# Optic Nerve Tortuosity on Earth and in Space

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**INTRODUCTION:** Spaceflight Associated Neuro-ocular Syndrome (SANS) results from long-duration spaceflight and presents with a constellation of signs (e.g., optic disc edema, choroidal folds, globe flattening, refractive error shifts, etc.). Optic nerve tortuosity (ONT) has been detected in approximately 47% of astronauts after long-duration spaceflight but has not yet been fully analyzed. This review examines terrestrial ONT in order to better understand how the condition is caused and measured.

**METHODS:** References were identified by PubMed and ScienceDirect searches covering 1955 to October 2018 using the terms "optic nerve tortuosity," "optic nerve kinking," "optic disc torsion," "optic kinking," and "ocular torsion." Additional references were identified by searching relevant articles.

**RESULTS:** ONT measurements have evolved and become more objective. One measure consists of meeting two criteria: 1) lack of optic nerve congruity in >1 coronal section; and 2) subarachnoid space dilation. This "criteria measure" is objective, sensitive, and specific for determining the presence of tortuosity. Another measure is the tortuosity index, which offers additional benefits by measuring the degree of ONT, including the potential to track changes over time. There are numerous terrestrial ONT causes, including intracranial hypertension, hydrocephalus, Chiari malformation, neurofibromatosis, glaucoma, and progeria, among others.

**DISCUSSION:** To accurately measure ONT, it is crucial to adhere to objective, standardized techniques. The tortuosity index offers the potential to measure intraindividual change in ONT. Among the varied conditions associated with ONT, one commonality is pressure change. The impact of intracranial pressure on the vascular system and vice versa may offer insight into what is occurring in space.

**KEYWORDS:** space medicine, ophthalmology, Spaceflight Associated Neuro-ocular Syndrome, optic nerve tortuosity.

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Spaceflight Associated Neuro-ocular Syndrome (SANS)—a constellation of symptoms known by many names, including Visual Impairment and Intracranial Pressure syndrome,[49] Space Obstructive Syndrome,[44] and Microgravity Ocular Syndrome[30]—is characterized by both functional changes in visual performance and structural changes in neuro-ocular anatomy.[21] These changes pose a significant threat to the health of astronauts as well as the success of missions. NASA's Human Research Program has determined that, while acceptable for low Earth orbit and lunar visit/habitation, this risk requires mitigation before a deep space journey or planetary exploration can be attempted.[16] Current research is focused on understanding the etiological mechanisms and risk factors for SANS, developing ways to monitor and measure associated changes, and mitigating risk through the development of preventative or treatment options.

While the current diagnostic criteria of SANS is edema extending ≥270° around the optic disc, the syndrome is associated with a constellation of eye findings, including posterior globe flattening, hyperopic refractive shift, choroidal and retinal folds, and other changes.[21] The Human Research Program's 2017 SANS Evidence Report found that astronauts with optic nerve kinking had a larger optic nerve sheath diameter than those without, and raised the question of whether optic nerve tortuosity is related to SANS.[40]

Optic nerve tortuosity (ONT), or abnormal curvature of the optic nerve, is a radiological finding detectable on brain magnetic resonance imaging (MRI). To establish reliable findings

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among different research studies and to effectively monitor astronauts pre- and postflight, it is crucial to establish and agree upon a method for identifying and monitoring ONT. This paper examines current techniques for defining, measuring, and monitoring ONT. Additionally, it explores terrestrial causes of ONT and relates those causes to potential mechanisms by which ONT may occur in space.

**Defining and Measuring Tortuosity**

ONT has largely been a subjective description from an expert. However, efforts have been made to create an objective definition using a systematic and quantitative approach. ONT has been defined as "lack of congruity of the optic nerves in more than one coronal sections and dilation of the subarachnoid space surrounding optic nerves."[2] These findings together were found to be 89% sensitive and 93% specific.[2] Meanwhile, absence of these factors in addition to absence of deviation of the optic nerve within the axial section effectively ruled out ONT. With these findings as criteria, it is prudent to include coronal, axial, and sagittal sections with T2-weighted sequences with 2–3 mm cuts through the orbit when evaluating for ONT. Dilation of the subarachnoid space surrounding the optic nerves is hypothesized to be due to tortuosity, causing strain on the arachnoid layer of meninges surrounding the optic nerve and creating the potential for enlargement.

A team from Washington University has developed a tortuosity index to quantitatively score tortuosity. Using T1-weighted 3D magnetization prepared rapid gradient echo sequence with 1-mm sagittal slices, the full extent of both optic nerve from optic chiasm to globe was identified.[19] A straight line from the first and last point along the nerve was compared to an estimation of the tortuous length of the nerve by summing all the short segment lengths computed between adjacent coronal slices. A tortuosity index was calculated using the ratio of these lengths minus 1. The precision of this approach exceeded that of a subjective scoring system. This same method was used for calculating the tortuosity index in a retrospective study examining optic tortuosity in glaucoma, ocular hypertension, and control groups, but axial T1 and T2, coronal T1, and coronal STIR images with slice thickness of 3–4 mm were used.[9]

While many researchers examine optic tortuosity overall, some studies measure only either horizontal or vertical tortuosity. The literature has found that horizontal tortuosity is more indicative of intracranial hypertension than vertical tortuosity.[1,5,29] Additionally, many studies use a subjective consensus assessment by radiologists to determine the presence of ONT as opposed to the previously mentioned quantitative approaches. Differences in methodology should be noted when considering the results of studies. Though there have not yet been significant advancements in determining intracranial pressure (ICP) through imaging, and lumbar puncture (LP) remains the gold standard, knowing these associations is critical when determining how to measure findings and interpreting results.

ONT is a change in the nerve itself and, in extreme cases, can appear as kinking. Optic nerve kinking angle provides another means by which to evaluate tortuosity. A study investigating postoperative visual impairment after removal of pituitary macroadenomas measured optic nerve kinking angle, defined as "the angle between a line parallel to the planum sphenoidale and a line parallel to the intracranial optic nerve at the optic canal orifice."[15] That this study found the degree of optic nerve kinking angle as an independent predictor of postoperative visual improvements indicates that this angle may be a useful correlate for potential visual recovery in other causes of optic nerve kinking.

**Terrestrial Causes**

ONT has been found in many conditions, including idiopathic intracranial hypertension (IIH), intracranial tumors, neurofibromatosis, hydrocephalus, Chiari malformation, and others.[36] However, more important than individual cases is the unifying factor that explains why ONT is seen in such variable conditions: pressure.

Pressure can either be direct in the form of a mass directly imposing on the optic nerve or it can be indirect in the form of a change in intracranial pressure. The optic nerve is particularly susceptible to the impact of pressure due to the fixation of the distal and proximal ends of the optic nerve. These fixation points also make the optic nerve particularly vulnerable to stretching, tearing, and torsion, as evidenced by cases where the optic nerve is injured due to sudden, traumatic duction of the eyeball even in absence of any signs of contusion, either local or systemic.[22]

Brain masses, in some cases raising ICP and in others directly putting pressure on the optic nerve, indicate potential mechanisms by which ONT or kinking occurs. A few examples of brain masses that have been linked to ONT include optic gliomas associated with neurofibromatosis type 1,[18,19,23] meningiomas, petrous apex meningoceles,[47] pituitary macroadenomas,[15] and unruptured giant aneurysms.[31] While there are numerous terrestrial cases of masses directly causing tortuosity, this direct impingement model is probably not applicable to spaceflight, as astronauts have not had evidence of these masses during any phase of their missions.

The relationship between ONT and pressure is illustrated by its strong association with papilledema. Papilledema is defined as swelling of the optic nerve due to increased ICP and it is a medical emergency. While papilledema and enlargement of the optic nerve are nearly always bilateral in terrestrial cases of increased ICP, this is not always the case with intracranial tumors where edema is typically more severe on the side of the tumor.[6] In a study investigating IIH in children, increased ONT, optic nerve sheath enlargement with target sign, intraocular protrusion of the optic nerve, and posterior globe flattening were distinctive features of papilledema.[34]

There are many studies linking ONT with increased ICP. For instance, in a pediatric posterior fossa brain tumor case, papilledema as well as ONT and restricted diffusion in the optic nerve heads were found; these findings resolved upon resolution of raised ICP, demonstrating that MRI can be used to detect the presence of increased ICP and monitor posttreatment resolution of papilledema. Perhaps more importantly, it

indicates that ONT is linked to intracranial pressure changes.[35] The idea that ONT is dynamic and related to ICP is further supported by a study showing that, when comparing pre-LP MRI and post-LP MRI, there are changes in optic nerve angle with short-term cerebrospinal fluid (CSF) pressure reduction.[17] Another study of hydrocephalus in children found that, while serial change in ventricular size is an imperfect indicator of ongoing hydrocephalus, reduction in optic nerve sheath diamater and reduction in optic disc bulging and tortuosity after endoscopic third ventriculostomy or tumor resection was a better indicator.[39] These cases illustrate the dynamic nature of ONT, indicating the importance of establishing a baseline and objectively measuring changes as opposed to presence/absence of tortuosity as well as the potential to return to baseline after changes in tortuosity occur.

The importance of radiographic signs in clinical management is illustrated by a study that found children with Chiari malformation who had signs such as ONT and optic nerve sheath diameter were managed surgically, while most patients without these signs were managed conservatively.[3] The fact that these neuroradiological signs are used as the basis for surgical intervention indicates a clinically recognized relationship between specific neuro-opthalmic signs and ICP.

Perhaps the most discussed terrestrial analog for SANS is IIH. IIH is a diagnosis of exclusion, with elevated ICP in the absence of hydrocephalus and vascular or structural abnormalities and with normal CSF content.[11] This syndrome commonly presents with visual changes and headaches in women with obesity, and is thought to be related to venous insufficiency.[8,32]

Common MRI findings in IIH include ONT, intraocular protrusion of the optic nerve, flattening in the posterior aspect of the globe, and enlarged optic nerve sheath. An empty sella, widening of the foramen ovale, and transverse venous sinus stenosis have also been found in IIH.[1,4,8] These findings have been shown both in adults and children,[12,14,24] though the literature is inconclusive regarding how age affects certain findings. For instance, one study showed that findings such as scleral flattening, ONT, and increased perioptic CSF may be less frequent in prebuscent children with IIH with ONT present in 20% of prepubescent patients.[13] However, another study found that, in children with IIH, 90.9% exhibited ONT, which was the most common finding of intracranial hypertension.[14]

While the exact frequencies may vary based on method and study population, it is clear that ONT does frequently occur in the setting of intracranial hypertension. The explanation for this appears to be that the optic nerve may kink freely under pressure, resulting in horizontal or vertical tortuosity.[12] While the literature has found that horizontal tortuosity is more indicative of intracranial hypertension than vertical tortuosity,[1,5,29] more research is required to explore why this is the case and to understand the exact pressure dynamics the optic nerve is exposed to in intracranial hypertension on Earth. A complete understanding of these forces on the optic nerve will allow us to anticipate how these forces will change and the resulting findings in space.

While these many findings in IIH are helpful, they are not necessarily unique to IIH, and IIH is considered a diagnosis of exclusion. For instance, while a study on the validity of cross-sectional neuroimaging signs in IIH found that posterior globe flattening, ONT, pituitary deformity, and empy sella turcica were all significantly associated with IIH, they found that only posterior globe flattening strongly suggested a diagnosis of IIH, with a specificity of 100% and a sensitivity of 43.5%.[1] Interestingly, in patients with sigmoid sinus dehiscence/diverticulum with pulsatile tinnitus, imaging findings of IIH including flattened posterior sclera, tortuosity of the optic nerve, protrusion of the optic nerve, and increased optic nerve sheath diameter occur more frequently than in healthy individuals, suggesting an association between the two conditions.[50] IIH, and any cause of increased ICP and papilledema, is a serious concern as post-papilledema optic atrophy and even blindness can result. In one case report of fumlinant idiopathic intracranial hypertension, central retinal vein occlusion occurred bilaterally, leading to blindness.[43] While central retinal vein occlusion is not a common complication of IIH, it is a very serious one and demonstrates the impact of intracranial hypertension on the vascular system.

When discussing the factor connecting these varied conditions, the importance of pressure becomes obvious. Notably, pressure changes are important when considering ONT, which is perhaps why it is a complex finding to interpret, relying on clinical context. In a retrospective study examining optic tortuosity in glaucoma and ocular hypertension, the mean tortuosity index was higher for both groups compared to controls. Furthermore, the glaucoma group had a significantly higher mean tortuosity index than the ocular hypertension group.[9] While the underlying cause of increased tortuosity is not definitively known, it has been suggested that increased pressure in the globe causes disproportionate posterior pushing due to the soft, posterior retrobulbar adipose tissue compared to the hard, anterior orbital walls of the frontal bone. Additionally, there is loss of optic nerve volume in severe glaucoma,[38] which may lead to loss of optic nerve thickness, allowing easier folding and kinking.

Hutchinson-Gilford Progeria is another condition in which ONT is found. It has been proposed that remodeling of the facial bones may lead to optic nerve redundancy by progressively shortening the distance between the optic chiasm and the bony orbit.[42] There has been no evidence of such dramatic remodeling in space, but the key concept of changing distance between the optic chiasm and the bony orbit should be considered when examining changes in space.

### ONT in Space

Spaceflight-associated changes in optic nerve geometry have not been fully established, as a definitive pre- to postflight comparison of ONT or kinking in astronauts has not yet been completed. However, the presence of postflight ONT and kinking has been detected in some astronauts[20,27,33] and is illustrated in **Fig. 1** and **Fig. 2**; **Fig. 3** and **Fig. 4** of normal optic nerves without tortuosity have been provided for comparison (unpublished images, Lifetime Surveillance of Astronaut Health, NASA, Johnson Space Center, Houston, TX). As NASA pursues expeditionary spaceflight, it is essential to establish whether changes

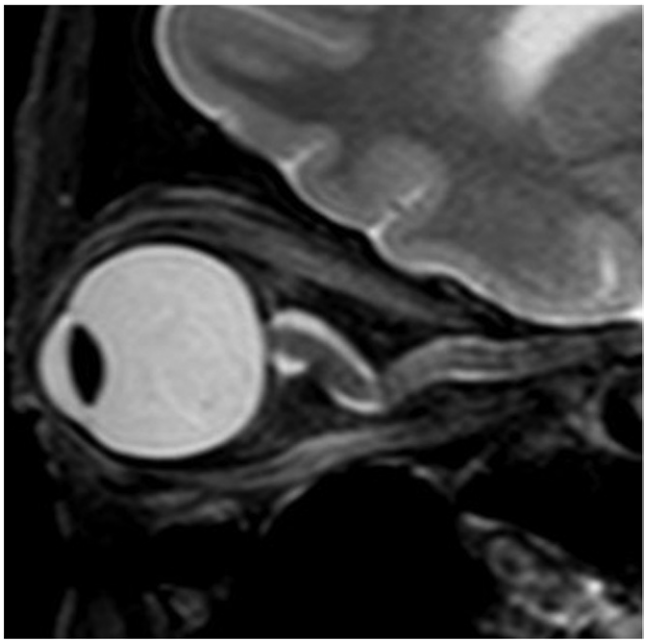

**Fig. 1.** Sagittal T2-W1. Sagittal section of the orbit showing ONT in an astronaut postflight. MRI image provided by the Lifetime Surveillance of Astronaut Health (LSAH) Program, NASA Johnson Space Center.

in optic nerve geometry occur during spaceflight, as well as the degree of change, to determine if the condition presents a risk to the vision and health of astronauts.

As mentioned, pressure changes appear to be the consistent factor underlying ONT changes in terrestrial patients. The optic nerve is particularly susceptible to the impact of pressure changes due to the fixation of its distal and proximal ends.

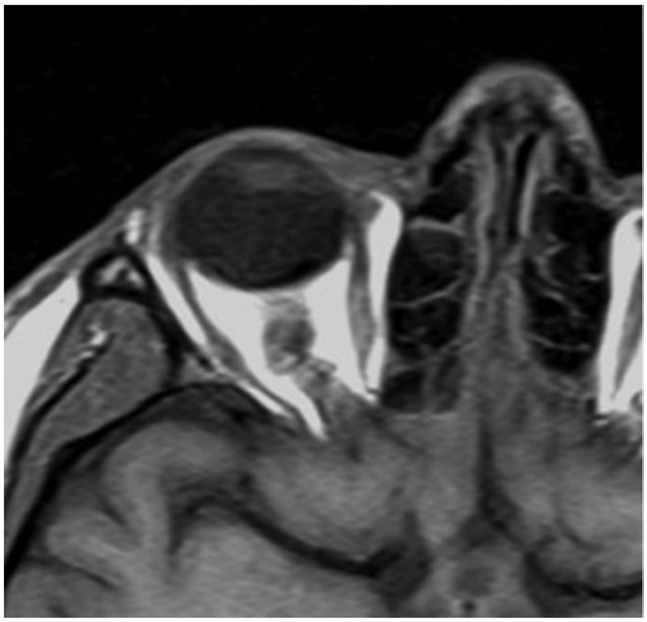

**Fig. 2.** Axial T1-W1. Transverse section of the orbit showing ONT in an astronaut postflight. MRI image provided by the Lifetime Surveillance of Astronaut Health (LSAH) Program, NASA Johnson Space Center.

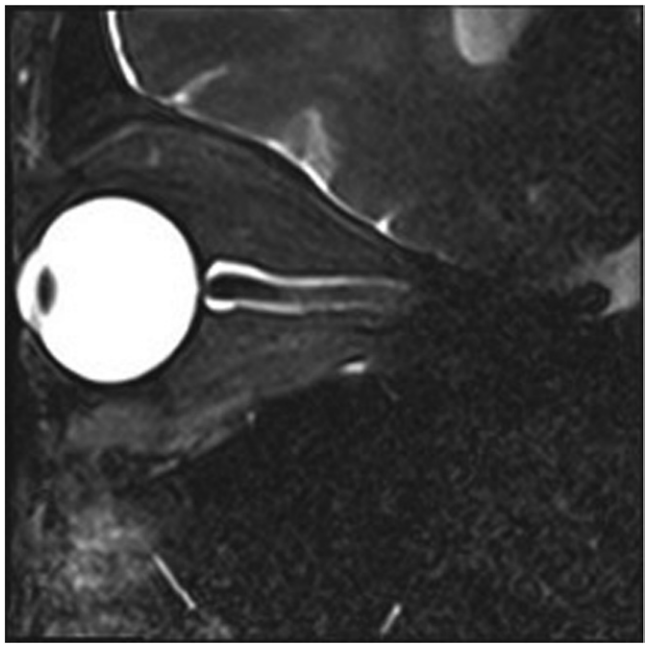

**Fig. 3.** Sagittal T2-W1. Sagittal section of the orbit showing normal optic nerve without ONT preflight; not an intra-astronaut pre- to postflight comparison. MRI image provided by the Lifetime Surveillance of Astronaut Health (LSAH) Program, NASA Johnson Space Center.

These fixation points also make the optic nerve particularly vulnerable to stretching, tearing, and torsion. It is important to consider the physiological challenges in microgravity that could potentially result in ONT-inducing pressure changes. While pressure can either be applied directly in the form of a mass

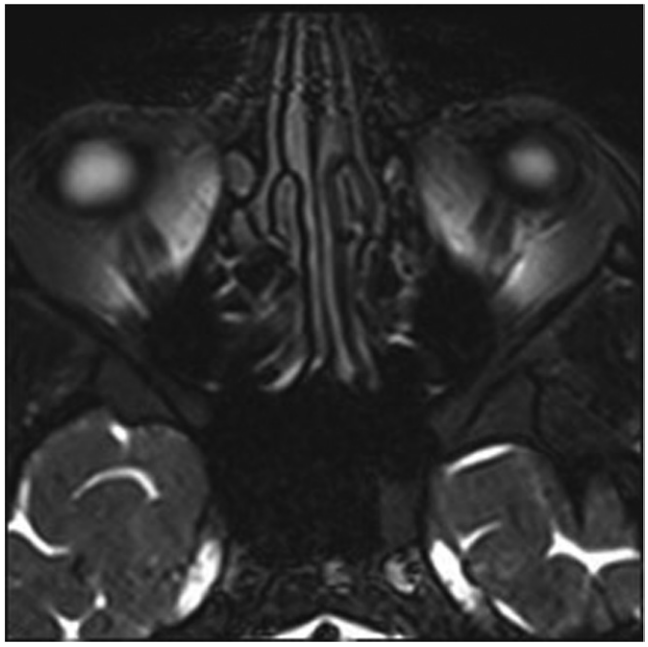

**Fig. 4.** Axial T2-W1. Transverse section of the orbit showing normal optic nerve without ONT preflight; not an intra-astronaut pre- to postflight comparison. MRI image provided by the Lifetime Surveillance of Astronaut Health (LSAH) Program, NASA Johnson Space Center.

imposing on the optic nerve or indirectly in the form of a change in intracranial pressure, the latter appears more relevant to what might occur in space. Intracranial tumors or other masses have not been detected in astronauts after long-duration spaceflight.[20]

Perhaps the most concerning and most consistent neuro-ocular finding during spaceflight is optic disc edema. In fact, edema extending ≥270° around the optic disc is currently the diagnostic criterion for SANS. While it has not yet been established that ICP changes in space, terrestrially papilledema is seen as a key indicator of increased ICP. Furthermore, a cephalic fluid shift, potentially with cerebral venous congestion, occurs in astronauts in microgravity as well as in research participants in head-down tilt studies.[10,37,46] As the Monro-Kellie doctrine describes and as illustrated in **Fig. 5**, the cranium has a fixed volume and elevation of ICP can result from increased intracranial blood, cerebrospinal fluid, or brain volume.[45] While changes in venous and CSF volume may initially compensate for extra volume or mass, there is a point where compensation is no longer possible and ICP increases. Increases in intracranial vascular volume and/or CSF volume in the cranium via cephalic fluid shift and cerebral venous congestion could increase ICP.

As previously discussed, ONT and increased optic nerve sheath diameter are other key indicators of increased ICP and are even used as the basis of surgical intervention in children.[3] Thus, a high level of suspicion of increased ICP is warranted in cases where changes in ONT are found. Additional findings in SANS, including posterior globe flattening and hyperopic shift, raise concern for increased ICP. Indeed, these two findings appear causally related as posterior globe flattening has been linked to shorter axial lengths both in terrestrial cases of IIH and case reports of astronauts,[7,28,29] accounting for the hyperopic shift. This constellation of findings has raised suspicion of ICP as a contributing factor in the development of SANS.

Early findings suggest that SANS has gross signs of right-side bias. If this is indeed the case, a potential explanation involving asymmetric findings would be differences in vasculature. Notably, astronauts have shown signs of venous stasis while in space. Given findings that the right internal jugular vein is often significantly larger than the left,[25,26,41] pre-spaceflight differences in vasculature may result in asymmetric findings during flight as cephalic fluid shift and possible venous stasis occurs. Further research should establish whether these asymmetric changes are significant, but also examine whether asymmetric ONT changes correspond to asymmetric optic disc edema findings.

Another potential contributing factor is bone remodeling. As seen in Hutchinson-Gilford Progeria, remodeling of the bones of the head can lead to ONT.[42] While bone remodeling that occurs in space is certainly not as externally visible as what occurs in Hutchinson-Gilford Progeria, research on mice in 15 d of microgravity has found that cephalic fluid shifts accompanying microgravity induce a statistically significant increase in bone volume and a trend increase in average cortical thickness.[48] If similar changes occur in astronauts, the distance between the optic nerve's fixation points may be altered and ONT may result. It is also possible that increased bone volume or cortical thickness could reduce intracranial volume and increase intracranial pressure and be further exacerbated by cephalic fluid shifts.

If changes in ONT occur during long-duration spaceflight, this might indicate additional risk to the vision and health of astronauts. While SANS has not yet induced any permanent loss in visual performance in crewmembers during 6-mo and 1-yr spaceflight missions, increases in SANS severity and duration may lead to irreversible changes. Therefore, it is essential to further quantify these neuro-ophthalmological changes associated with SANS and to determine potential

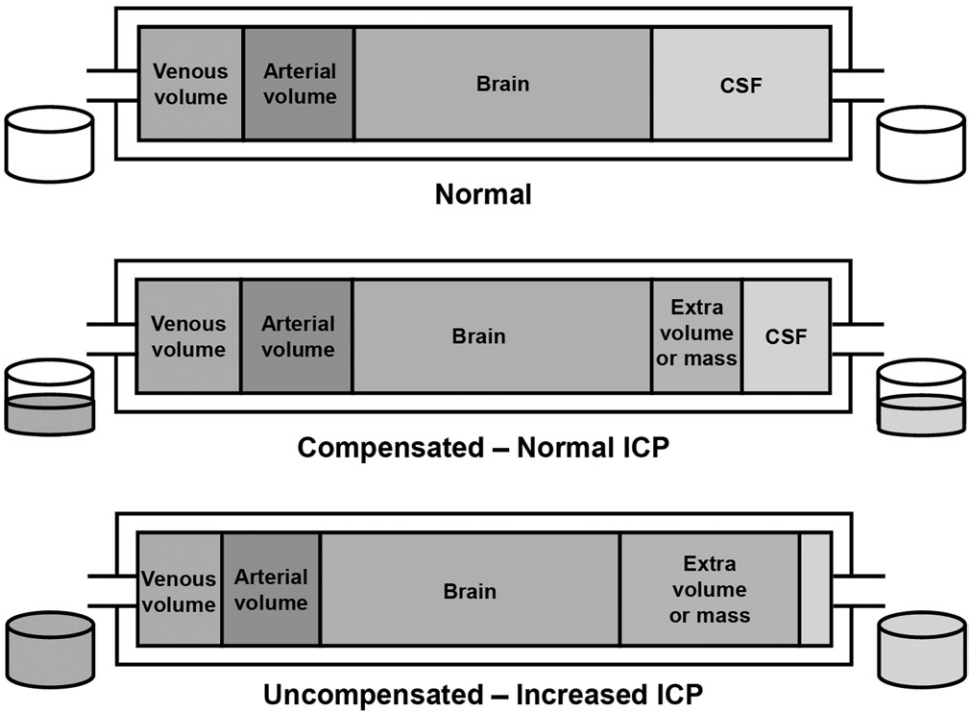


**Fig. 5.** Monro-Kellie Doctrine: image demonstrating that an increase in volume of cranial constituents (vascular, CSF, or tissue volume) must be compensated by a decrease in volume of another constituent. The top image illustrates normal distribution of venous, arterial, brain, and CSF volume with no alteration in pressure. The middle image illustrates the impact of extra volume or mass on the distribution of volumes and that venous and CSF volume can compensate for some changes in extra intracranial volume or mass without alterations in ICP. The bottom image illustrates that there is limitation to this compensation, at which point ICP increases.

countermeasures before embarking on longer exploratory spaceflight missions.

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