# Non-Invasive Intracranial Pressure Monitoring and Its Applicability in Spaceflight

Hugo Félix; Edson Santos Oliveira

**INTRODUCTION:** Neuro-ophthalmic findings collectively defined as Spaceflight-Associated Neuro-ocular Syndrome (SANS) are one of the leading health priorities in astronauts engaging in long duration spaceflight or prolonged microgravity exposure. Though multifactorial in etiology, similarities to terrestrial idiopathic intracranial hypertension (IIH) suggest these changes may result from an increase or impairing in intracranial pressure (ICP). Finding a portable, accessible, and reliable method of monitoring ICP is, therefore, crucial in long duration spaceflight. A review of recent literature was conducted on the biomedical literature search engine PubMed using the search term "non-invasive intracranial pressure". Studies investigating accuracy of noninvasive and portable methods were assessed. The search retrieved different methods that were subsequently grouped by approach and technique. The majority of publications included the use of ultrasound-based methods with variable accuracies. One of which, noninvasive ICP estimation by optical nerve sheath diameter measurement (nICP_ONSD), presented the highest statistical correlation and prediction values to invasive ICP, with area under the curve (AUC) ranging from 0.75 to 0.964. One study even considers a combination of ONSD with transcranial Doppler (TCD) for an even higher performance. Other methods, such as near-infrared spectroscopy (NIRS), show positive and promising results [good statistical correlation with invasive techniques when measuring cerebral perfusion pressure (CPP): r = 0.83]. However, for its accessibility, portability, and accuracy, ONSD seems to present itself as the up to date, most reliable, noninvasive ICP surrogate and a valuable spaceflight asset.

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The concept of space exploration still poses numerous questions and obstacles to our perception of not only the unknown universe, but also of the changes an environment of microgravity can impose upon human physiology. This absence of gravity has been hypothesized and increasingly proven, in several studies,[67,86,132] to cause pathological visual changes in astronauts, such as papilledema, globe flattening, and dilation of the optic nerve sheath. Such optical abnormalities, linked to cerebrospinal fluid shift and intracranial hypertension, led the NASA Space Medicine Division and its flight surgeons to describe these symptoms as a Visual Impairment and Intracranial Pressure syndrome (VIIP).[85] This syndrome was recently redefined as Spaceflight-Associated Neuro-ocular Syndrome (SANS), consisting of chronic, mildly elevated intracranial pressure (ICP) in space, precipitated by alterations in the hemodynamics of intracranial blood and cerebrospinal fluid circulation privation of hydrostatic pressures.[134] NASA has even proposed clinical practice guidelines to classify VIIP/SANS severity using a four-classed ordinal scale based on a refractive change greater than 0.5 diopter.[3]

This is currently considered to be one of the leading priority health risks for long-duration spaceflight, although visual changes were detected even with short-duration exposure.[67] A recent study[72] tried to assess the theorized elevation of ICP in zero gravity by simulating microgravity during parabolic flight. It revealed that absence of gravity does not pathologically elevate ICP per se but does prevent the normal lowering of ICP when standing. Its authors also conclude that the human brain and eye are protected by the daily circadian cycles in regional intracranial pressures, without which pathology appears to occur. These findings suggest increased ICP may not be the sole mechanism in the development of SANS. A different etiological possibility

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may reside in localized events occurring at the optical nerve. Contrarily to generically assumed homogeneity of ICP throughout the brain, an additional theory suggests a compartmentalization of cerebrospinal fluid (CSF) in the optic nerve sheath, where a microgravity-induced flow imbalance may lead to pressure elevation within the sheath and structure distension.[73,74,86] An alternate compartmentalization theory proposes the optic nerve and globe may retract posteriorly as a result of brain upward shift, compressing CSF within the optic nerve, leading to localized pressure elevation and expansion.[75,118] All these theories are not mutually exclusive, but merely show the possible multifactorial etiology of the still not fully understood SANS.

All things considered, the search for a method of monitoring ICP in, perhaps, anyone who partakes in spaceflight seems justified. Unfortunately, standards for ICP monitoring consist of direct or indirect invasive measurement techniques,[128] the gold standard being intraventricular or intraparenchymal catheterization.[14] Invasively measuring ICP poses several obstacles for application in spaceflight. Known complications that include risk of infection and hemorrhage, obstruction, and malposition of probes, although rare, seem forceful, and impracticable to impose on otherwise healthy individuals, without any kind of traumatic or nontraumatic brain injury, who are in flight or on the International Space Station, for example. Lumbar puncture for measurement of epidural pressure, although slightly more practicable and with less complications, is misleading for assessing ICP adequately and has been shown to overestimate ICP values, require lengthy monitoring, proper positioning, and, sometimes, require sedation and anesthesia that may heighten pressure readings.[22,29,135] As more of a neuraxis CSF pressure measurement, any mass or obstruction may also impact ICP estimation.[135]

This work will, therefore, be divided into two parts. Firstly, a review of the literature in recent years to try to ascertain which noninvasive methods show the best accuracy, or correlation to the gold standard in measuring ICP and, secondly, an investigation and reflection into which of these seem the most adequate for application in space travel at present or in the near future. There have been some studies extensively reviewing noninvasive ICP methods and whether they can accurately replace invasive ones,[60,98,135] but, to our knowledge, there is no study reviewing and discussing their applicability in spaceflight.

## METHODS

A review of recent literature was performed with a first search conducted on February 24th, 2020, on the public access databases of MedLine/PubMed with the keywords "non-invasive intracranial pressure". Works were filtered for solely human applications in the past 5 yr, resulting in a total of 106 studies found. The inclusion criteria for this research were the use of noninvasive, portable methods for intracranial pressure monitoring with clinical application. Papers without clinical or experimental application of any method were excluded. Articles with application of a nonportable method and, therefore, deemed impracticable in the context of spaceflight (i.e., MRI, CT scan) were also excluded. Only articles available full-length in their original, or translated to, English language, were accepted in the review (**Fig. 1** flow chart). The total number or articles included in the review was 32, divided and classified according to which method was used, considering that some studies researched or compared assessment in two. They are categorized and arranged by author, approach, and method used, with sample size, use of invasive measuring, main findings, and statistical measures of accuracy in **Table I**, **Table II**, and **Table III**.

## RESULTS

### Audiological Based Methods

The concept behind acoustic methods of noninvasive ICP (nICP) monitoring stems from anatomical continuity of the

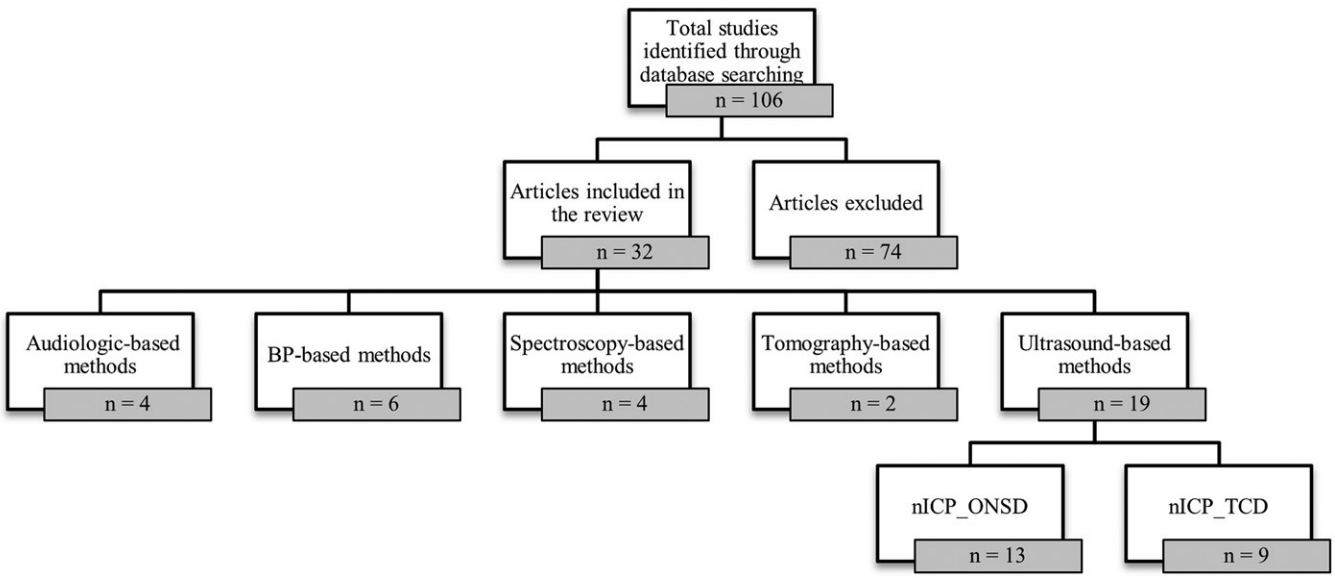


**Fig. 1.** Flow chart explaining articles included, categorized by method assessed, and exclusion criteria.

**Table I.** nICP Methods Used by Each Study and Key Information.

| CATEGORY & METHOD | AUTHORS | SAMPLE | iICP | STUDY FINDINGS AND CONCLUSIONS | SENS | SPEC | AUC | R |
|---|---|---|---|---|---|---|---|---|
| Audio logic | | | | | | | | |
| OAE | Giraudet et al.[47] | 24 (TBI) | Intra-parenchymal | Changes in CM phase correlated with ICP changes R = 0.66; $P < 0.0001$ | 0.83 | 0.81 | 0.84 | 0.66 |
| OAE | Levinsky et al.[78] | 39 (intracranial pathology) | Intra-parenchymal | Cut off value for pulsatile nICP to be 5 mmHg yields the sens. of 0.55 and spec. of 0.65. | 0.51/ 0.55 | 0.85/0.65 | 0.753/ 0.65 | |
| TMD | Evensen et al.[37] | 28 (intracranial pathology) | Intra-parenchymal | Satisfactorily in only 4/28 individuals (14%). | 0.65 | 1 | | |
| TMD | Finch et al.[42] | 20 (healthy) | NA | Difference between sitting and supine Vm values was statistically significant (right $P = 0.0002$; left $P = 0.0003$). | | | | 0.34/ -0.38 |
| BP | | | | | | | | |
| SphygmoCor | Evensen et al.[36] | 29 (hydro cephalus) | Intra-parenchymal | Negative Predictive Value was 42% for both the Interpatient and the Intrapatient approach. Central aortic BP can under certain conditions serve as a source for nICP, but results are not consistent. | 0.67 | 0.63 | | |
| SR model | Lee et al.[76] | 8 (VM) | NA | SR method successfully tracked ICP on the VM phase (intracranial hypertension) compared to the PI method. | | | | |
| TOF, ICM+ | Petkus et al.[97] | 61 (TBI) | Intra-parenchymal/ intra-ventricular | Standard deviation of the difference between VRx and PRx averaged per monitoring sessions was 0.192. Statistically significant differences between survivors and nonsurvivors found in average PRx,VRx values | | | | 0.843 |
| MRI, ODM | Gerstl et al.[45] | 4 (children, IIH) | Lumbar puncture | nICP by venous ODM (ICP = 23-28 cmH2O) correlated with higher levels for LP opening pressure (ICP = 20-40 cmH2O. | | | | |
| Spectroscopy | | | | | | | | |
| NIRS | Esnault et al.[35] | 8 (BI) | Intra-parenchymal | ROC curve showed the inability for rSO2 to detect cerebral hypoxia episodes (AUC = 0.54). rSO2 cannot be used as a substitute for PbtO2 to monitor oxygenation. | | | | -0.54 ($r^2$ 0.29) |
| NIRS | Dias et al.[32] | 18 (TBI) | Intra-parenchymal | Larger discrepancy (> 10 mm Hg) between real CPP and CPPopt more likely to have had adverse outcomes ($P = 0.04$) | | | | 0.83 |
| TCB | Hawthorne et al.[53] | 10 (TBI) | ND | The most significant relationship between ICP and TCB was found using Zc and R0 normalized per patient ($P < 0.0001$, r2 = 0.32). | | | | 0.57 ($r^2$ 0.32) |
| Tomography | | | | | | | | |
| OCT | Ahuja et al.[1] | 113 (papilledema) | NA | Positive correlation was found between Frisen grading of papilledema and RNFL thickness measurements {r = 0.7952 and 95% confidence interval: 0.6590–0.8809} | | | | 0.7952 |
| OCT | Anand et al.[4] | 5 (IIH) | Lumbar puncture | Mean RNFL thickness decreased in all subjects, with nonsignificant trends. Mean decrease in average RNFL thickness was 32 ± 36 µm. RPE/BM angle significantly decreased in all subjects. | | | | |

nICP: non-invasive intracranial pressure monitoring; iICP: invasive intracranial pressure monitoring; Sens: sensitivity; Spec: specificity; AUC: area under the curve; OAE: otoacoustic emissions; TBI: traumatic brain injury; CM: cochlear microphonic potential; ICP: intracranial pressure; TMD: tympanic membrane displacement; NA: not applicable; BP: blood pressure; SR: simple resistance; VM: Valsalva maneuver; PI: pulsatility index; TOF: time of flight; ICM+: Cambridge data storage and analysis software; VRx: volumetric reactivity index; PRx: pressure reactivity index; MRI: magnetic resonance imaging; ODM: ophthalmodynamometry; IIH: idiopathic intracranial hypertension; LP: lumbar puncture; NIRS: near-infrared spectroscopy; BI: brain injury; ROC: receiver operating characteristic; CPP: cerebral perfusion pressure; CPPopt: optimized cerebral perfusion pressure; TCB: transcranial bioimpedance; ND: not determined; OCT: optical coherence tomography; RNFL: retinal nerve fiber layer; RPE/BM: retinal pigment epithelium/Bruch's membrane.

**Table II.** nICP Methods Used by Each Study and Key Information, Part 2.

| CATEGORY & METHOD | AUTHORS | SAMPLE | iICP | STUDY FINDINGS AND CONCLUSIONS | SENS | SPEC | AUC | R |
|---|---|---|---|---|---|---|---|---|
| US/BP | | | | | | | | |
| TCD | Schmidt et al.[113] | 39 (BI) | ND | cnICP calibration method showed the best results. | | | | |
| TCD, tonometry | Kurazumi et al.[68] | 15 (healthy) | NA | Increases in ICP recognized during Placebo/HDT and CO2/ HDT. Combination of 3% CO2 (6 mmHg increases in PETco2) and 210° HDT did not increase ICP significantly compared to 210° HDT alone. | | | | |
| US/Spectroscopy | | | | | | | | |
| DCS, TCD | Baker et al.[9] | 18 (healthy) | NA | The slope (± 95 CI) between aCPPTCD and aCPPDCS is 0.97 (± 0.04); R = 0.88 (p < 0.001) | | | | |
| US | | | | | | | | |
| TCD | Siaudvytyte et al.[119] | 40 (glaucoma) | NA | Positive correlation between ICP and neuroretinal rim area was observed (r = 0.51, *P* = 0.001). | | | | 0.51 |
| TCD | Cardim et al.[21] | 53 (diagnosis) | Lumbar puncture | Correlations between ΔICP and ΔnICP were better represented by nICP_PI, nICP_BB. Best scenario was obtained with TCD pulsatility index. | | | | 0.45(PI)/0.30 (BB) |
| TCD | Koskinen et al.[66] | 12 (hydro cephalus) | Lumbar puncture | Underestimation of ICPNon-Inv was greater at higher pressures. | | | | 0.74 |
| TCD, ONSD | Robba et al.[103] | 1 (glioma) | NA | PI, FVdICP and ONSD increased compared to baseline measurement, reaching a maximum value of 1.12, 27 mmHg and 7 mm, respectively. | | | | |
| TCD, ONSD | Robba et al.[104] | 40 (laparoscopy) | NA | ICPFvd showed the highest AUC after PP and at the TP+PP time point compared with baseline. | | | 0.75 (ONSD)/0.8 (FVd)/0.7(PI) | |
| TCD, ONSD | Robba et al.[105] | 22 (intracranial diseases) | Intra parenchymal/ intra ventricular | ICP ONSD correlated the strongest with invasive ICP (r = 0.61) compared to the other methods (ICP FVd: r = 0.26, p value = 0.001; PI: r = 0.19, p value = 0.02; vPI: r = 0.056, p value = 0.51). | 0.85 | 0.85 | 0.91 (ONSD)/0.67 (FVd) | 0.61 (ONSD)/0.26 (FVd)/0.19 (PI) |
| TCD, ONSD | Robba et al.[106] | 64 (BI) | Intra parenchymal/ intra ventricular | nICP derived from ONSD has the strongest correlation with invasive ICP. | 0.866/ 0.872 | 0.826/ 0.767 | 0.91/0.81/0.93 | 0.76/0.72/0.81 |

nICP: non-invasive intracranial pressure monitoring; iICP: invasive intracranial pressure monitoring; Sens: sensitivity; Spec: specificity; AUC: area under the curve; US/BP: ultrasound/ blood pressure; TCD: transcranial Doppler; BB: "black box" method; BI: brain injury; cnICP: model reconstruction of constant shift of nICP; HDT: head down tilt; DCS: diffuse correlation spectroscopy; CI: confidence interval; aCPPTCD: ; aCPPDCS: ; NA: not applicable; nICP_PI: non-invasive intracranial pressure pulsatility index; nICP_BB: non-invasive intracranial pressure "black box" method; ONSD: optical nerve sheath diameter; PI: pulsatility index; FVdICP or ICPFvD: intracranial pressure measured with the diastolic component of trans-cranial Doppler cerebral blood flow velocity; AUC: area under the curve; PP: pneumoperitoneum; TP: Trendelenburg positioning.

perilymphatic space with extensions of the subarachnoid space, where an elevated CSF pressure is conceived to alter sound transmission by attenuation of otoacoustic emissions (OAE).[31]

Table I presents two studies estimating the accuracy of nICP monitoring by OAE vs. invasive ICP (iICP) measurement via intraparenchymal probes. Giraudet et al.[47] shows the most

**Table III.** nICP Methods Used by Each Study and Key Information, Part 3.

| CATEGORY & METHOD | AUTHORS | SAMPLE | iICP | STUDY FINDINGS AND CONCLUSIONS | SENS | SPEC | AUC | R |
|---|---|---|---|---|---|---|---|---|
| ONSD | Chen et al.[24] | 84 (diagnosis) | Lumbar puncture | With a reduction in CSF pressure, 80 subjects (95%) showed an immediate drop in ONSD. | | | | 0.451 |
| ONSD | Choi et al.[25] | 34 (children, hydro cephalus) | NA | The mean (SD) ONSD were 5.4 (0.6) mm (right) and 5.3 (0.7) mm (left) before surgery and 4.4 (0.5) mm (right) and 4.5 (0.7) mm (left) after surgery, respectively | | | | |
| ONSD | Li et al.[80] | 130 | Lumbar puncture | ICP had a significant correlation with ONSD in the right, left and both eyes, but no correlation with age and gender. ONSD of 5.6 mm had a sensitivity of 86% and a specificity of 71% for identifying high ICP. | 0.86 | 0.71 | | 0.6 |
| ONSD | Liu et al.[81] | 110 (diagnosis/ symptoms) | Lumbar puncture | 92.3% of cases with normal ICP and 85.7% of cases with high ICP were correctly classified (a total correction rate 90.0%). The sensitivity is 85.7%, and the specificity is 92.3%. | 0.862 | 0.731 | 0.861 | 0.61 |
| ONSD | Padayachy et al.[96] | 174 (children) | Intra parenchymal | Best diagnostic accuracy for detecting an ICP ≥ 20 mmHg over the entire patient cohort was 5.5 mm, sensitivity 93.2%, specificity 74% and odds ratio of 39.3. | 0.932 | 0.74 | 0.84 | ($R^2$ = 0.53) |
| ONSD | Raffiz et al.[99] | 41 (BI) | Intra parenchymal | ONSD value of 5.205mm is 95.8% sensitive and 80.4% specific in detecting raised ICP. ONSD measurement in predicting raised ICP is higher in the Traumatic group compared to Nontraumatic group. | 0.958 | 0.804 | 0.964 | 0.82 |
| ONSD | Steinborn et al.[120] | 81(children and adolescents) | Lumbar puncture | The optimal cut-off value for predicting elevated ICP was 6.0 mm with a sensitivity of 82% and specificity of 74%. | 0.82 | 0.74 | 0.875 | |
| ONSD | Kim et al.[62] | 35 (CSB) | NA | Mean ONSD increased significantly after CSB (5.15 6 0.38 mm vs. 4.75 6 0.32 mm, p, 0.001). | | | | |
| ONSD, CT | Bhandari et al.[13] | 69 (hydro cephalus) | NA | Strong correlation between the ONSD measured by USG and CT (r = 0.95, $P < 0.001$). | | | | |

nICP: non-invasive intracranial pressure monitoring; iICP: invasive intracranial pressure monitoring; Sens: sensitivity; Spec: specificity; AUC: area under the curve; ONSD: optical nerve sheath diameter; CSF: cerebral spinal fluid; ICP: intracranial pressure; CSB: cervical sympathetic block; CT: computed tomography; USG: ultrasonography.

statistically accurate results when the alarming ICP increase is set at +7.5 mmHg, ensuring sensitivity of 83%, specificity of 81%, area under the curve (AUC) of 0.84, and a Pearson correlation coefficient of R = +0.66 ($P < 0.0001$, $N = 24$) with ICP changes in a 95% confidence interval.

A similar audiological concept evaluates tympanic membrane displacement (TMD) as a surrogate of ICP measurement. Alterations in hydrostatic pressure of the perilymph produce small but measurable variations in the dynamics and reflexes of the middle ear ossicles, consequently changing TMD responses to auditory stimulation.[102] Evensen et al.'s[37] study showed satisfactory results of the mean-wave amplitude (time averaged peak-to-peak value of the ICP waveform) threshold of 4 mmHg with 65% sensitivity and 100% specificity using TMD.

### Blood Pressure Based Methods

The intracranial compartment can be perceived as a "black box" system whose pathological changes can be described indirectly by its transformation of the input signal, arterial blood pressure (ABP), into the output signal, ICP. This relationship can be explored by associating ICP to the central aortic blood pressure (BP) waveform estimated from the radial artery BP waveform using a SphygmoCor (ATCOR, Sydney, Australia) system.[36] Predictive ability of interpatient approaches for a threshold of 4 mmHg yielded sensitivity and specificity results of 67 and 63%, respectively, when compared to iICP measurements. Lee et al.[76] proposed an ICP estimator with ABP and a simulation of cerebral blood flow, applying a simple resistance model to healthy patients resting and performing a Valsalva maneuver. This technique showed a significant difference ($P < 0.05$, $N = 8$) between the two phases. However, in this category, the study that presented the most favorable statistic results is from Petkus et al.,[97] where a significant correlation ($r = 0.843$, $P < 0.001$; 95% confidence interval 0.751–0.903, $N = 61$) was found between invasively monitored ICP and the noninvasively calculated volumetric reactivity index based on real-time measurements of intracranial blood volume reactions to changes in ABP using a needle sensor in the radial artery, and a head frame bearing a pair of ultrasonic transducers on either side of the patient's head.

Additionally included in this category is ICP estimation from central retinal vein pressure, known as venous ophthalmodynamometry. This technique, hailed as a valuable and accurate method,[43] produced a single study in this research demonstrating comparable results between venous ophthalmodynamometry estimated ICP and lumbar puncture (LP) opening pressure, although with a sample too small for statistical analysis.[45]

### Spectroscopy-Based Methods

Measuring transmission and absorption of light, specifically near-infrared light, as it passes through live tissue and present chromophores (such as oxyhemoglobin and deoxyhemoglobin) has been conceived as a breakthrough spectroscopy-based concept (**Fig. 2**) in noninvasive measurement of intracranial ischemia, hematoma, edema, and even ICP and cerebral perfusion pressure.[46,63]

Dias et al.[32] studied an estimation of optimized cerebral perfusion pressure (CPPopt), a method for individualization of cerebral perfusion pressure (CPP) oriented management, based on determination of cerebrovascular reactivity using the pressure reactivity index: a moving correlation coefficient between slow waves of ICP and ABP.[7] Applying near-infrared spectroscopy (NIRS), they achieved statistically significant correlation between this CPPopt and invasively measured "real" CPP ($r = 0.83$, $P < 0.0001$, $N = 18$). However, less positive results were established in another application[35] of NIRS in regional saturation in oxygen monitoring ($rSO_2$) vs. brain tissue oxygen tension monitoring ($PbtO_2$). An indirect relationship was established [$r = -0.54$ ($-0.62$ – $-0.45$), $r^2 = 0.29$, $P < 0.0001$, $N = 8$] between $rSO_2$ and ICP, but detection of cerebral hypoxia via $rSO_2$ had a sensitivity of 14.9% and specificity of 67.6% (threshold of 60% in $PbtO_2 < 15$ mmHg). For increasingly severe cerebral hypoxia, $PbtO_2 < 10$ mmHg and $PbtO_2 < 5$ mmHg, sensitivity also slightly increased (24.4 and 27%, respectively).

A different spectroscopy-based method was exercised by Hawthorne et al.[53] in which the authors used bioimpedance, the ability of biological tissue to impede electric current, and modeled the parameters of $Z_c$ (impedance at the characteristic frequency) and $R_0$ (resistance to a direct current) against ICP using unadjusted and adjusted linear models. The most significant relationship between ICP and these transcranial bioimpedance parameters was found by adjusting for multiple patient specific variables and using $Z_c$ and $R_0$ normalized for each of the 10 patients ($P < 0.0001$, $r^2 = 0.32$, $N = 10$).

### Tomography-Based Methods

Working with near-infrared light, optical coherence tomography (OCT) is a high resolution noninvasive imaging technique capable of obtaining retinal topography cross-sectional information.[55] OCT can detect and quantify diffuse thickening of the retinal nerve fiber layer (RNFL) in eyes with papilledema, optic disk swelling that is secondary to elevated intracranial pressure.

The correlation between these RNFL thickness measurements and increased ICP-induced optic disk swelling saw positive values ($r = 0.7952$ and 95% confidence interval: 0.6590–0.8809) from Ahuja et al.[1] in 113 patients. Besides RNFL,


**Fig. 2.** Functional near infrared spectroscopy sensor (head band) with optode locations visualized on anterior view brain surface image to the left and a modern, portable, clinical diffuse correlation spectroscopy system to the far right (adapted from Ayaz et al.[8] and Durduran et al.[34]).

Anand et al.[4] measured other parameters: peripapillary retinal pigment epithelium/Bruch's membrane angulation, transverse neural canal diameter, and the highest vertical point of the internal limiting membrane from the transverse diameter (papillary height). The study showed nonsignificant decreases in mean RNFL thickness (pre-LP: 196 ± 105 μm; post-LP: 164 ± 77 μm, $P = 0.1$) and transverse neural canal diameter (pre-LP: 1985 ± 559 μm; post-LP: 1590 ± 228 μm, $P = 2.0$) in all five patients with suspected idiopathic intracranial hypertension. The most favorable results in this study are attributed to the retinal pigment epithelium/Bruch's membrane angulation (pre-LP: 1985 ± 559 μm; post-LP: 1590 ± 228 μm, $P = 2.0$) which decreased in all subjects.

### Ultrasound-Based Methods

***nICP_ONSD.*** Another approach to ICP estimation studies an extension of the subarachnoid space around the optic nerve to the back of the eyeball. This sheath enveloping the optic nerve with an interspace suffused with CSF is distensible and a raised CSF pressure can not only compress the structures enveloped (optic nerve, central retinal artery, and vein), but also influence the diameter of this optic nerve sheath (ONSD),[107] measurable noninvasively with ultrasound (**Fig. 3**).

Among all studies included, Raffiz et al.[99] showed the most favorable results, in which the ONSD value of 5.205 mm was found to be 95.8% sensitive and 80.4% specific in detecting raised ICP, generating an AUC of 0.964 ($N = 41$). The authors also separated findings in patients with traumatic vs. nontraumatic brain injuries, concluding that the overall sensitivity and specificity of ONSD measurement in predicting raised ICP is higher in the traumatic group. A similar trend in positive results can be found in studies that pitch nICP_ONSD against iICP, and an analysis of AUC values for this estimation can be seen in **Fig. 4**.

Studies with larger samples: Liu et al.[81] ($N = 110$), Padayachy et al.[96] ($N = 174$), and Steinborn et al.[120] ($N = 81$) show smaller AUC values of 0.861, 0.84, and 0.875, respectively. Still, in the least favorable AUC value study, Padayachy et al.[96] found that ONSD measurement of 5.5 mm for detecting ICP > 20 mmHg resulted in 93.2% sensitivity, 74% specificity, and an odds ratio of 39.3.

***nICP_TCD.*** Transcranial Doppler (TCD) applicability for nICP assessment is based on cerebrovascular dynamics through blood flow velocity (FV) and ICP increase-changing parameters and models such as pulsatility index (nICP_PI), waveform analysis of diastolic FV (nICP_FVd), previously mentioned ABP-related "black box" method (nICP_BB), or critical closing pressure (nICP_CrCP).[20,89]

Looking solely at statistically significant correlations of nICP_TCD methods with iICP, we detect variable results in this review, ranging from r = 0.30 (with nICP_BB, $P < 0.05$, $N = 53$)[19] to 0.74 (based on a two-method measurement of the external and internal segments of the ophthalmic artery; $P < 0.001$, $N = 58$).[66] In this first study, the four methods discussed above were assessed for predicting changes in ICP; nICP_PI and nICP_BB presented best correlation with iICP measured by LP (r = 0.45 and r = 0.30, respectively), and nICP_FVd and nICP_CrCP presented nonsignificant correlations (r = −0.17, $P = 0.21$ and r = 0.21, $P = 0.13$, respectively).

***Studies assessing both nICP_ONSD and nICP_TCD.*** A few studies[103,104,106] pitched these two ultrasound-based techniques with somewhat contradictory results. While primarily showing that nICP_FVd estimation of increased ICP had the largest AUC after pneumoperitoneum and the Trendelenburg position, when compared to nICP_ONSD and nICP_PI (0.8 vs. 0.75 and 0.7, respectively),[104] Robba et al.[105] subsequently demonstrated a

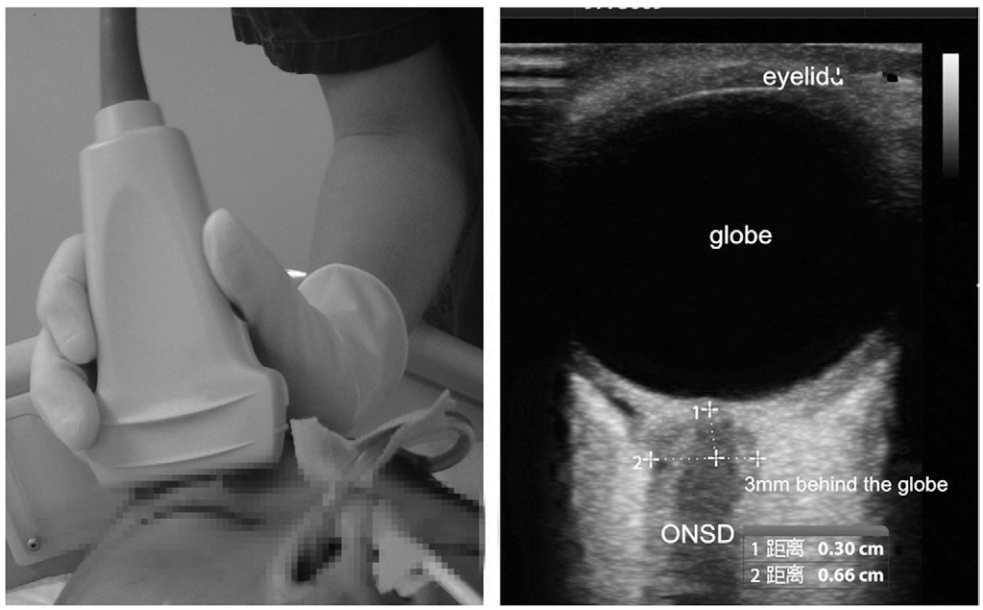


**Fig. 3.** Demonstration of ONSD measurement with the positioning of the ultrasound probe on the closed eyelid, measuring the width of ONSD at 3 mm behind the globe (adapted from Gao Y et al.[44]).

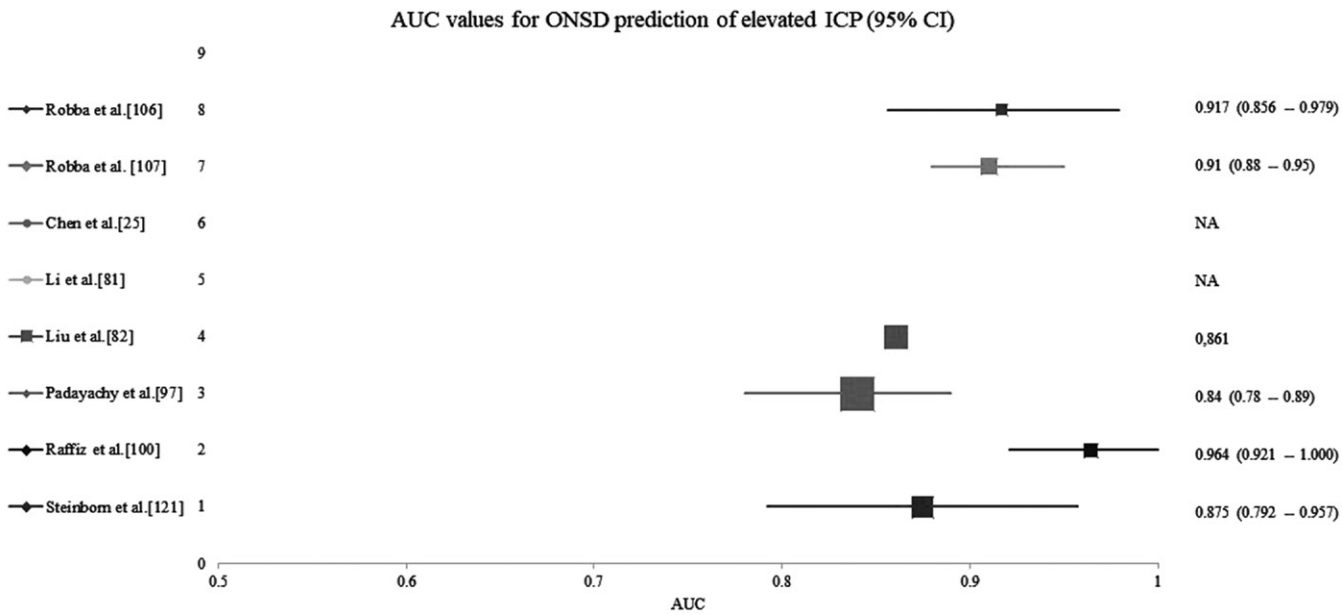


**Fig. 4.** Forest plot showing AUC prediction values of nICP_OSND in all the studies comparing this method to iICP monitoring.

stronger correlation of nICP_ONSD with iICP (r = 0.61, $N$ = 22) when compared to nICP_FVd (r = 0.26, $P$ = 0.001) and nICP_PI (r = 0.19, $P$ = 0.02). As for AUC values, nICP_ONSD likewise demonstrated the highest ability (0.91) to predict intracranial hypertension, for a threshold of 20 mmHg.

Lastly, Robba et al.[106] propose a method based on the combination of the two best correlated parameters in their cohort [ONSD and FV of stroke volume (FVsv) = nICP_ONSD+FVsv], which achieved an AUC for prediction of ICP > 20 mmHg of 0.93 ($N$ = 64), performing better than the two methods, nICP_ONSD (AUC = 0.91) and nICP_FVsv (AUC = 0.81), isolated.

## DISCUSSION

The anatomical extension of the subarachnoid space and fluid surrounding the optic nerve and communicating with the hindmost portion of the eyeball served as a primordial rationalization of ICP estimation: raised intraocular pressure (IOP) as a result of raised ICP.[110]

A few early studies established this connection between IOP and ICP with a variety of different devices, such as the noncontact tonometer,[117] the Tono-Pen XL,[70] and the Schiøtz tonometer.[109] Results were quite unambiguous toward a high correlation between IOP and ICP, reaching remarkable sensitivity and specificity of 1.0 in the study that applied Tono-Pen XL.[70] Follow-up studies,[27,93] however, disproved the aforementioned correlation. Han et al.[51] measured IOP by using the Goldmann applanation tonometer, considered to be the gold standard in tonometry, and found no statistically significant correlation between IOP and ICP. They criticize the assessment and use of Schiøtz tonometry, as it is reviewed as having the poorest correlation with the Goldmann method.[130] As another justification for the disparity in studies' results, one can point out that the most accurate estimations of ICP were established in patients with extreme values of IOP, as corroborated by Hayreh's[54] work, which states that an acute rise in ICP > 50 mmHg is required to cause significant elevations in IOP. In subsequent studies, the Tono-Pen XL[49] and a portable pneumotonometer[26] both failed to provide a significant correlation between IOP and ICP.

However, despite unfavorable results in ICP estimation, a more recent study[79] suggests improved correlation with ICP employing handheld devices, such as the disposable Goldmann applanation prism.[131] Recently, other IOP measurement devices such as the live AVIA[5] or rebound tonometry[71,115] (shown to have good agreement with the gold standard[58,92]), have recently been used in studies researching ocular changes in simulated microgravity. Anderson et al.[5] successfully trained 19 healthy subjects to self-administer IOP measurements using the Tono-Pen AVIA and Scott et al.[115] noninvasively measured IOP with an applanation rebound tonometer during head-down tilt (HDT) rest and exercise, demonstrating that IOP increased when moving from the supine position to −15° HDT while resting, and decreased in the latter position during exercise. It is important to note that, despite tonometry's lacklustre performance in ICP estimation, the extreme portability, simple and easy storage, and learning curve of self-administrating use of the 6" Tono-Pen AVIA demonstrated in Anderson et al.'s[5] study proves to be valuable. Subjects were trained on the procedure to collect the IOP measurement in something as little as 2 d.[5]

Seeing as SANS findings include radiographic eye pathology and elevated IOP,[75] the impact of ICP on IOP remains a field of investigation.[94] Albeit still maintaining arguable use in spaceflight, tonometry falls flat accuracy-wise as a method of noninvasively measuring ICP. Thus, in researching newer noninvasive methods of monitoring ICP during spaceflight, using the search terms "intracranial pressure" with "spaceflight" yielded some interesting results pertaining to recent and innovative research

in this field, yet, ultimately, retrieving insufficient results for a solid review. The choice was to broaden the search to "non-invasive intracranial pressure" methods in all settings, in a recent timeline, compare efficiencies, and, subsequently, discuss each method's applicability to spaceflight. This discussion was aided by spaceflight-specific searches.

In this research of literature in the past 5 yr, coincidentally, no studies were found assessing ocular tonometry for ICP estimation. Contrastingly, two ultrasound-based methods occupied the bulk of the results, comprising a presence of 59% (19 of the 32 studies included assessed ultrasound techniques). One of those methods is TCD.

The use of TCD as a method of evaluating ICP by means of the Pourcelot index and decrease of the mean flow velocity in the middle cerebral arteries was one the first applications documented with success.[64,65] Bellner et al.[12] applied the pulsatility index (PI) to TCD measurements, demonstrating strong correlation between PI and ICP, independent of the type of intracranial pathology. These results were refuted by Figaji et al.[41] and Behrens et al.,[11] whose work with children with severe traumatic brain injuries and with patients suffering from idiopathic normal pressure hydrocephalus, respectively, showed that PI was not a reliable predictor of ICP. In this second analysis, however, a mathematical model of the intracranial dynamics was simulated alongside the in vivo experiments, using a computer to reproduce data in healthy subjects, and it showed a strong relationship between ICP and PI. However, it still had compromising results, attributed to individual variation in physiological parameters associated with pathology or even anatomical structure variations.

Similar to limitations observed in studies applying tonometry, TCD measuring displays a stronger correlation between PI and ICP/cerebral perfusion pressure when said values are extremely high.[12,41] In Bellner's[12] work, patients had PI values > 3.0, which is technically unfeasible. Other limitations that compromise the efficiency of the TCD are the thickening of the temporal bone or even physiological factors like $P_aCO_2$ that have a notable fluctuating effect on PI, depending on the patient's level of consciousness.[127] Here, the use of ratios[11] along with head frames in patients[127] can help eliminate oscillation in blood flow velocity measurements caused by inclination angles for better results.

Four studies included in this research estimated ICP with TCD by pulsatility index (nICP_PI). PI is a middle cerebral artery assessment index based on systolic (FVs), diastolic (FVd), and mean (FVm) flow velocities, which can be calculated according to Gosling's method [PI = (FVs − FVd)/FVm).[50,104] The established correlation with ICP for this method ranged from 0.19[105] to 0.45.[19] Robba et al.[104] pitted PI against another flow velocity-based technique, based on CPP estimation, derived from the work of Czosnyka et al.,[28] where ICP is estimated as the difference of mean arterial blood pressure and noninvasive CPP (ICP FVd = ABPm − CPP). This middle cerebral artery diastolic flow velocity method (nICP_FVd) presented higher AUC value then nICP_PI when distinguishing patients undergoing abdominal laparoscopic surgery before and after pneumoperitoneum and the Trendelenburg position. Several studies[103,105,113] assessed the flow velocity technique with disparate correlations, ranging from −0.17[19] to 0.72.[106] This last study achieved the highest correlation, performing venous TCD and calculating systolic flow velocity in the straight sinus (FVsv). This venous approach to blood flow velocity showed more promising results than arterial counterparts.

Another nICP estimator based on CPP and blood flow velocity consists in critical closing pressure of cerebral circulation (nICP_CrCP).[89,125] Even though nICP_CrCP has been shown to significantly increase during HDT,[68] it revealed a nonsignificant correlation of 0.21 ($P$ = 0.13) with iICP.[19] In Kurazumi et al.'s[68] study, one more TCD technique was tested, with equal positive results to nICP_CrCP: the "black box" method (nICP_BB). Based on the signal transformation from ABP to ICP, nICP_BB samples FV, ABP, and invasively measured ICP curves, using a mathematical formula to describe their relationships in a weight function and estimating a simulated nICP.[114] This method retrieved a positive correlation with iICP (r = 0.30, $P$ = 0.03, $N$ = 53).[19]

Nonetheless, the various results are divergent. Comparing the four different methods (nICP_PI, nICP_BB, nICP_CrCP, and nICP_FVd), nICP_PI is identified as the most reliable,[19,21] but a review of literature on these TCD methods stated otherwise, postulating that PI can increase independently of increases in ICP.[19]A fifth method based on two-depth Doppler ultrasound monitoring of pulsations in the blood flow velocity in the internal and external ophthalmic artery[66,119] and the aforementioned venous approach to TCD flow velocity (FVsv) show the most promising results.[106]

Taking advantage of ultrasound accessibility and portability, transorbital ultrasonic evaluation of the optic nerve sheath and its expansion during CSF pressure variations has been theorized and demonstrated to contribute information on acutely increased ICP.[56,57] ONSD establishes a tight anatomical and pathophysiological relationship with SANS, whose severity is further subjectively assessed by nerve sheath distension and/or globe flattening.[3] It is hypothesized that ONSD increases as responsive remodeling to microgravity and spaceflight-induced changes, such as brain upward shift in CSF[118] or high levels of $CO_2$,[33] and a maladaptive remodeling of the optical nerve sheath to these changes is what contributes to the SANS phenomena.[100] Therefore, ultrasonographically measured ONSD has been one of the most promising noninvasive ICP measurement surrogates,[2,95] achieving strong statistical correlations with more sophisticated (although less portable) imaging methods, such as CT scan[13,95] and MR imaging.[10]

ONSD shows the most unequivocally positive results in estimating nICP, as seen in Fig. 2, surpassing TCD accuracy, even when directly compared.[105,106] In a recent systematic review, the pooled area under the receiver operating characteristic curve was 0.94 (95% confidence interval 0.91 to 0.96, $I^2$ = 60.9%) for detection of elevated ICP with ONSD sonography.[40] The relationship with astronaut symptoms and signs, demonstrated accuracy, and being a rapid, noninvasive, and repeatable technique whose

results are not affected by change in probe position[23] confer promising results to ONSD as a surrogate to iICP. ONSD is, in its core, an ultrasonographic methodology that relies on a portable workstation, progressively more and more able to integrate, retrieve, adjust, and display patient data effectively as well as a probe with increasing stability and sensitivity in diagnostic performance, with the advantages previously described in contrast with transcranial methodologies.[23,44]

Possible downsides to this technique are the fact that the ONSD range in the general healthy population is reasonably wide, with a possible sex difference in ONSD measurements[48] with cut-off values for identifying high ICP ranging from 5.205–6 mm;[80,105,120] higher sensibility and specificity in traumatic patients, opposed to nontraumatic patients or patients with more chronic elevation of ICP;[44] and limited lateral spatial resolution of conventional ultrasound techniques or ultrasound artifacts, resulting in discrepancies in measurements.[69]

Few studies have assessed ONSD changes and ultrasound method accuracy in healthy individuals subjected to microgravity. This may be since it seems unreasonable to submit healthy individuals to invasive ICP monitoring. Nevertheless, one such study evaluated 3-D structural optic nerve measurements in HDT, showing acute response to increased ICP, but only compared its accuracy to 2-D measurement.[30] Laurie et al.[71] demonstrated an ONSD increase in HDT, likewise without counterpointed iICP monitoring. ICP has also been shown to increase in HDT via TCD[68,87] and, by means of compression sonography of the internal jugular vein during HDT and exercise,[115] parabolic flight[88] and dry immersion[6]—a novel model of microgravity exposure. One interesting study investigated potential in-flight evaluation of SANS through ultrasound guided lumbar puncture and succeeded, not only in direct measurement of ICP by a trained radiologist during flight, but additionally in teaching nonexperienced volunteers, achieving technical success in 9 of the 11 attempts.[77] Such research proves the current investment in ONSD, which is practiced both terrestrially and on-orbit by NASA, for ocular and SANS surveillance.[15]

At the time of this revision, no studies were found applying UltraFast ultrasound techniques in ICP estimation. UltraFast ultrasound enables visualization of rapid dynamic responses of biological tissues which cannot be observed and analyzed by conventional ultrasound imaging.[52] UltraFast imaging's higher spatial resolution, relatively to conventional ultrasound, by higher yield and reduction in scan time, allows improved evaluation of a wider and more sensitive range of relevant physiological processes while reducing motion artifacts.[61,123,124] Indeed, UltraFast Doppler has been proven to be sensitive enough to be used in mapping subtle hemodynamic changes in brain vascularization and represent an alternative in functional imaging activity.[82,83] The high temporal resolution of UltraFast ultrasound imaging may prove a solution to conventional ultrasound resolution and artifact-related shortcomings, especially in blood flow techniques, since reducing scan time improves comfort and compliance, thereby minimizing motion during a scan.[124]

Also assessed in this revision were such methods ranging from OAE to NIRS. TMD, seen here in Evensen et al.'s study,[37] showed apparent satisfactory and promising results, but only in 14% of the individuals tested. TMD also failed to demonstrate any strong evidence in detecting changes from sitting to supine posture.[42] This is a method with known limitations for accurate ICP estimation, depending on physiological properties of a healthy middle and inner ear; for instance, present stapedial reflex[101] or a patent cochlear aqueduct.[111] Another limitation is the intersubject variability, requiring individual baseline measurement, which is also a requirement with OAE,[17] the other acoustic method present in this research. This need for individual baseline measurement was confirmed in a recent study, precisely assessing OAE validity and showing its capability of detecting ICP changes in a SANS context.[129] OAE shows more robust results than TMD in this review, with an AUC of 0.65[78] and 0.84[47] when compared with invasive intraparenchymal ICP measurement. However, even with positive results, acoustic methods of nICP measurement experience limitations pertaining to audiological factors, with OAE also showing a vulnerability to sensorineural or conductive hearing loss.[18]

ABP is often monitored conjointly when estimating ICP with other methods, such as TCD, playing an important role in some of the techniques, as seen with the "black box" method,[19,68] or with FV techniques, as seen in Schmidt et al.'s[113] nICP calibrations. Recently, an approach relying on a mathematical model-based analysis of synchronized ABP and middle cerebral artery blood FV waveform measurements obtained a sensitivity of 71%, specificity of 86%, and an AUC of 0.83 for nICP estimation.[38] In addition, Iwasaki et al.[59] were the first to use these conjoint noninvasively obtained middle cerebral artery blood FV and radial ABP to systematically examine changes in nICP, as well as hemoglobin concentration and flow velocity before and after spaceflight in 11 astronauts. Despite showing nICP did not change postflight (ANOVA, $P = 0.139$), the recognizable next step remains as we still lack in-flight studies.

Some studies in this revision plotted nICP estimation models based primarily on ABP. Inconsistent results arose from Evensen et al.'s[36] attempt at nICP estimation from central aortic BP, deeming such approach inadequate for the clinical setting. Petkus et al.[97] used a needle sensor in the radial artery for the ABP measurements, devising a "time of flight" measurement principle that used a transducer-bearing head frame transmitting and receiving ultrasound waves though intracranial media. This monitoring system significantly correlated with iICP measurement ($r = 0.843$, $P < 0.001$, $N = 61$). One can derive from these results that BP-based methods may not be a reliable surrogate when isolated. Still, they remain an important asset, especially when combined with other methods, often ultrasound, for its discussed availability, easiness to use, and current experimental exploration in this field.

Auspiciously, the constant scientific breakthroughs in medical devices provide increased portability and accessibility to methods reviewed here that previously might not have been included, an example being OCT.

OCT uses near-infrared light to create high resolution cross-sectional representations of anatomical structures, providing reliable and highly reproducible quantitative measures of the changes of the retinal structure surrounding the optic nerve.[4,122] It has been used, and is currently used, by NASA for ocular surveillance postflight and during ISS missions,[15,39,112] and has even shown optic disc swelling in astronauts after long-duration spaceflight.[84] OCT demonstrated measurable anatomical changes in the optical nerve head occurring immediately following ICP changes after lumbar CSF drainage, even though in a small sample size study ($N = 5$).[4] The only study in this review where statistical conclusions were produced, a positive correlation was found between Frisen grading of papilledema and RNFL thickness measurements in a broader sample ($r = 0.7952$, $N = 113$).[1] These findings demand further investigation with OCT, as it is valuable and applicable equipment, available recently in an increased scan rate second-generation device, already employed by NASA.[90] This is a method already employed in a fixed station on the Harmony node of the International Space Station which can and should be considered as a possibility for in-flight testing.

Also assessed in the studies included in this review is an additional near-infrared optical technique that justifies further consideration. NIRS was introduced in neonatal care, making use of the Lambert-Beer law to quantify indices of cerebral oxygenation by converting changes in absorption at different wavelengths into signals from oxyhemoglobin and deriving estimates of changes in cerebral blood flow.[108,133] It is an easy-to-use, flexible, inexpensive, and portable device that enables continuous and repeated bedside monitoring, promising even smaller and economical iterations advancing in time and technology.[108,126] Dias et al.[32] demonstrated good correlation ($r = 0.83$, $P < 0.0001$, $N = 18$) between a new method of autoregulation-guided treatment (CPPopt) based on continuous evaluation of cerebrovascular reactivity (pressure reactivity index) measurements using NIRS and real cerebral perfusion pressure, a pressure gradient from which we can infer ICP. On the other hand, a third generation NIRS monitor showed a low ability to detect cerebral hypoxia in a study advising against its use as a substitute for invasive monitoring.[35]

Baker et al.[9] stands as the only study in this revision using the high temporal resolution diffuse optical technique variant of NIRS, known as diffuse correlation spectroscopy (DCS). When opposed to NIRS, DCS retrieves a higher fraction of the true brain hemodynamics, higher brain and hypercapnia response sensitivity.[116] Despite some susceptibility to motion artifacts, it shows good accuracy when compared to middle cerebral artery measuring transcranial Doppler[9,16] and other noninvasive flow modalities, such as ASL-MRI and xenon-CT.[91] The penetration depth of DCS is, still, limited when compared to MRI and CT.[16] Newly discovered methodology by operating DCS in the time domain has been shown to bypass some of these issues.[121] Further studies are thoroughly needed, but these spectroscopy-based avenues present a promising technology for cerebral physiology monitoring.

In summary, analyzing the studies in this review of recent literature, despite some techniques in the manner of OCT and NIRS/DCS showing some promise in the field of nICP estimation, they require further studies assessing their accuracy and application in microgravity environments. As of now, from all the methods outlined, ultrasound-based ones are currently the most ubiquitous, with ONSD retrieving the best noninvasive, portable, and accessible approximation to the invasive gold standards of ICP measurement. Furthermore, applying a combination of methods, even purely ultrasonic methods shown by measuring ONSD and FVsv,[106] has retrieved encouraging results. One can also hypothesize a combination of ONSD and nICP_TCD approach to ophthalmic artery flow velocity, one of the most promising TCD-based methods,[66,119] for future clinical experimentation.

Noninvasive methods still fall short when compared to the invasive gold standards of ICP measurement, but some concepts show potential. Ultrasonic measurement of the ONSD is a portable, accessible, and applicable method to spaceflight that shows the most robust results among noninvasive ICP estimation techniques, but combinations of methods should not be discarded. Further testing with broader samples and different clinical conditions is a necessity, not only to accurately assess these methods, but also to cement the relationship of ICP with SANS.

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