrhages were seen soon after the procedure in 7 eyes, and on follow-up in a total of 15 eyes. In posterior ciliary artery occlusion, retinal hemorrhages were seen soon after the procedure in one eye, and on follow-up in a total of three eyes. In eyes with CRV, all eyes had extensive scattered retinal hemorrhages. **Conclusion:** The findings of this experimental study, and my basic, experimental, and comprehensive clinical studies on CRVO, suggest the following concept of the pathogenesis of TS: Compression of the CRV plays a crucial role in the development of TS. The CRV is compressed, as it lies in the subarachnoid space of the optic nerve sheath, by raised cerebrospinal fluid pressure and/or accumulated blood. This results in retinal venous stasis and raised venous pressure in the retinal veins, leading to venous engorgement, rupture of the retinal capillaries and retinal hemorrhages. The clinical importance of compression of the CRV and not occlusion of CRV in TS is that optic nerve sheath decompression by opening it and releasing the blood and raised cerebrospinal fluid (CSF) pressure, would result in immediate decompressing of the CRV in the subarachnoid space and restoration of normal circulation and prevent visual loss.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1359_22

Quick Response Code:

Key words: Central retinal vein compression, retinal hemorrhages, subarachnoid hemorrhage, Terson syndrome

Terson syndrome (TS) was originally described by Moritz Litten in 1881[1] as vitreous bleeding following aneurysmal subarachnoid hemorrhage (SAH); its name "Terson syndrome" (TS) was given in 1900 by French ophthalmologist Albert Terson.[2] The pathogenesis of TS is highly controversial. It has been reported that the higher the intracranial pressure, the higher the risk of developing TS.[3,4] The source of retinal hemorrhages and their connection to the SAH in TS has been deliberated extensively and is still contentious.

Postulated theories about the pathogenesis of TS

There is voluminous literature dealing with the pathogenesis of TS. Many theories have been postulated to explain it. Following is a summary of them, and the fundamental flaws in them.

An early theory suggested that blood simply tracks from the intracranial subarachnoid space into the optic nerve sheath, then penetrates the sclera in the porous region, and finally appears in the vitreous space within the eyeball. However, no such pathway exists,[5] and that invalidates this theory.

It has been postulated that a sudden rise in the intracranial pressure (ICP) associated with SAH results in the rupture of retinal vessels. If a sudden rise of ICP caused the rupture of retinal vessels, then TS would develop immediately, as in Valsalva retinopathy; however, TS can develop several days or even weeks after the sudden rise in ICP.[6] An acute rise in the ICP is found in several conditions without any rupture of retinal vessels. Furthermore, no mechanism is known by which an acute rise in ICP can cause the rupture of retinal vessels.

It has been proposed that the blood may enter the vitreous cavity around the retinal vessels near the optic disc, and inside the eye, the blood may spread in the intra-retinal, sub-internal limiting membrane, or along the retinal vessels. There is no anatomical basis for blood to travel from the subarachnoid space of the optic nerve sheath to the optic disc and the eyeball along the retinal vessels.[5]

It has also been reported that blood around the optic nerve in the subarachnoid space infiltrates the intraocular space through the perivascular space around the central retinal vessels within the optic nerve. However, the perivascular space around the central retinal vessels within the optic nerve does not extend

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Received: 11-Jun-2022 Revision: 23-Aug-2022
Accepted: 27-Sep-2022 Published: 30-Nov-2022

Cite this article as: Hayreh SS. Pathogenesis of Terson syndrome. Indian J Ophthalmol 2022;70:4130-7.

into the eyeball.[5] Thus, blood in the subarachnoid space cannot get to the retina.

Recently, the glymphatic system has been proposed to play a role in TS.[7] Kumaria *et al*.[7] hypothesized that the glymphatic pathway is the only extravascular anatomical conduit between the subarachnoid space and the retina. They put forward the view that raised ICP causes subarachnoid blood in the skull to be refluxed through glymphatic channels into the globe, resulting in intraocular hemorrhage. However, the existence of glymphatic channels from the subarachnoid space to the retinal vessels in the eye has never been demonstrated so far.[8]

Other reports have described occlusion of the central retinal vein (CRV) by a variety of mechanisms in TS. These include the following:

1. Raised ICP, due to SAH, results in seepage of cerebrospinal fluid (CSF) through the optic canal into the optic nerve sheath and leads to the dilation of the retrobulbar optic nerve sheath and compression of the CRV. My study[9] of the optic nerve sheath in 20 rhesus monkeys and 80 human optic nerves showed that the dilated retrobulbar portion of the optic nerve sheath is a normal anatomical feature of the sheath in monkeys and humans, and not a pathological change. The outer layer of the optic nerve sheath is a thick fibrous tissue and not elastic tissue; therefore, it cannot distend by the increased pressure in the sheath.
2. According to another theory, a sudden rise in ICP with SAH results in compression of the CRV and retinal venous stasis, and retinal hemorrhages. According to this theory, a sudden rise in ICP is thought to decrease venous return to the cavernous sinus from the veins that drain the globe.

All these theories are inadequate to explain the exact mechanism of the association between SAH and retinal hemorrhages in TS. That was my basis to conduct this experimental study.

Methods

The study was conducted in 68 rhesus monkeys by experimental occlusion of the central retinal artery (CRAO in 39 orbits), posterior ciliary arteries (PCAO in 8 orbits), and CRV (CRVO in 21 orbits) [Fig. 1]. The question arises: what was the rationale of my experimental study design?

Rationale of the experimental study design

I have been conducting basic, experimental, and clinical research on ocular vascular occlusive and optic nerve disorders for about 70 years. On rare occasions, in my past research studies, I experienced totally unexpected findings. Out of scientific curiosity, I explored those mysteries further; which in some cases led to new seminal discoveries. For example, in 1963, I experimentally investigated the pathogenesis of optic disc edema in raised ICP.[10] The most popular theory at that time was that the raised intracranial CSF pressure, leading to raised CSF pressure in the optic nerve sheath, resulting in compression of the CRV and consequent optic disc edema production. I decided to experimentally explore this by occluding the CRV. That led to the seminal discovery that CRVO is of two types: *nonischemic* and *ischemia*,[11] with very different clinical features, visual outcomes, complications, prognoses, and management.[12] Currently, this is the accepted concept. My studies on the pathogenesis of optic disc edema in raised ICP finally showed that the optic disc edema was due to axoplasmic flow stasis.[10]

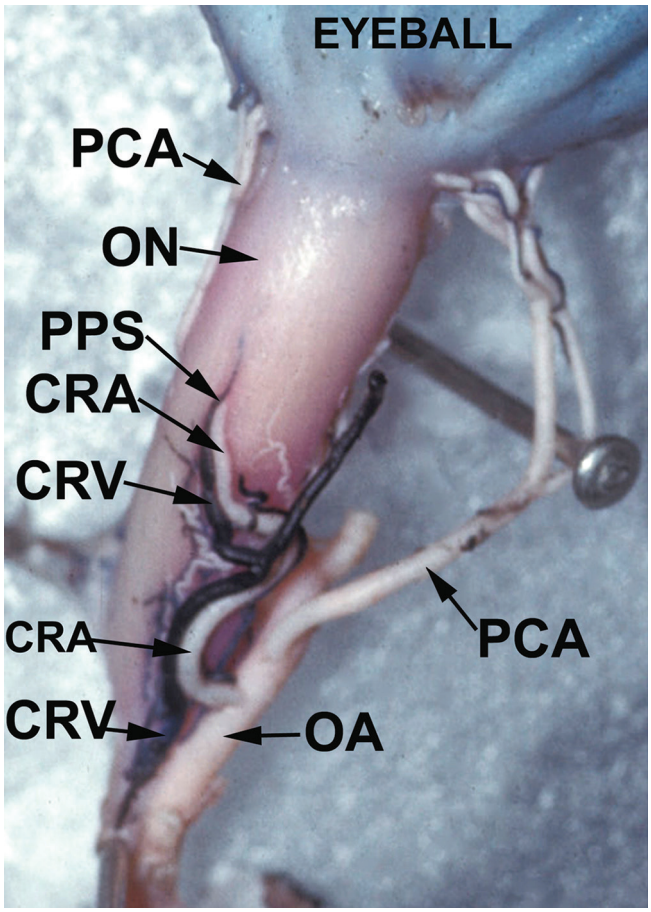

Figure 1: Inferior surface of the intraorbital part of the optic nerve (ON), shows the central retinal artery (CRA), central retinal vein (CRV), and posterior ciliary arteries (PCA) and their site of penetration into the sheath of the optic nerve. OA = ophthalmic artery. PPS = point of penetration of sheath by the central retinal artery and vein

Several years ago, when I experimentally occluded the central retinal artery occlusion (CRAO) in rhesus monkeys, I found occasional eyes developed a dome-shaped macular hemorrhage, typically seen in TS. That was a completely unexpected, finding, because it is well established that CRAO always produces retinal infarction, but never retinal hemorrhages. This unexpected finding prompted me to explore further in the present study.

The central retinal artery, posterior ciliary arteries, and CRV were exposed by lateral orbitotomy in rhesus monkeys. In most monkeys, after orbitotomy slow leakage of blood from the orbital venous plexuses kept obscuring my views of these vessels. To have a clear view of the vessels, first I needed a bloodless clear field; for that, all animals required a tamponade of the orbital apex by cotton swabs plugs – that also exerted pressure on the various tissues at the apex of the orbit and the CRV lying outside the optic nerve posteriorly [Fig. 1]. The exerted compression needed by the tamponade to achieve a bloodless clear field varied markedly among different orbits; which caused a variable degree of compression of the CRV. There was no clinical method to calibrate and evaluate the

extent of CRV compression during surgery. Post-op fundus examination showed markedly variable retinal venous dilation in all these eyes– definite proof of CRV compression.

The central retinal arteries and CRV were separated from one another by microdissection near their site of penetration into the optic nerve sheath (PPS in Fig. 1). The central retinal artery or CRV were occluded at their points of entry/exit at the optic nerve sheath, and posterior ciliary arteries were occluded at their point of entry into the eyeball [Fig. 1].

Color fundus photography and fluorescein fundus angiography were performed before, soon after occluding the vessels, and serially thereafter to document the fundus and vascular changes, including retinal findings and ocular circulation.

Results

Retinal hemorrhages following CRAO

Fig. 2 shows some examples of various types and locations of hemorrhages in this group. There were 39 eyes in this group. Retinal hemorrhages were seen soon after the procedure in 7 eyes, and on follow-up in a total of 15 eyes (38%). The hemorrhages were in the macular region in seven [Fig. 2a, b, c, f], perimacular region in seven [Figs. 2c, d, f], the peripheral retina in four [Figs. 2c, e, f], and on the optic disc in six [Figs. 2g and h]. The eyes also had engorged retinal veins.

The follow-up length of the eyes after the procedure was 3–350 (median 61.5 ± 57.2) days.

Retinal hemorrhages following posterior ciliary arteries occlusion

There were eight eyes in this group. Retinal hemorrhages were seen soon after the procedure in one eye, and on follow-up in a total of three eyes (37.5%). Figs. a and b in Fig. 3 show examples of fundus changes, such as some hemorrhages and engorged retinal veins, in this group. Fig. (b) also shows choroidal infarcts. The hemorrhages were in the macular region in two, and on the optic disc in two.

The follow-up length of the eyes after the procedure was 15–150 (median 98 ± 49.1) days.

Retinal hemorrhages following central retinal vein occlusion (CRVO)

Fig. c and d in Fig. 3 show examples of fundus change due to CRV—including some examples of various types and locations of retinal hemorrhages in this group. Fig. (c) also shows cottonwool spots, as are seen in ischemic CRVO. Fig. (d) shows a large macular subhyaloid hemorrhage, in addition to other retinal hemorrhages. Many of these eyes also developed macular and optic disc edema.

There were 21 eyes in this group. All eyes developed engorged retinal veins and scattered retinal hemorrhages, such

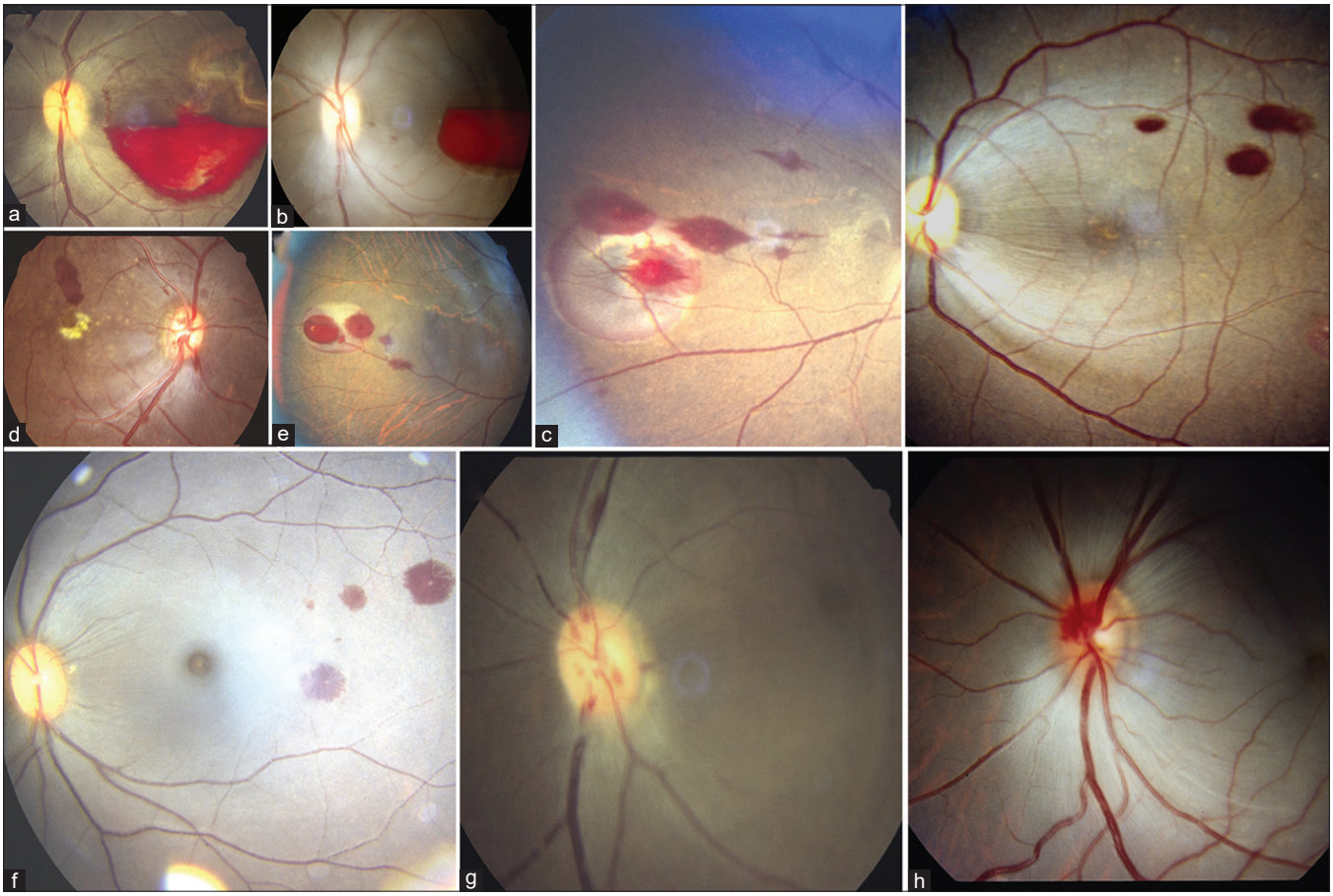

Figure 2: Eight eyes with central retinal artery occlusion show retinal hemorrhages and engorged retinal veins. (a and b show dome-shaped macular hemorrhage); (d, g, and h show disc hemorrhage) (c,e and f show peripheral hemorrhages)

as those seen in TS. It could be argued that in my previous report of six animals with identical CRVO procedures,[11] there were engorged retinal veins, but developed little or no retinal hemorrhages. How to reconcile this discrepancy?

My first CRVO study[11] was in young healthy monkeys, and CRVO was of two types: (a) with CRVO alone, and (b) with both CRV and central retinal artery occluded. CRVO alone produced engorged retinal veins and little or no retinal hemorrhages, that is, "*nonischemic CRVO*." However, CRVO combined with central retinal arterial occlusion (ischemia) produced engorged retinal veins and extensive retinal hemorrhages, that is, "*ischemic CRVO*." As I mentioned above, that led to the seminal discovery that CRVO is of two types: *nonischemic* and *ischemia*.[11]

By contrast, the current CRVO study was done in old, atherosclerotic, and hypertensive monkeys. It is well-established that these general health problems collectively make humans and monkeys predisposed to ischemic vascular disorders. Because of those associated ischemic factors, CRVO in this group of monkeys resulted in the development of "*ischemic CRVO*," with extensive retinal hemorrhages [Fig. 3c, d] and even cotton wool spots [Fig. 3c].

Why did I have old, atherosclerotic, and hypertensive monkeys? My primary research interest deals with ocular vascular occlusive diseases. It is well-established that ocular vascular occlusive disorders are most seen in elderly, atherosclerotic, and hypertensive persons. To have experimental research findings valid to humans from this group of monkeys, I decided to produce a large colony of rhesus monkeys with old age, atherosclerosis, and hypertension.

Discussion

Many theories have been postulated to explain the development of retinal hemorrhages in TS, but all of them have a variety of problems. To understand the pathogenesis of TS, it is essential to consider the following issues.

TS in 1900 was characterized by the presence of intravitreal hemorrhage. This statement by Terson in 1900 is no longer valid; since then, several studies have reported isolated intraretinal

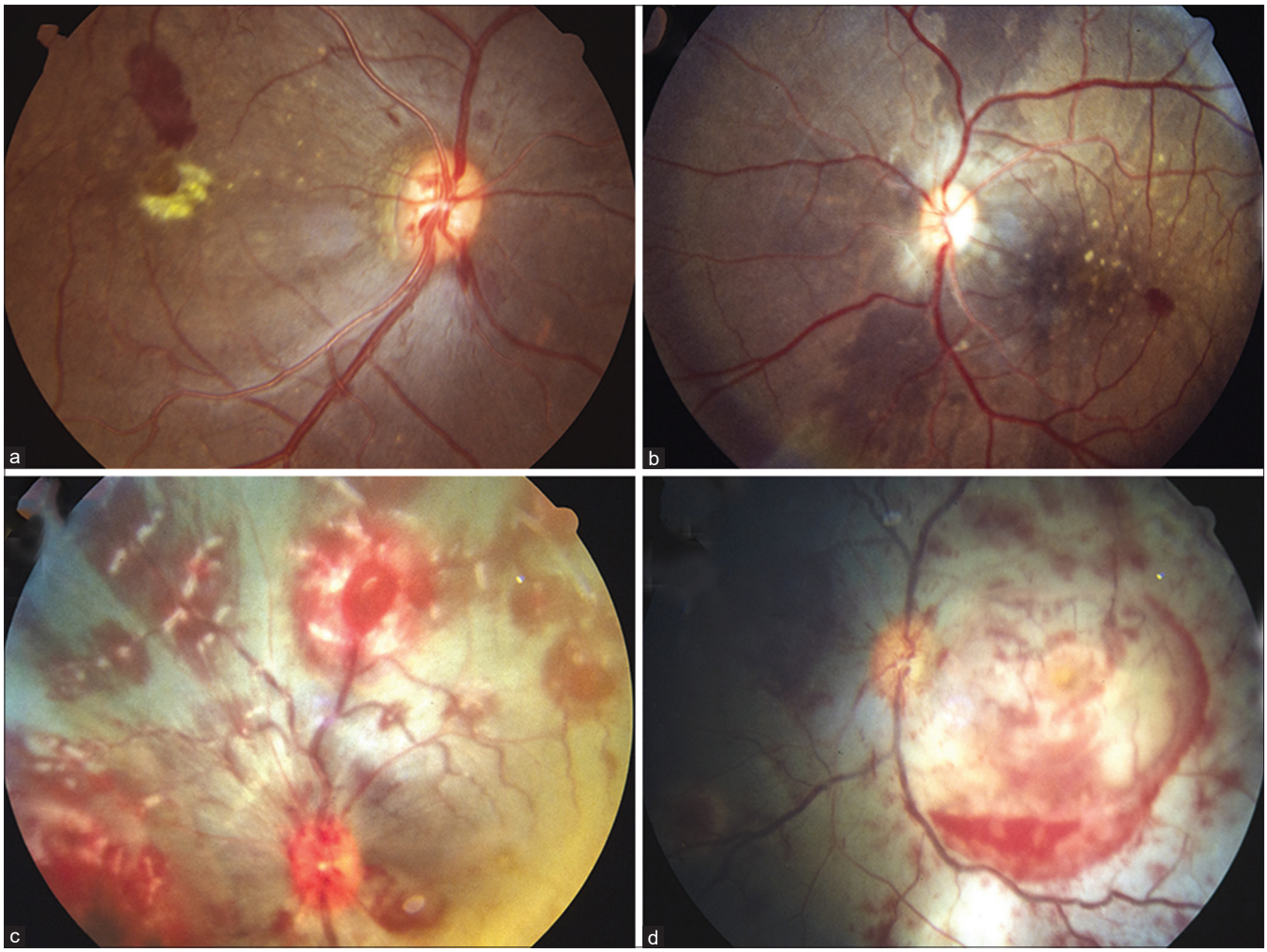

Figure 3: (a and b) Two eyes with posterior ciliary artery occlusion. (a) Shows macular and disc hemorrhages, drusen, and engorged retinal veins. (b) Shows choroidal infarcts and watershed zone between the two areas of choroidal infarcts; macular hemorrhage and drusen, and engorged retinal veins. (c and d) Two eyes with central retinal vein occlusion. (c) shows extensive retinal and optic disc hemorrhages and cotton wool spots, and engorged retinal veins (Ischemic CRVO). (d) shows macular subhyaloid hemorrhage, retinal hemorrhages, and engorged retinal veins

hemorrhages in TS as well. Scientific knowledge advances constantly, and, with that, definitions of diseases change.

The experiments conducted in this study were aimed at investigating the pathogenesis of TS, not previously published, with the purpose of determining whether TS's pattern of retinal hemorrhages can be caused by experimental vaso-occlusive lesions in the orbit.

Role of the optic canal in TS

The optic canal plays a critical role in the development of TS. In cases of raised ICP or intracranial SAHs, the region of the optic canal is crucial to the dynamics of transfer of the CSF and SAH from the cranial cavity into the sheath of the optic nerve. I investigated the optic sheath anatomy in a comprehensive study of 80 human specimens.[9] The dura of the sheath in the optic canal is firmly bound to the adjoining bone by numerous thick, fibrous bands [Fig. 4], which reduces the space of the sheath to a fine capillary-sized subarachnoid space [Fig. 4b], and the space appears as a trabecular meshwork.

To reach the orbital part of the sheath, the CSF and hemorrhages in the cranial cavity must percolate through the capillary subarachnoid space meshed trabecular network in the region of the optic canal [Fig. 4]. The facility of communication from the cranial cavity to the sheath of the optic nerve shows marked interindividual variations in the canal from free communication to almost none. This has the following implication. Unilateral or bilateral absence of CSF and the number of hemorrhages in the optic nerve sheath may be due to a difference in the facility of their transmission through the canal.

The sheath is a little loose behind the eyeball compared to elsewhere. Due to this looseness of the sheath near the eyeball and the space available here, any blood which enters the sheath from the cranial cavity tends to accumulate in a larger amount in this region behind the eyeball than in the posterior orbital part [Fig. 5].

An anatomical study[13] of 100 human specimens showed that no communication existed between the perivascular space around the central retinal vessels in the optic nerve and the subarachnoid space of the sheath.

Incidence of TS

All patients with SAH do not develop TS. As discussed, the characteristics of the optic canal must play a major role in the incidence of TS.

In my experimental study, the incidence depended upon the amount of CRV compression by the tamponade at the apex of the orbit. That varied markedly.

Laterality of TS in Relation to Subarachnoid Hemorrhages

TS may be unilateral or bilateral in patients, with a rise in ICP and the amount of SAH. Although there is a bilateral rise in ICP and SAH, intraocular hemorrhages are usually present in only one eye. Regarding this issue, it is relevant to note the finding of my experimental study[10] in rhesus monkeys, where I produced high CSF pressure and optic disc edema by gradually inflating an intracranial balloon. In that study, the amount of optic disc edema was usually not equal on the two sides and the optic disc edema generally appeared first on the side of the intracranial balloon and was also more marked on that side. To

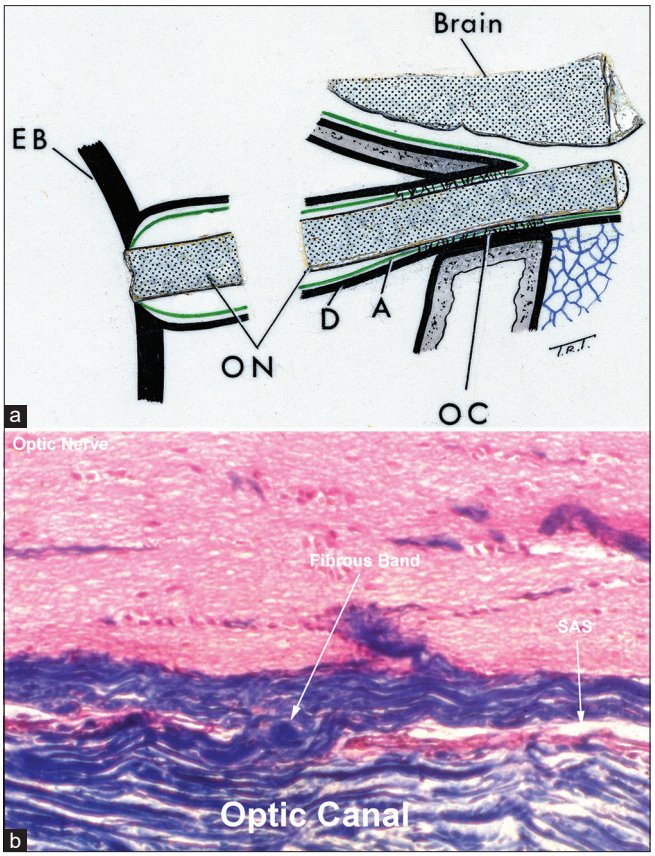

Figure 4: (a) Schematic diagram showing various regions of the sheath of the optic nerve and multiple fibrous bands in the optic canal. A = Arachnoid; D = Dura; EB – Eyeball; OC = Optic canal; ON = Optic nerve. (b) Longitudinal section of the optic nerve in the region of the optic canal, shows a capillary subarachnoid space (SAS) and fibrous band connecting the optic nerve with the surrounding sheath. (Mason's trichrome staining)

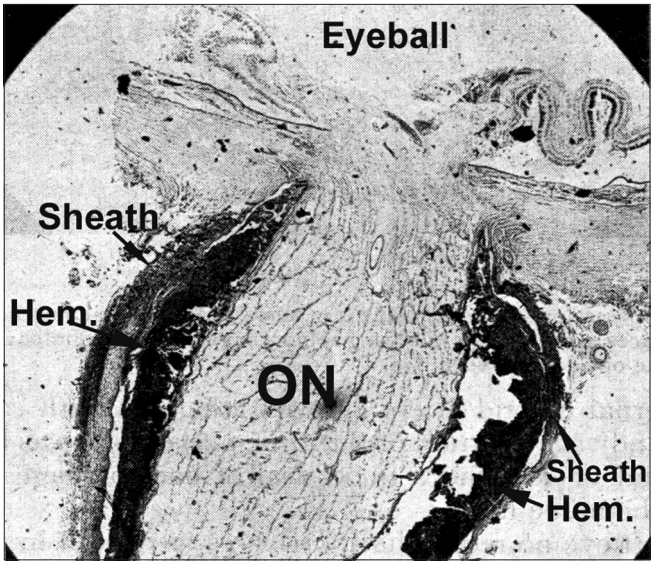

Figure 5: Antero-posterior longitudinal section of the optic nerve in a TS patient. Massive hemorrhages fill the distended subarachnoid space and sheath. Hem. = hemorrhage; ON = optic nerve; sheath = ON sheath. (Reproduced from Br J Ophthalmol 1943;27:383–414.)

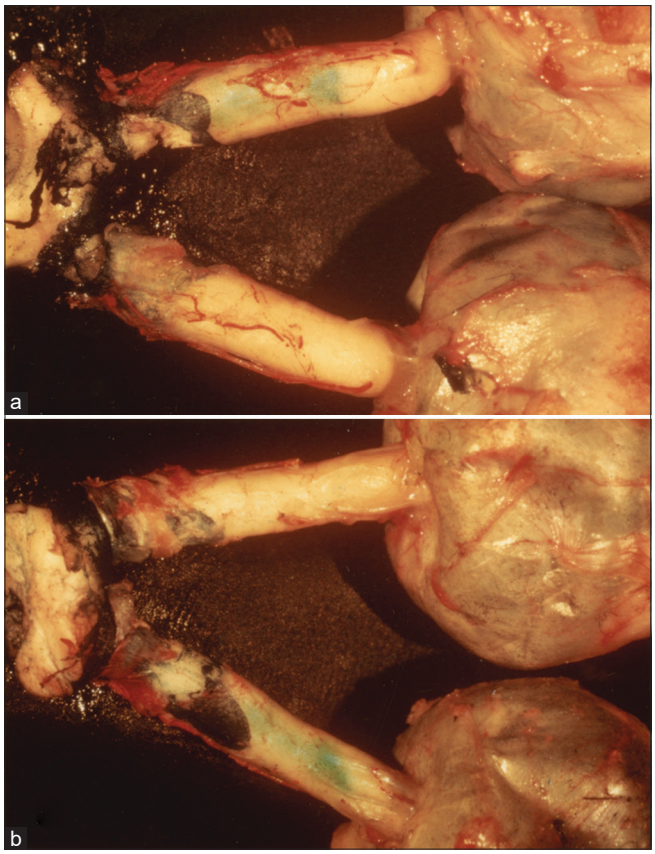

Figure 6: Both eyeballs, optic nerves, and optic chiasm show a distribution of blue dye in the sheath of the optic nerve of a monkey, on the side of an intracranial balloon to produce raised intracranial pressure. (a) From the superior aspect. (b) From the inferior aspect

investigate whether the location of a brain tumor determines the severity of optic disc edema, I injected two monkeys with Prussian blue solution into the cerebellomedullary cistern just before their death. There was a marked difference in the severity of edema of the optic disc between the two sides. More filling of the sheath of the optic nerve with the dye was seen on the side with more marked edema of the disc [Fig. 6], which was also the side of the balloon. A similar mechanism may also be playing a role in the development of unilateral or bilateral retinal hemorrhages in TS despite raised ICP and subarachnoid hemorrhages in TS.

Cause of retinal hemorrhages in TS

The circumstances and amount under which and the number of retinal hemorrhages developing in human CRVO[14] and TS are very different. Evidence suggests that in TS sudden compression of the CRV during its course in the subarachnoid space [Fig. 7], closes the lumen of the vein → raised venous pressure → venous stasis and retinal hemorrhages. In human CRVO, in contrast, there has been progressively increasing narrowing of the CRV lumen by arteriosclerosis/atherosclerosis over months or years, with a gradually and progressively increasing impediment to the retinal venous circulation, which gives time for development collaterals to compensate for the block. However, in the case of TS, in contrast, there is sudden acute compression of the CRV, resulting in the sudden onset of the severe rise of venous pressure and venous stasis, with no time to develop collaterals. In this experimental model, the compression of the CRV was by the tamponade effect of the cotton wool plugs at the apex of the orbit. Therefore, the monkey experimental model used in this study simulates TS and not CRVO. Also, in the human TS, the site of compression of the CRV is by the large, accumulated blood in the optic nerve sheath [Figs. 5 and 7] and raised CSF pressure. The effect of

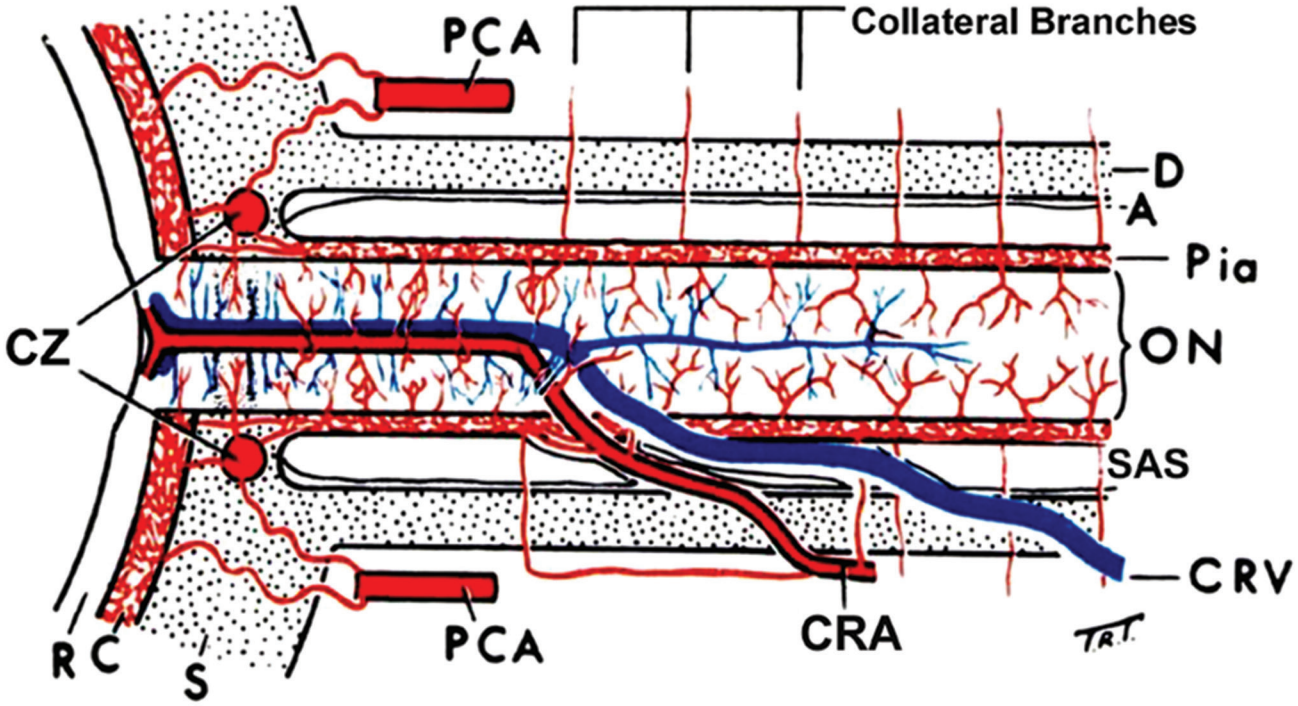

Figure 7: Schematic representation of blood supply of the optic nerve, and course of the central retinal vein in the subarachnoid space of the sheath. A = arachnoid; C = choroid; CRA = central retinal artery; CRV = central retinal vein; D = dura; ON = optic nerve; PCA = posterior ciliary arteries; R = retina; S = sclera; SAS = subarachnoid space

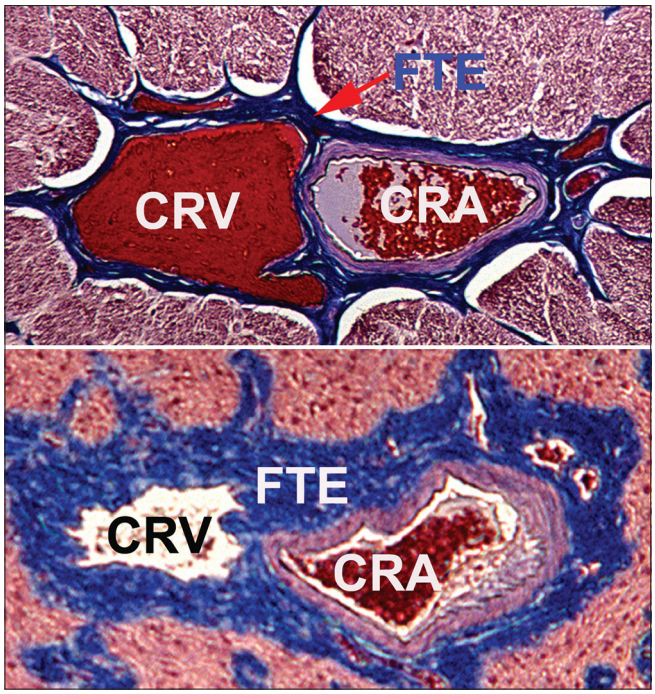

Figure 8: Transverse section through the center of the intraorbital part of the optic nerve showing central retinal artery and vein lying side by side in close apposition, enclosed by a common fibrous tissue envelope

compression of the CRV and the resulting marked retinal venous stasis is identical, irrespective of the site of compression of the vein in the sheath of the optic nerve or at the apex of the orbit.

Relevance of my experimental study to the pathogenesis of TS

To put my novel experimental study in proper perspective for the pathogenesis of TS, one must consider the following facts.

1. Clinical[15] and experimental[16] studies in CRAO have shown that eyes with CRAO immediately develop retinal ischemia and infarction, but NO retinal hemorrhages.
2. PCAO is commonly seen in giant cell arteritis[17]; those eyes show choroidal infarction and arteritic anterior ischemic optic neuropathy, but no retinal hemorrhages. Similarly, experimental[18] PCAO developed choroidal infarction, but no retinal hemorrhages.

Therefore, the question arises, why did experimental CRAO and PCAO in this study show development of retinal hemorrhages such as those reported in TS [Figs. 2, 3a, b]? For that, one must look at the study design and its relevance to the pathogenesis of TS. In the current experimental study, to stop the constant orbital venous leak during surgery, the apex of the orbit was plugged with cotton wool swabs. Because of the narrow apex of the orbit, which compressed the CRV in the posterior part of the orbit [Fig. 1]; compression of the CRV was confirmed by the development of the retinal venous stasis, marked engorgement of the retinal veins, rupture of retinal venous capillaries and retinal hemorrhages. The almost invariable absence of development of ischemic CRVO confirmed that the CRV was not completely closed.

Pathogenesis of TS

The following concept of the pathogenesis of TS is based on the findings of this experimental study, and on my basic, experimental, and comprehensive clinical studies[12] on CRVO. All this information suggests the following pathogenesis of TS.[19]

Compression of the CRV causing raised central retinal venous pressure and venous stasis plays a crucial role in the development of TS. In the current study, the site of compression of the CRV was outside the optic nerve in the narrow posterior part of the orbit [Fig. 1], by the pressure from cottonwool swab plugs in that narrow orbital region to control oozing of the blood. However, in TS in humans, the CRV, is compressed as it lies in the subarachnoid space of the optic nerve sheath [Figs. 5 and 7]. SAH is associated with intracranial hypertension.[20] It has been reported that the higher the intracranial pressure, the higher the risk of developing TS.[3,4] For transfer of the CSF and SAH from the cranial cavity into the subarachnoid space of the optic nerve sheath, the extent of patency of the optic canal [Fig. 4b], plays a critical dynamic role. Rarely, the optic canal may be completely closed, so that CSF and hemorrhages cannot infiltrate into the optic nerve sheath→ no development of TS. These findings explain the frequency and the amount of blood reaching the optic nerve sheath. The raised CSF pressure and/or accumulated blood in the optic nerve sheath, separately or collectively, compress the CRV in the subarachnoid space in the sheath [Figs. 7 and 8].

It could be argued that my experimental model does not resemble TS, with no blood in the subarachnoid space of the optic nerve sheath; hence it cannot provide the required information about the pathogenesis of TS. However, my experimental study has shown that the basis for retinal hemorrhages in TS is *retinal venous stasis and raised venous pressure produced by compression of the CRV*. In TS patients, a large amount of accumulated blood in the sheath of the optic nerve[Fig. 6], and/or raised CSF pressure in the sheath of the optic nerve, compress the CRV to produce raised pressure in the retinal veins and retinal venous stasis and retinal hemorrhages. In my experimental study, the tamponade at the apex of the orbit compressed the CRV and produced retinal venous stasis, raised venous pressure, and retinal hemorrhages. The crucial issue of CRV compression → retinal venous stasis → raised venous pressure → retinal hemorrhages exactly mimic TS in the experimental study.

Conclusion

The findings of this experimental study, and my basic, experimental, and comprehensive clinical studies on CRVO, suggest the following concept of the pathogenesis of TS: Compression of the CRV plays a crucial role in the development of TS. The CRV is compressed, as it lies in the subarachnoid space of the optic nerve sheath, by raised cerebrospinal fluid pressure and/or accumulated blood leading to retinal venous stasis and raised venous pressure in the retinal veins, retinal venous engorgement, rupture of the retinal capillaries and retinal hemorrhages.

The clinical importance of compression of the CRV and NOT occlusion of CRV in TS is that the optic nerve sheath decompression by opening it and releasing the blood and raised CSF pressure, would result in immediate decompressing of the CRV in the subarachnoid space and restoration of normal circulation and prevent visual loss, a phenomenon like the optic nerve sheath decompression in raised CSF pressure relieving the optic disc edema in intracranial hypertension.[10]

Financial support and sponsorship

Supported by grant EY-1576 from the National Institutes of Health, USA.

Conflicts of interest

There are no conflicts of interest.

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