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State-of-the-Art Review: Non-invasive assessment of cerebrospinal fluid pressure

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Abstract

Measurement of intracranial pressure (ICP) is critical for the evaluation and management of many neurological and neurosurgical conditions. The invasiveness of ICP measurement limits the frequency with which ICP can be evaluated, hampering the clinical care of patients with ICP disorders. Thus, there has been substantial interest in developing non-invasive methods for the assessment of ICP. Numerous approaches have been applied to the problem although none appears to represent a complete solution. The goal of this review is to familiarize the reader with the currently available methods to non-invasively evaluate ICP.

Keywords

intracranial pressure; non-invasive; cerebrospinal fluid

Introduction

Measurement of intracranial pressure (ICP) is critical for the evaluation and management of many neurological and neurosurgical conditions. An intraventricular catheter connected to an external pressure transducer is considered the gold standard for ICP measurement,¹ but this highly-invasive method is only justifiable in neurocritical care settings. Therefore, lumbar puncture (LP) is typically used in routine practice to measure ICP, and in the absence of an obstruction, LP opening pressure corresponds closely with the ventricular pressure.² Yet, LP is still an invasive, and often painful,³ test that provides only a snapshot of the ICP, a quantity which varies substantially over time, particularly in certain disease states.¹ Therefore, accurate non-invasive methods of assessing ICP would be extremely valuable for monitoring disorders of ICP, even though the majority of disorders require an initial sample of the cerebrospinal fluid (CSF) to evaluate its composition.

In infants, the fontanels are open and provide an easy window for the non-invasive evaluation of ICP. Indeed, fontanometers have been developed that provide reliable, continuous information about changes in ICP and cerebral compliance.⁴ In adults, the cranial cavity has very few windows for the non-invasive monitoring of ICP. The difficulty

of directly accessing the intracranial contents adds noise to measurements and provides other challenges to the estimation of ICP in adults.

Currently, two general approaches are available for the non-invasive assessment of ICP: (1) qualitative markers that suggest the possibility of increased ICP, and (2) quantitative measures of the patient's specific ICP or a estimation of the change in ICP after a invasively determined pressure. While a simple test that definitively differentiated normal from high ICP would have substantial clinical utility, quantitative measures would be even more powerful, particularly for the long-term monitoring of ICP. However, many quantitative studies suffer from a key statistical problem: they report a significant association exists between a given measure and the *mean* ICP by a modeling method such as linear regression. However, for a new quantitative marker to be clinically valuable, it must be predictive of a specific *individual's* value rather than the mean, which is a much more difficult task. For example, one can intuitively see how much easier it would be to predict the average age of the children attending an elementary school than to predict the age of a particular child chosen at random from that school.

Beyond the common symptoms and signs of increased ICP, such as headache, diplopia, transient visual obscurations, nausea, vomiting, sixth nerve palsy, and papilledema, there are numerous qualitative and quantitative approaches to the non-invasive evaluation of ICP which we will review in the following broad categories: neuroradiologic epiphenomena, optic, otic, electrophysiologic, and fluid dynamic (Table).

Neuroradiologic epiphenomena

Several neuroradiologic epiphenomena of increased ICP have been described. In severe head injury, computed tomography (CT) is frequently used, and several findings have been associated with increased ICP, including absent or compressed basal cisterns and third ventricle, midline shift, and intracerebral hemorrhage.^{5,6} However, these findings have only been studied in head trauma and are unlikely to be of significant value in other settings. Furthermore, even in head trauma, the predictive value of these findings remains unclear: when Mizutani *et al.* developed a multivariate predictive model using 39 checkpoints, they were only able to predict the ICP within ± 10 mmHg (13.6 cm H₂O) in 80% of patients.⁷

On magnetic resonance imaging (MRI), the epiphenomena of increased ICP include empty sella turcica, optic disc protrusion into the globe, flattening of the posterior globe, prominence of the perioptic nerve CSF spaces, tortuosity of the optic nerve, cerebral transverse venous sinus stenosis, and meningoceles.^{8,9} Some of these findings have been described in patients with normal ICP occurring both in isolation and in combination;¹⁰ however, an increasing number of these epiphenomena occurring in the same patient appears to be associated with a higher likelihood of raised ICP.¹¹ Indeed, 3 or more of these signs occurring in the same patient is extremely suggestive of increased ICP,¹¹ although there are occasional exceptions,¹⁰ similar to spontaneous venous pulsations (SVPs).

Ophthalmic

Since the optic nerve sheath is a dural extension and the perioptic nerve CSF is generally in communication with the cerebral CSF, it is little surprise that the eye is one of the primary windows available for ICP evaluation. The ophthalmic techniques that evaluate ICP do so via both anatomic and physiologic assessments.

Spontaneous venous pulsations

Spontaneous venous pulsations (SVPs) are a subtle, rhythmic variation of the retinal vein caliber seen on the optic disc. They occur due to the variation in the pressure gradient caused by differences in the intraocular and CSF pulse pressure as the retinal vein traverses the lamina cribosa,¹² and SVPs were recently demonstrated to be in phase with the ICP.¹³ SVPs are not observed in about 10% of normal patients; so their absence is generally not interpretable,¹⁴ but several studies have suggested that SVPs are only present when the ICP is normal.^{12,14}

However, a recent prospective study found that the sensitivity of the presence of SVPs for normal ICP was 94%,¹⁵ suggesting that SVPs are not 100% sensitive for normal ICP. Interpretation is further complicated because many conditions, such as idiopathic intracranial hypertension (IIH), have fluctuations in the ICP that could allow SVPs to be observed during a period when the ICP is normal.¹² Furthermore, SVPs are often evaluated in the sitting position which leads to a lower, and potentially normal, cranial ICP compared with the lateral decubitus position in which ICP is typically measured.¹⁴

Studies so far suggest that the absence of SVPs occurs relatively commonly in normal patients and in many causes of optic disc edema not related to increased ICP.¹² In contrast, the presence of SVPs indicates that the IOP is close to the central retinal venous pressure.¹⁶ Since central retinal venous pressure correlates closely to ICP, SVPs are a very sensitive sign for normal ICP, but like any diagnostic test, their presence should be interpreted in the context of the overall clinical scenario.

Intraocular pressure

Intraocular pressure (IOP) is one measure for which the issue of mean vs. individual prediction discussed previously is particularly relevant. For example, a highly significant positive association between ICP and the mean IOP has been demonstrated ($p < 0.001$), but ICP alone only explains 10% of the variation on average for a given individual's IOP ($R^2=0.109$) leading to poor accuracy.¹⁷ This means that while IOP does generally increase as ICP increases, it is not useful for predicting a given patient's ICP.

Venous ophthalmodynamometry

Venous ophthalmodynamometry uses the influence of IOP on SVPs, which when present indicates that the IOP is close to the central retinal venous pressure, by applying pressure to the globe to increase the IOP until the central retinal vein collapses. This external pressure is then added to the baseline IOP, providing the venous outflow pressure that has been shown to closely correlate with the ICP.^{16,18} In fact, a recent study of 102 patients with

extraventricular catheters, showed that increased central retinal vein pressure (>30 mmHg or 40.8 cmH₂O) had a 84% sensitivity and 93% specificity for increased ICP (>15 mmHg or 20.4 cmH₂O); however, this is probably inadequate sensitivity to avoid invasive ICP measurement in most settings.

Optic nerve sheath diameter

Several studies have demonstrated in controlled conditions that the optic nerve sheath expands linearly in most persons after a pressure threshold is achieved; however, this initial threshold varies between individuals, ranging between 15 - 30 mmHg (20.4 - 40.8 cmH₂O).¹⁹ The expansion has been shown to be reversible, at least in the acute setting.¹⁹ Ultrasound is the most commonly used technique to assess the optic nerve sheath diameter, although both magnetic resonance imaging (MRI) and computed tomography (CT) have also been used.^{20,21} Several studies have demonstrated that enlargement of the optic nerve sheath is strongly associated with increased ICP in emergency department and neurocritical care patients.^{19,20,22,23} Similarly, the optic nerve sheath has been shown to be enlarged in patients with IIH compared with controls.²⁴

While most studies have used an optic nerve sheath cutoff of 5 mm, cutoffs from 4.5 - 5.8 mm have been used, and studies have also defined increased ICP by different thresholds, anywhere between 14.7 - 30 mmHg (20 - 40.8 cmH₂O).^{19,20,22-25} Limitations of ultrasound to assess the optic nerve sheath include other hypoechoic artifacts that can be confused with the optic nerve-optic nerve sheath complex, interexamination variability based on sonographer experience, and the small size of the structure relative to the tiny differences differentiating normal vs. abnormal optic nerve sheath diameters.²² These limitations combined with the variety of optic nerve sheath cutoffs proposed, different ICP thresholds evaluated, heterogeneousness of populations studied, and variation in methods used make it difficult to determine whether this technique has sufficient sensitivity and specificity for the non-invasive evaluation and monitoring of patients with possible or known disorders of ICP.

Optical coherence tomography

While optical coherence tomography (OCT) can be used for quantitative measurement and monitoring the retinal nerve fiber layer (RNFL) in papilledema, there are significant limitations to its use in clinical practice. For example, automated algorithms fail when disc edema is severe and reductions in the RNFL thickness do not necessarily represent improvements in edema, but can instead represent optic nerve atrophy.

Recently, a deflection of the peripapillary retinal pigment epithelium (RPE) and Bruch's membrane into the eye has been noted in 67% of patients with papilledema; this OCT finding is not typically seen in normal controls or in patients with other causes of disc edema, suggesting its potential use to differentiate papilledema from other causes of disc edema or pseudo-disc edema.²⁶ Interestingly, the deflections normalized when disc edema resolved and they correlated with changes in clinical condition. Although this finding requires further validation, it appears likely that evaluation of the peripapillary RPE/Bruch's membrane angle by OCT will be another useful technique for qualitatively evaluating and

monitoring papilledema. However, whether these findings correlate with changes in ICP remains to be shown.

Scanning laser tomography

Scanning laser tomography (SLT) represents an alternative method to OCT by which the RNFL can be evaluated. However, Kupersmith *et al.* have found that SLT shows decreased retardance in regions of early axonal injury.²⁶ Thus, SLT, unlike OCT, may be able to differentiate edema from atrophy in papilledema. While one study has shown a significant relationship between optic nerve head volume and height with ICP, its predictive ability at the individual level is not sufficient to reliably estimate the ICP.²⁷

Pupillometry

Quantitative pupillometers can measure subtle changes in the pupillary light response. Taylor *et al.* studied a commercially available handheld pupillometer (ForSite, NeuroOptics Inc., Irvine, CA) and found that in normal individuals the pupil size decreases on average by 34% in response to a standardized light stimulus. After head trauma, the response decreased to 20%, and a 10% change was associated with an ICP over 20 mmHg (27.2 cmH₂O) in these patients, suggesting that changes in pupil size measured with a pupillometer may reflect variations in the ICP.

However, pupil reactivity is subject to several factors that limit its utility, including certain medical, ocular, and non-ICP related neurological conditions, various medications, the emotional state of the individual, and the time of day.²⁸ Furthermore, it is unclear whether the initial findings in head trauma will translate to other causes of increased ICP.

Otic

Like the eye, the ear has direct communication with the CSF and provides another window for the non-invasive evaluation of CSF pressure. Techniques to estimate ICP related to the ear leverage the direct connection between the perilymph of the cochlea and the CSF in the posterior cranial fossa via the cochlear aqueduct.

Ocular vestibular evoked myogenic potentials

Ocular vestibular evoked myogenic potentials (oVEMPs) are short-latency electromyographic activity of the extraocular muscles evoked by vestibular stimulation. They can be recorded with surface electrodes beneath the eye contralateral to the stimulated ear. A recent study of 20 healthy volunteers found a decreasing amplitude of oVEMPs with increasing head down position, and the authors suggested that oVEMPs may be suited for non-invasive ICP monitoring.²⁹

Tympanic membrane displacement

Displacement of the tympanic membrane (TM) can be measured during the acoustic middle-ear reflex. Displacement of the TM is altered when increased ICP translates into increased perilymphatic pressure via the cochlear aqueduct that alters the position of the stapes in the oval window.³⁰

While the technique appears to have relatively good test-retest reliability in the same test session, there is substantial intersubject variability. Furthermore, the test is subject to additional limitations: (1) a substantial proportion of the population does not have a patent cochlear aqueduct, and (2) pathology along the acoustic middle-ear reflex arc can interfere with measurement.³⁰

The usefulness of tympanic membrane displacement for evaluation of increased ICP appears to be limited by its intersubject variability, but its good reliability makes it a candidate for monitoring changes in the status of patients in whom the ICP has already been established by other means.³¹

Otoacoustic emission

An alternative to TM displacement measurements is otoacoustic acoustic emissions (OAEs), a sound generated by the inner ear which can be evoked by several techniques. In particular, distortion product OAEs (DPOAEs) have been shown to change with ICP.³²⁻³⁴ Changes in DPOAEs require a patent cochlear aqueduct like TM displacement, but are not subject to the additional components of the middle-ear reflex arc, such as the brainstem, required by TM displacement measurements. Like TM displacement, OAEs are subject to significant intersubject variability with good intrasubject reliability. Therefore, they may also be valuable for monitoring patients when the ICP has already been established by another method.

Electrophysiologic

Visual evoked potentials and electroencephalography are two electrophysiologic methods that have been evaluated with respect to ICP.

Visual evoked potentials

Two studies by York *et al.* in the early 1980s found a relatively strong relationship ($R^2=0.7$) between ICP and the N₂ latency of the visual evoked potential (VEP).^{35,36} No ophthalmic examination appears to have been performed to rule out ophthalmic disease that could affect the VEP, but the strong inpatient correlations with ICP were quite remarkable.³⁵ More recent studies, however, have suggested that high variability in normal subjects limits the ability of VEP to predict ICP.³⁷

Electroencephalography

A recent study of 62 patients showed a relatively strong correlation between a pressure index derived from electroencephalography (EEG) power spectrum analysis and the invasively determined ICP.³⁸ Further validation of EEG power spectrum analysis will be needed to determine its clinical utility.

Fluid dynamic

Ultrasound, MRI, and infrared spectroscopy have been applied to directly study the dynamic changes in ICP, cerebral blood flow, and cerebral compliance.

Two-depth transcranial Doppler

Two-depth transcranial Doppler assessment of ICP relies on the same principle as blood pressure measurement with a sphygmomanometer. The ophthalmic artery is affected by the ICP intracranially while the extracranial segment can be affected by externally applied pressure to the orbit. The pressure cuff is used to gradually compress the orbital tissues while Doppler ultrasound is used to determine the point at which blood flow in the intra- and extracranial segments of the ophthalmic artery equalizes. At this point, the externally applied pressure is equal to the ICP.³⁹

Ragauskas *et al.* showed an excellent agreement between the absolute ICP determinations using two-depth transcranial Doppler and those simultaneously measured by LP in a group of patients undergoing neurological evaluation with ICP ranging from 4.4-24.3 mmHg (6-33 cmH₂O).³⁹ Indeed, 98% of patients' measurements were within ± 4 mmHg (5.4 cmH₂O) of the LP determined ICP, a margin of error typical of some invasive monitoring methods, although ± 3 mmHg (4.1 cmH₂O) is considered ideal.⁴⁰ While this would appear very promising, a more recent study by the same group reported rather poor sensitivity (68%) of the technique for differentiating high and low ICP based on a cutoff of 20 mmHg (27.2 cmH₂O).⁴¹

Magnetic resonance imaging based elastance index

MRI using velocity-encoded cine phase-contrast pulse sequences can be used to measure the transcranial blood and CSF volumetric flow rates which allow a derivation of the ICP via an elastance index.⁴² Intracranial pressure predicted by this dynamic MRI method has been shown to have an excellent correlation ($R^2=0.965$, $p<0.005$) with invasively measured ICP. Likewise, normal values have been shown to be a strong predictor of resolution of symptoms of high ICP in patients with hydrocephalus without surgical intervention⁴³ and to correlate with the shunt valve opening pressure in children with hydrocephalus.⁴⁴ Nevertheless, this technique requires further study in a larger cohort of patients to fully evaluate its diagnostic capabilities.

Ultrasound time of flight

Several techniques for the non-invasive ICP evaluation have been developed based on the measurement of acoustic properties of the intracranial structures by the propagation speed and attenuation of ultrasound.^{45,46} Using advanced signal processing, the dynamic monitoring of the ICP waves can be translated into a non-invasive ICP measurement. In a group of 40 patients with a wide range of ICPs from approximately 0-70 mmHg (0-95 cmH₂O), there was a very strong correlation ($R^2=0.99$).⁴⁶ Like the MRI-based techniques discussed above, further study is needed.

Near-infrared spectroscopy

Near-infrared spectroscopy is a method by which regional changes in cerebral blood oxygenation, and thereby regional blood flow, can be monitored.⁴⁷ A study of near-infrared spectroscopy during CSF infusion studies and among patients with traumatic brain injury

show that changes in oxygenation correlate with vasogenic ICP slow waves.⁴⁸ The applicability of these findings to other settings is unclear.

Conclusion

Countless techniques have been brought to bear on the problem of non-invasive ICP assessment and monitoring, but so far, no individual technique clearly represents a complete solution. It may be possible to improve upon the capabilities of a single technique by combining it with other complementary techniques. Indeed, this approach has already met with some success.^{49,50}

However, because the diagnostic criteria for many conditions, such as IIH, rely not only upon the ICP itself, but on the CSF contents, even if an accurate non-invasive method of assessing ICP was available, one could not yet fully escape the need for invasive ICP measurements, at least for diagnosis. It is likely though that as technology advances we will be able to even non-invasively estimate the contents of the CSF. In fact, such a method currently exists for CSF lactic acid.⁵¹

As emphasized by Horton in a recent editorial on the results of the Idiopathic Intracranial Hypertension Treatment Trial,⁵² “performing lumbar punctures in a patient with IIH is often difficult and erroneous readings of CSF pressure are not uncommon. Even if the opening pressure is recorded accurately, it represents only a single value for a parameter that varies substantially during the course of a normal day. There is an urgent need for a reliable, noninvasive technique to measure human ICP.” Although several promising methods have been suggested for the non-invasive assessment of ICP, none is currently reliable for predicting a given patient’s ICP.

References

1. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry*. 2004; 75:813–821. [PubMed: 15145991]
2. Langfitt TW, Weinstein JD, Kassell NF, Simeone FA. Transmission of Increased Intracranial Pressure: I. Within the Craniospinal Axis. *J Neurosurg*. 1964; 21:989–997. [PubMed: 14238966]
3. Gafson AR, Giovannoni G. Towards the incorporation of lumbar puncture into clinical trials for multiple sclerosis. *Mult Scler J*. 2012; 18:1509–1511.
4. Wayenberg JL, Raftopoulos C, Vermeylen D, Pardou A. Non-invasive measurement of intracranial pressure in the newborn and the infant: the Rotterdam teletransducer. *Arch Dis Child*. 1993; 69:493. [PubMed: 8285752]
5. Hiler M, Czosnyka M, Hutchinson P, Balestreri M, Smielewski P, Matta B, Pickard JD. Predictive value of initial computerized tomography scan, intracranial pressure, and state of autoregulation in patients with traumatic brain injury. *J Neurosurg*. 2006; 104:731–737. [PubMed: 16703877]
6. Eisenberg HM, Gary HE, Aldrich EF, Saydjari C, Turner B, Foulkes MA, Jane JA, Marmarou A, Marshall LF, Young HF. Initial CT findings in 753 patients with severe head injury. *J Neurosurg*. 1990; 73:688–698. [PubMed: 2213158]
7. Mizutani T, Manaka S, Tsutsumi H. Estimation of intracranial pressure using computed tomography scan findings in patients with severe head injury. *Surg Neurol*. 1990; 33:178–184. [PubMed: 2315829]
8. Ridha MA, Saindane AM, Bruce BB, Riggeal BD, Kelly LP, Newman NJ, Biousse V. Magnetic Resonance Imaging Findings of Elevated Intracranial Pressure in Cerebral Venous Thrombosis

Versus Idiopathic Intracranial Hypertension with Transverse Sinus Stenosis. *Neuro-Ophthalmol.* 2013; 37:1–6.

9. Bialer OY, Rueda MP, Bruce BB, Newman NJ, Biousse V, Saindane AM. Meningoceles in Idiopathic Intracranial Hypertension. *Am J Roentgenol.* 2014; 202:608–613. [PubMed: 24555598]
10. Kelly LP, Saindane AM, Bruce BB, Ridha MA, Riggeal BD, Newman NJ, Biousse V. Does bilateral transverse cerebral venous sinus stenosis exist in patients without increased intracranial pressure? *Clin Neurol Neurosurg.* 2013; 115:1215–1219. [PubMed: 23219404]
11. Mallery R, Woo J, Tamhankar M, Shindler K, Chen Y, Medina E, Digre K, Friedman D, Liu G. MRI Findings of elevated intracranial pressure in pseudotumor cerebri syndrome with and without papilledema (S39.006). *Neurology.* 2014; 82 S39.006.
12. Jacks AS, Miller NR. Spontaneous retinal venous pulsation: aetiology and significance. *J Neurol Neurosurg Psychiatry.* 2003; 74:7–9. [PubMed: 12486256]
13. Morgan WH, Lind CRP, Kain S, Fatehee N, Bala A, Yu DY. Retinal Vein Pulsation Is in Phase with Intracranial Pressure and Not Intraocular Pressure. *Invest Ophthalmol Vis Sci.* 2012; 53:4676–4681. [PubMed: 22700710]
14. Levin BE. The clinical significance of spontaneous pulsations of the retinal vein. *Arch Neurol.* 1978; 35:37–40. [PubMed: 619871]
15. Wong SH, White RP. The Clinical Validity of the Spontaneous Retinal Venous Pulsation. *J Neuro-Ophthalmol March* 2013. 2013; 33:17–20.
16. Firsching R, Schütze M, Motschmann M, Behrens-Baumann W. Venous ophthalmodynamometry: a noninvasive method for assessment of intracranial pressure. *J Neurosurg.* 2000; 93:33–36. [PubMed: 10883902]
17. Li Z, Yang Y, Lu Y, Liu D, Xu E, Jia J, Yang D, Zhang X, Yang H, Ma D, Wang N. Intraocular pressure vs intracranial pressure in disease conditions: A prospective cohort study (Beijing iCOP study). *BMC Neurol.* 2012; 12:66. [PubMed: 22862817]
18. Motschmann M, Müller C, Kuchenbecker J, Walter S, Schmitz K, Schütze M, Behrens-Baumann W, Firsching R. Ophthalmodynamometry: a reliable method for measuring intracranial pressure. *Strabismus.* 2001; 9:13. [PubMed: 11262696]
19. Hansen HC, Helmke K. Validation of the optic nerve sheath response to changing cerebrospinal fluid pressure: ultrasound findings during intrathecal infusion tests. *J Neurosurg.* 1997; 87:34–40. [PubMed: 9202262]
20. Geeraerts T, Newcombe VF, Coles JP, Abate MG, Perkes IE, Hutchinson PJ, Outtrim JG, Chatfield DA, Menon DK. Use of T2-weighted magnetic resonance imaging of the optic nerve sheath to detect raised intracranial pressure. *Crit Care.* 2008; 12:R114. [PubMed: 18786243]
21. Gibby WA, Cohen MS, Goldberg HI, Sergott RC. Pseudotumor cerebri: CT findings and correlation with vision loss. *Am J Roentgenol.* 1993; 160:143–146. [PubMed: 8416612]
22. Rajajee V, Vanaman M, Fletcher JJ, Jacobs TL. Optic Nerve Ultrasound for the Detection of Raised Intracranial Pressure. *Neurocrit Care.* 2011; 15:506–515. [PubMed: 21769456]
23. Kimberly HH, Shah S, Marill K, Noble V. Correlation of Optic Nerve Sheath Diameter with Direct Measurement of Intracranial Pressure. *Acad Emerg Med.* 2008; 15:201–204. [PubMed: 18275454]
24. Bäuerle J, Nedelmann M. Sonographic assessment of the optic nerve sheath in idiopathic intracranial hypertension. *J Neurol.* 2011; 258:2014–2019. [PubMed: 21523461]
25. Rosenberg JB, Shiloh AL, Savel RH, Eisen LA. Non-invasive Methods of Estimating Intracranial Pressure. *Neurocrit Care.* 2011; 15:599–608. [PubMed: 21519957]
26. Kupersmith MJ, Sibony P, Mandel G, Durbin M, Kardon RH. Optical Coherence Tomography of the Swollen Optic Nerve Head: Deformation of the Peripapillary Retinal Pigment Epithelium Layer in Papilledema. *Invest Ophthalmol Vis Sci.* 2011; 52:6558–6564. [PubMed: 21705690]
27. Heckmann JG, Weber M, Jünemann AG, Neundörfer B, Mardin CY. Laser scanning tomography of the optic nerve vs CSF opening pressure in idiopathic intracranial hypertension. *Neurology.* 2004; 62:1221–1223. [PubMed: 15079033]
28. Fountas KN, Kapsalaki EZ, Machinis TG, Boev AN, Robinson JS III, Troup EC. Clinical implications of quantitative infrared pupillometry in neurosurgical patients. *Neurocrit Care.* 2006; 5:55–60. [PubMed: 16960298]

29. Jerin C, Gürkov R. Posture-induced changes of ocular vestibular evoked myogenic potentials suggest a modulation by intracranial pressure. *Exp Brain Res*. 2014;1–7. [PubMed: 24240388]
30. Silverman CA, Linstrom CJ. How to Measure Cerebrospinal Fluid Pressure Invasively and Noninvasively. *J Glaucoma* June. 2013;16–17.
31. Samuel M, Burge DM, Marchbanks RJ. Tympanic membrane displacement testing in regular assessment of intracranial pressure in eight children with shunted hydrocephalus. *J Neurosurg*. 1998; 88:983–995. [PubMed: 9609292]
32. Büki B, Avan P, Lemaire JJ, Dordain M, Chazal J, Ribári O. Otoacoustic emissions: a new tool for monitoring intracranial pressure changes through stapes displacements. *Hear Res*. 1996; 94:125–139. [PubMed: 8789818]
33. Olzowy B, Gleichenstein G von, Canis M, Mees K. Distortion product otoacoustic emissions for assessment of intracranial hypertension at extreme altitude? *Eur J Appl Physiol*. 2008; 103:19–23. [PubMed: 18188584]
34. Voss SE, Horton NJ, Tabucchi THP, Folowosele FO, Shera CA. Posture-induced changes in distortion-product otoacoustic emissions and the potential for noninvasive monitoring of changes in intracranial pressure. *Neurocrit Care*. 2006; 4:251–257. [PubMed: 16757834]
35. York DH, Pulliam MW, Rosenfeld JG, Watts C. Relationship between visual evoked potentials and intracranial pressure. *J Neurosurg*. 1981; 55:909–916. [PubMed: 7299465]
36. York D, Legan M, Benner S, Watts C. Further Studies with a Noninvasive Method of Intracranial Pressure Estimation. *Neurosurg* April 1984. 1984; 14:456–461.
37. Andersson L, Sjölund J, Nilsson J. Flash visual evoked potentials are unreliable as markers of ICP due to high variability in normal subjects. *Acta Neurochir (Wien)*. 2012; 154:129–129. [PubMed: 21959964]
38. Chen H, Wang J, Mao S, Dong W, Yang H. A New Method of Intracranial Pressure Monitoring by EEG Power Spectrum Analysis. *Can J Neurol Sci*. 2012; 39:483–487. [PubMed: 22728855]
39. Ragauskas A, Matijosaitis V, Zakelis R, Petrikonis K, Rastenyte D, Piper I, Daubaris G. Clinical assessment of noninvasive intracranial pressure absolute value measurement method. *Neurology*. 2012; 78:1684–1691. [PubMed: 22573638]
40. Citerio G, Piper I, Chambers IR, Galli D, Enblad P, Kiening K, Ragauskas A, Sahuquillo J, Gregson B. Multicentre clinical assessment of the Raumedic Neurovent-P intracranial pressure sensor: a report by the BrainIT Group. *Neurosurgery*. 2008; 63:1152–1158. [PubMed: 19057328]
41. Ragauskas A, Bartusis L, Piper I, Zakelis R, Matijosaitis V, Petrikonis K, Rastenyte D. Improved diagnostic value of a TCD-based non-invasive ICP measurement method compared with the sonographic ONSD method for detecting elevated intracranial pressure. *Neurol Res*. 2014 1743132813Y.0000000308.
42. Alperin NJ, Lee SH, Loth F, Raksin PB, Lichtor T. MR-Intracranial Pressure (ICP): A Method to Measure Intracranial Elastance and Pressure Noninvasively by Means of MR Imaging: Baboon and Human Study. *Radiology*. 2000; 217:877–885. [PubMed: 11110957]
43. Glick RP, Niebruegge J, Lee SH, Egibor O, Lichtor T, Alperin N. Early experience from the application of a noninvasive magnetic resonance imaging-based measurement of intracranial pressure in hydrocephalus. *Neurosurgery*. 2006; 59:1052–1060. discussion 1060–1061. [PubMed: 17143240]
44. Muehlmann M, Koerte IK, Laubender RP, Steffinger D, Lehner M, Peraud A, Heinen F, Kiefer M, Reiser M, Ertl-Wagner B. Magnetic resonance-based estimation of intracranial pressure correlates with ventriculoperitoneal shunt valve opening pressure setting in children with hydrocephalus. *Invest Radiol*. 2013; 48:543–547. [PubMed: 23695081]
45. Fountas KN, Sitkauskas A, Feltes CH, Kapsalaki EZ, Dimopoulos VG, Kassam M, Grigorian AA, Robinson JS, Ragauskas A. Is non-invasive monitoring of intracranial pressure waveform analysis possible? Preliminary results of a comparative study of non-invasive vs. invasive intracranial slow-wave waveform analysis monitoring in patients with traumatic brain injury. *Med Sci Monit Int Med J Exp Clin Res*. 2005; 11:CR58–63.
46. Michaeli D, Rappaport ZH. Tissue resonance analysis: a novel method for noninvasive monitoring of intracranial pressure. *J Neurosurg*. 2002; 96:1132–1137. [PubMed: 12066918]

47. Ghosh, AMbc; Elwell, C.; Smith, MM. Cerebral Near-Infrared Spectroscopy in Adults: A Work in Progress. *Anesth Analg* Dec 2012. 2012; 115:1373–1383.
48. Weerakkody RA, Czosnyka M, Zweifel C, Castellani G, Smielewski P, Brady K, Pickard JD, Czosnyka Z. Near infrared spectroscopy as possible non-invasive monitor of slow vasogenic ICP waves. *Acta Neurochir Suppl.* 2012; 114:181–185. [PubMed: 22327689]
49. Golzan, SM.; Avolio, A.; Graham, SL. Non-invasive cerebrospinal fluid pressure estimation using multi-layer perceptron neural networks. 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); 2012. p. 5278-5281.
50. Zhong JI, Li Y, Minhui X, Yihua Z. Realization of a comprehensive non-invasive detection of intracranial pressure analyzer based upon FVEP and TCD. *Acta Neurochir Suppl.* 2012; 114:127–129. [PubMed: 22327677]
51. Goh JH, Mason A, Al-Shamma'a AI, Field M, Shackcloth M, Browning P. Non Invasive Microwave Sensor for the Detection of Lactic Acid in Cerebrospinal Fluid (CSF). *J Phys Conf Ser.* 2011; 307:012017.
52. Horton JC. Acetazolamide for Pseudotumor Cerebri: Evidence From the NORDIC Trial. *JAMA.* 2014; 311:1618–1619. [PubMed: 24756510]

Table**Approaches to the non-invasive assessment of cerebrospinal fluid pressure**

Method	Finding/value associated with increased ICP
<u>Neuroradiologic epiphenomena</u>	
<i>Computed tomography</i>	Presence of any in patients with head trauma
- Midline shift	
- Absent/compressed basal cisterns	
- Absent/compressed third ventricle	
- Intracerebral hemorrhage	
<i>Magnetic resonance imaging</i>	Presence of an increasing number, especially 3
- Empty sella turcica	
- Optic disc protrusion into the globe	
- Flattening of the posterior globe	
- Prominence of the perioptic nerve CSF spaces	
- Tortuosity of the optic nerve	
- Cerebral transverse venous sinus stenosis	
- Meningoceles	
<u>Ophthalmic</u>	
<i>Spontaneous venous pulsations</i>	Presence associated with <i>normal</i> ICP
<i>Intraocular pressure</i>	Increasing values
<i>Venous ophthalmodynamometry</i>	Increasing central retinal venous pressure
<i>Optic nerve sheath diameter</i>	Diameter > 5 mm by ultrasound
<i>Optical coherence tomography</i>	Deflection of peripapillary RPE/Bruch's membrane into eye
<i>Scanning laser tomography</i>	Increasing optic nerve head volume/height
<i>Pupillometry</i>	Decreased light response
<u>Otic</u>	
<i>Ocular vestibular evoked myogenic potentials</i>	Decreasing amplitude
<i>Tympanic membrane displacement</i>	Negative displacements
<i>Otoacoustic emission</i>	Phase lead of components below 2 kHz
<u>Electrophysiologic</u>	
<i>Visual evoked potentials</i>	Increasing N ₂ latency
<i>Electroencephalography</i>	Decreasing pressure index derived from spectrum analysis
<u>Fluid Dynamic</u>	
<i>Two-depth transcranial Doppler</i>	Increasing difference between intracranial and intraorbital ophthalmic artery pressure
<i>Magnetic resonance imaging based elastance index</i>	Increasing elastance index derived from transcranial CSF and blood flow and CSF velocity
<i>Ultrasound time of flight</i>	Impaired cerebral autoregulation
<i>Near-infrared spectroscopy</i>	High positive correlation between Hb and HbO ₂

CSF=cerebrospinal fluid, ICP=intracranial pressure, RPE=retinal pigment epithelium