Cerebrospinal fluid pressure and the eye

William H Morgan,1 Chandrakumar Balaratnasingam,1 Christopher R P Lind,2 Steve Colley,3 Min H Kang,1 Philip H House,1 Dao-Yi Yu1

ABSTRACT

Cerebrospinal fluid pressure (CSFP) interacts with intraocular pressure (IOP) and blood pressure to exert a major influence upon the eye, particularly the optic nerve head region. There is increased interest regarding the influence of CSFP upon disorders affecting this region, in particular glaucoma and idiopathic intracranial hypertension. Additionally, a high proportion of astronauts develop features similar to idiopathic intracranial hypertension that persist for years after returning to Earth. The factors that affect the CSFP influence upon the optic nerve and globe are likely to influence the outcome of various ophthalmic disorders.

INTRODUCTION

The optic nerve head separates the central nervous system and cerebrospinal fluid pressure (CSFP) from the intraocular structures and intraocular pressure (IOP). The lamina cribrosa and its constituent neural, vascular and connective tissue elements are very sensitive to alterations in pressure across this region, with follow-up effects into the rest of the eye. Such changes influence the occurrence of glaucoma, idiopathic intracranial hypertension and venous occlusions.

ANATOMY

The optic nerve subarachnoid space (ONSAS) surrounds the optic nerve as it leaves the cranial cavity up to the posterior globe where it is terminated anteriorly by the sclera.1 Along its path there are numerous trabeculae and septae whose shape varies with some thickening towards the termination of the subarachnoid space (figure 1).2 Internal to the ONSAS lies the pia mater and then the optic nerve proper. Externally lies the dura mater and intracranial orbital tissue. On closer examination using tracer and specialised immunohistochemical stains, lymphatic structures containing CSF material can be identified in the tissue surrounding the termination of the ONSAS.1–5 These lymphatic structures appear more prominent in lower mammals, such as rodents.6 7

PRESSURES AND DIFFERENCES

IOP averages 15 mm Hg with a normal range of 10–21 mm Hg in most populations2 and is generated by the balance between production from the ciliary body and egress through the trabecular meshwork and uvea. There is a small increase with age from 15.8 mm Hg at age 50 years to 16.1 mm Hg at age 80 years, although this effect is linked to the rise in systemic blood pressure.8 9

CSF is formed in the choroid plexus and flows through the ventricular system into the subarachnoid space where some is thought to flow down the ONSAS traversing the trabeculae and septae present in it.10 The bulk of CSF is thought to drain out through the arachnoid granulations, however, up to 30% of CSF drains out via lymphatics in the olfactory bulb and ONSAS in lower mammals11 with an unknown proportion flowing out through these systems in primates and humans (figure 1). The CSFP, like IOP, is pulsatile having a small phase difference with peak IOP lagging behind peak CSFP but their trough pressures coincide.12 Unlike IOP, the CSFP is markedly altered by postural changes, with the normal range of CSFP in the lateral decubitus position being 5 to 15 mm Hg but in the sitting position being −10 to 0 mm Hg at eye level.13 Although IOP doesn’t change as much as CSFP with postural change it does increase by 2–4 mm Hg when lying down from sitting.14–16 Hence, one should take into account the posture when interpreting results of CSFP measurements. CSFP tends to reduce with age in adulthood, from mean 11.5 mm Hg in less than 50 year-olds to 9.0 mm Hg in 70 year-olds.15

Production and drainage of CSF and aqueous are influenced by hydroxysteroid dehydrogenase with increased CSFP effect in obesity.16 Stimulation of certain regions of the rat brain increases IOP, CSFP and blood pressure to varying degrees and varying latency.17 It is likely that other humeral and neural stimuli influence CSFP and IOP.

MEASUREMENT OF CSFP

Currently, invasive techniques involving lumbar puncture or cranial burr holes are required for CSFP measurement. The development of non-invasive techniques for CSFP measurement would be a major advance for diagnosis and monitoring of various disorders. Previous attempts using transcranial Doppler, tympanic membrane reflectivity and optic nerve sheath diameter by ultrasound or MRI have given largely inaccurate measurements.18 19 The two most promising avenues being currently explored are refinement of ophthalmodynamometric measures of venous pulsation pressure (figure 2) and balancing intracranial/orbital ophthalmic artery flow velocities.20–22 Some groups have begun using multivariate algorithms incorporating blood pressure and body mass index as indirect indicators of CSFP; however one should remain aware of the limitations and dependencies of this technique.23 24

RELATIONSHIP BETWEEN ONSAS PRESSURE AND INTRACRANIAL PRESSURE

It has been assumed that ONSAS pressure is equivalent to intracranial pressure and is likely to be the case in healthy animals.25 However, the work of Killer and coauthors clearly demonstrates the
presence of significantly large trabeculae, resembling fenestrated sheets along the ONSAS pathway (figure 1) and that in some conditions, such as normal tension glaucoma and others, there is relative stasis of CSF flow along this pathway.27 They may alter fluid flow along the ONSAS although the flexibility of the septae may not impede pressure transmittance. However, significant trabecular changes such as following meningitis or other diseases may effectively block CSF flow and cause a disruption of pressure transmittance. In the normal situation we tend to assume that the ONSAS pressure is equivalent to intracranial pressure, however, another factor must be considered and this is the orbital tissue pressure found to be 2.6–4.4 mm Hg in the supine position using needles inserted into the orbit.28 29 Tissue pressure measurement using needle insertion tends to give a slightly higher value than when less invasive micropipette techniques are used,30 so true orbital tissue pressure may be lower than these values. When a person is sitting or standing and the intracranial pressure falls to zero or below at eye level, this is likely to be transmitted along the ONSAS. If orbital tissue pressure is greater than the intracranial pressure then it will tend to compress and, hence, collapse the ONSAS and force CSF fluid back into the intracranial compartment. It may also compress regions of the ONSAS causing loculation with lack of pressure transmission. This presumed influence of orbital tissue pressure is supported by experimental data (figure 2) in the dog where below CSFP 0 mm Hg the ONSAS pressure remains at 0 mm Hg.

**Figure 1** Key anatomical features of the optic nerve and eye in relation to the optic nerve subarachnoid space demonstrating the path to the intracranial cavity. The variation in trabeculae is shown and adapted from Killer et al [2]. Glial lamina cribrosa (G) and scleral (collagenous) lamina cribrosa (S) are shown. Central retinal artery is omitted for clarity.

**Figure 2** The relationship of key pressures (±SEM) to intracranial cerebrospinal fluid pressure (CSFP) in the dog. A strong linear relationship is seen between optic nerve subarachnoid space pressure (ONSASP ●), retrolaminar tissue pressure (RLTP ○), venous pulsation pressure (VPP) by ophthalmodynamometry (▲) and intracranial cerebrospinal fluid pressure (CSFP ——) above certain levels. Below these CSFP levels the pressures are constant. VPP is the minimum intraocular pressure (IOP) required to induce retinal vein pulsation. Lines of best fit are included. The difference between ONSAS and RLTP occurs across the pia mater (pia) and the difference between intracranial CSFP and ONSAS pressure is probably due to orbital pressure (orbit).

**THE OPTIC NERVE RETROLAMINAR TISSUE PRESSURE**

The retrolaminar tissue pressure (RLTP) is the interstitial pressure within the optic nerve neural tissue just posterior to the lamina cribrosa. It is not always equivalent to ONSAS pressure with a variable pressure difference occurring across the pia mater indicating some pial elastic effect upon the RLTP.25 When there is a low external pressure the elasticity of the pia mater tends to elevate RLTP and this has been demonstrated experimentally whereby at ONSAS pressures of 0 mm Hg in the dog, the retrolaminar pressure is 3 mm Hg and remains at this level until the ONSAS and intracranial pressures rise to 3 mm Hg or above (figure 2).25 Above this pressure, the tension exerted by
the pia mater reduces and the RLTP tends to equilibrate directly with the ONSAS. When the intracranial pressure is low there are likely to be two mechanisms that buffer the RLTP: the orbital tissue pressure tending to compress the ONSAS and the elasticity of the pia mater.

PRESSURE DIFFERENCE AND PRESSURE GRADIENT ACROSS THE LAMINA CRIBROSA

Tissue pressure measurements across the optic nerve into the retrolaminar region demonstrate a pressure gradient across the lamina cribrosa (figure 3). In the dog, having an IOP of 15 mm Hg and RLTP of 3 mm Hg at CSFP 0 mm Hg with a lamina thickness of 531 μm, the average translaminar pressure gradient (TLPG) is 23 mm Hg/mm tissue and this doubles to 47 mm Hg/mm tissue and this doubles to 47 mm Hg/mm tissue as the IOP rises to 28 mm Hg. In the human, the posterior (collagenous) lamina thickness measures mean 341 μm compared with 339 μm for the combined glial and collagenous lamina. The normal human TLPG is estimated at being between 20 mm Hg/mm and 33 mm Hg/mm tissue, with the true value probably relate largely to the eye resembling a Starling resistor. Monkey and dog experiments demonstrate that an average 8 mm Hg pressure difference between IOP and CSFP is required for the induction of venous pulsation.

ABNORMAL ANATOMY

Enlargement of the ONSAS

The ONSAS width is increased in many patients with raised CSFP. This is a significant relationship and has been used to estimate intracranial pressure non-invasively with several algorithms being published. However, enlargement of the ONSAS may be due to other factors such as loculation of CSF within the ONSAS. These may be part of the explanation for the observation that ONSAS width is increased in some patients with normal tension glaucoma.

Myopia

Persons with high myopia tend to have a thin lamina cribrosa (207 μm) compared with a normal 458 μm. Lamina thickness decreases in patients with moderately advanced glaucoma (201 μm) and patients with myopic glaucoma (78 μm). Such reductions in laminar thickness will double or quadruple the gradient effect of the pressure difference. This is likely to influence progression rates of glaucoma and may explain why patients with severe glaucoma and myopia tend to progress even at lower IOP levels. Persons with myopia also have an increased width of the ONSAS termination and a thin posterior sclera. Recent optical coherence tomography (OCT) scanning using swept source demonstrates that the posterior staphylomata frequently seen in persons with high myopia tend to overlap the region of the enlarged ONSAS termination. The presumed reason for the staphyloma is the pressure difference across the thinned sclera between the IOP compartment and the ONSAS compartment leading to posterior distortion of the sclera just as posterior distortion of the lamina cribrosa occurs in glaucoma. The smaller degrees of optic disc excavation seen in persons with myopia with glaucoma may in part be due to the fact that the gradient is occurring across and causing distortion of the sclera and lamina cribrosa.

Possible septal changes in ONSAS

In patients with idiopathic intracranial hypertension and normal tension glaucoma it has been observed that there is a lower flow of CSF from the intracranial compartment along the ONSAS and this may be due to thickened trabeculae leading to increased

References


Review

The normal human TLPG is estimated at being between 20 mm Hg/mm and 33 mm Hg/mm tissue, with the true value probably relate largely to the eye resembling a Starling resistor. Monkey and dog experiments demonstrate that an average 8 mm Hg pressure difference between IOP and CSFP is required for the induction of venous pulsation. Classical theories had taught that pulsation would be counter phase to IOP and that the systolic peak of IOP that would lead to venous compression, how recent work suggests that CSFP pulse drives venous pulse timing and so has a more dominant effect upon key venous haemodynamic properties. The reasons for spontaneous venous pulsation are complicated and probably relate largely to the eye resembling a Starling resistor. Monkey and dog experiments demonstrate that an average 8 mm Hg pressure difference between IOP and CSFP is required for the induction of venous pulsation.

ABNORMAL ANATOMY

Enlargement of the ONSAS

The ONSAS width is increased in many patients with raised CSFP. This is a significant relationship and has been used to estimate intracranial pressure non-invasively with several algorithms being published. However, enlargement of the ONSAS may be due to other factors such as loculation of CSF within the ONSAS. These may be part of the explanation for the observation that ONSAS width is increased in some patients with normal tension glaucoma.

Myopia

Persons with high myopia tend to have a thin lamina cribrosa (207 μm) compared with a normal 458 μm. Lamina thickness decreases in patients with moderately advanced glaucoma (201 μm) and patients with myopic glaucoma (78 μm). Such reductions in laminar thickness will double or quadruple the gradient effect of the pressure difference. This is likely to influence progression rates of glaucoma and may explain why patients with severe glaucoma and myopia tend to progress even at lower IOP levels. Persons with myopia also have an increased width of the ONSAS termination and a thin posterior sclera. Recent optical coherence tomography (OCT) scanning using swept source demonstrates that the posterior staphylomata frequently seen in persons with high myopia tend to overlap the region of the enlarged ONSAS termination. The presumed reason for the staphyloma is the pressure difference across the thinned sclera between the IOP compartment and the ONSAS compartment leading to posterior distortion of the sclera just as posterior distortion of the lamina cribrosa occurs in glaucoma. The smaller degrees of optic disc excavation seen in persons with myopia with glaucoma may in part be due to the fact that the gradient is occurring across and causing distortion of the sclera and lamina cribrosa.

Possible septal changes in ONSAS

In patients with idiopathic intracranial hypertension and normal tension glaucoma it has been observed that there is a lower flow of CSF from the intracranial compartment along the ONSAS and this may be due to thickened trabeculae leading to increased

References

flow resistance along the ONSAS. Reduced flow may have metabolic consequences by leading to stagnation and reduced removal of toxic metabolites as well as reduced delivery of necessary metabolites to regions, particularly near the termination of the ONSAS. It also may impact upon functioning of the lymphatic and neural tissues within this region.

**Raised translaminar pressure gradient**

The TLPG is most simply described by the difference between IOP and RLTP divided by the distance between the two pressure compartments. Physiologically speaking this means the difference between IOP and ONSAS pressure, allowing for the buffering effects of orbital pressure and the pia mater and divided by the lamina cribrosa thickness. One must also take into account changes in posture if one is using CSFP measurements from the lumbar spine. The caveats concerning general assumptions that the pressures are equivalent between the intracranial compartment, lumbar spine and ONSAS must be considered and weighed carefully at each set of observations. So, an increased TLPG can theoretically be caused by increased IOP and reduced CSFP and also by reduced buffering, that is, a lower orbital tissue pressure and reduced elasticity of the pia mater.

---

**Figure 3**  Micropipette tissue pressure measurements in dog (B) as the micropipette is passed from the vitreous region, the prelaminar region, the lamina and into the retrolaminar optic nerve. Oscillations from the respiratory and cardiac cycles can be seen. Intraocular pressure (A), cerebrospinal fluid pressure (C) and blood pressure (D). Lamina cribrosa was from 558 μm to 919 μm.

**Figure 4**  Central retinal arterial (CRA) (A–C) and central retinal venous (CRV) (D–G) endothelial morphology. Confocal microscope images and schematic outlines demonstrate endothelial morphology in the prelaminar, anterior lamina cribrosa, posterior lamina cribrosa and retrolaminar regions. In the posterior lamina cribrosa region, venous endothelial cells (F) appeared similar to the arterial endothelium displaying spindle-shaped morphology. Scale bar, 50 μm.
monkey model demonstrates glaucoma-like changes to the nerve 
prostaglandin analogues appear to hasten orbital fat atrophy.61 
the RL TP and exacerbate the TLPG. It is of some concern that 
changes may occur leading to reduced pressure buffering prop-
erties around the optic nerve, all of which would tend to lower 
pressure to drop slightly. Orbital tissues tend to atrophy with age leading 
to a rise in CSFP are well known causes of papilloedema 
resulting in compression of the central retinal and other veins, which is compounded by the direct effect of the 
raised CSFP causing elevated intraocular venous pressure.64 
This is thought to account for the venous engorgement, and 
probably results in some reduced anterior optic nerve perfusion 
leading to further damage to the ganglion cell axons. Idiopathic 
intracranial hypertension can be an aggressive disease63 but 
tends to respond well to treatments leading to a reduction in 
overall intracranial pressure or local ONSAS pressure through 
either optic nerve sheath fenestration or ventricular peritoneal 
shunting procedures.66 The relative place of these therapies is 
still somewhat controversial although optic nerve sheath fenes-
tration may be effective in patients with less tractable obstruct-
ion to the ONSAS fluid flow pathway but may not reduce 
intracranial pressure and headache.66 This may account for the 
observation that a single optic nerve sheath fenestration helps 
preserve vision in both eyes of just some subjects. 
Multivariate models for estimating CSFP suggest that CSFP 
elevation may be a risk factor for diabetic retinopathy 
development.23 

Prolonged space flight 
Prolonged space flight by astronauts in space for more than 
6 months frequently (20%) leads to a clinical syndrome bearing 
marked similarities to idiopathic intracranial hypertension with 
papilloedema, also some cotton wool spots as well as choroidal 
folds and a hyperopic refractive shift.67 MRI scans show elev-
od optic disks with an anteriorly shifted macula and dilated 
ONSAS.68 These subjects have increased intracranial pressure, 
which persists for months and years after their return to earth. 
The explanation for this phenomenon is likely to involve the 
fact that in microgravity there is a cephalad fluid shift with 
increased venous pressures and impaired lymphatic flow around 
the head.69 Both factors may conspire to impede CSF outflow 
and lead to an increased average CSFP which is not 
reduced or ameliorated by postural changes, that is, by standing. 
It is difficult to explain why the elevated CSFP persists for so 
long upon returning to earth but the most likely explanation 
involves a permanent change in the outflow system, either 
involving the arachnoidal granulations or the lymphatic outflow 
apparatus around the olfactory bulb, optic nerve and other 
regions. It is possible that in space with CSF stagnation along 
the ONSAS, toxic changes are occurring within the anterior 
optic nerve involving lymphatics leading to some permanent 
change in CSF outflow in this region. 

CONCLUSION 
We hope to have demonstrated that the influence of CSFP upon 
the eye and in particular the anterior optic nerve is significant 
and relevant to common ocular diseases. There is a rapidly 
growing body of literature reporting significant effects of CSFP 
upon glaucoma as well as diseases causing papilloedema and 
other disorders like diabetes. A simplistic understanding incor-
porating only CSFP and IOP without considering lamina cribrosa 
properties, orbital tissue, pia mater and subarachnoid space 
properties is unlikely to give a complete understanding of these 

Figure 5 Swept source OCT of eye with mild glaucoma (A) having a 
collagenous lamina cribrosa (LC) thickness approximating 300 μm. 
Some retrolaminar tissue (RLT) is shown. The choroid (C) and sclera (S) 
are well developed. In the highly myopic eye the sclera (S) is thin, 
particularly under the posterior staphyloma region, which overlies the 
large optic nerve subarachnoid space (ONSAS). One trabecula (T) is 
clearly seen. The collagenous LC is very thin and the RLT is clearly 
seen. Scale bars shown. 

mater leading to greater transmittance of low pressures from 
the orbit and ONSAS directly to the retrolaminar optic nerve. The 
classic example of raised TLPG is that of standard glaucoma 
when IOP is elevated.8 However, much recent work has shown 
that compared with normal subjects, CSFP is reduced in 
primary open angle glaucoma especially in normal tension glau-
coma.38 39 Additionally, recent work using a chronic low CSFP 
monkey model demonstrates glaucoma-like changes to the nerve 
fibre layer with disk rim haemorrhage.60 

As one ages the IOP tends to rise gradually and CSFP tends 
to drop slightly. Orbital tissues tend to atrophy with age leading 
to a sunken orbital appearance in many subjects and pia mater 
changes may occur leading to reduced pressure buffering prop-
erties around the optic nerve, all of which would tend to lower 
the RLTP and exacerbate the TLPG. It is of some concern that 
prostaglandin analogues appear to hasten orbital fat atrophy.61 
It should be clearly stated and understood that the pressures 
within the orbit and the changes of orbital pressure and pia 
mater are poorly understood at present. 

Reduced or reversed translaminar pressure gradient 
Idiopathic intracranial hypertension and other disorders that 
lead to a rise in CSFP are well known causes of papilloedema 
comprising anterior optic nerve swelling with an anterior shift 
of the lamina cribrosa along with retinal vein engorgement and 
tortuosity. Most of these features can be understood by consid-
ering the effect of raised CSFP and subsequent raised RLTP 
leading to a reversed pressure gradient with inhibition of ortho-
grade axonal transport and stasis predominantly within prelami-
nar and anterior (glial) laminar regions but also in the posterior 
(scleral) laminar and retrolaminar regions.62 63 The neural swel-
lings is associated with compression of the central retinal and 
other veins, which is compounded by the direct effect of the 
raised CSFP causing elevated intraocular venous pressure.64 
Reduced or reversed translaminar pressure gradient 
Idiopathic intracranial hypertension can be an aggressive disease63 but 
tends to respond well to treatments leading to a reduction in 
overall intracranial pressure or local ONSAS pressure through 
either optic nerve sheath fenestration or ventricular peritoneal 
shunting procedures.66 The relative place of these therapies is 
still somewhat controversial although optic nerve sheath fenes-
tration may be effective in patients with less tractable obstruct-
ion to the ONSAS fluid flow pathway but may not reduce 
intracranial pressure and headache.66 This may account for the 
observation that a single optic nerve sheath fenestration helps 
preserve vision in both eyes of just some subjects. 
Multivariate models for estimating CSFP suggest that CSFP 
elevation may be a risk factor for diabetic retinopathy 
development.23
common disorders. Some of our understanding is hindered by the lack of an accurate non-invasive measurement method for CSFP.

Correction notice This article has been corrected since it was published Online First. The provenance and peer review statement has been corrected.

Contributors WHM: has contributed to the conception, design and writing of the review manuscript. He has also contributed to the acquisition, analysis and interpretation of the data. CB: has contributed to the acquisition of the data. CRPL: has contributed to the acquisition of the data. D-YY: has contributed to the acquisition of the data. MHK: has contributed to the acquisition of the data. PHH: has contributed to the acquisition of the data. SC: has contributed to the writing of the manuscript. D-FY: has contributed to the acquisition of the data and the manuscript. MM: has contributed to the conception, design and writing of the manuscript. D-YY: has contributed to the acquisition of the data. CRPL: has contributed to the acquisition of the data. D-FY: has contributed to the acquisition of the data.

Funding Supported by an NHMRC project grant 1020367.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES


Cerebrospinal fluid pressure and the eye

William H Morgan, Chandrakumar Balaratnasingam, Christopher R P Lind, Steve Colley, Min H Kang, Philip H House and Dao-Yi Yu

Br J Ophthalmol 2016 100: 71-77 originally published online April 15, 2015
doi: 10.1136/bjophthalmol-2015-306705

Updated information and services can be found at:
http://bjo.bmj.com/content/100/1/71

These include:

References
This article cites 67 articles, 16 of which you can access for free at:
http://bjo.bmj.com/content/100/1/71#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Angle (1006)
- Glaucoma (988)
- Intraocular pressure (1002)
- Neurology (1355)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/