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, 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. Yet, LP is still an invasive, and often painful, test that provides only a snapshot of the ICP, a quantity which varies substantially over time, particularly in certain disease states. 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. In adults, the cranial cavity has very few windows for the non-invasive monitoring of ICP. The difficulty

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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. 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.

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 periorbital nerve CSF spaces, tortuosity of the optic nerve, cerebral transverse venous sinus stenosis, and meningoceles. Some of these findings have been described in patients with normal ICP occurring both in isolation and in combination; however, an increasing number of these epiphenomena occurring in the same patient appears to be associated with a higher likelihood of raised ICP. Indeed, 3 or more of these signs occurring in the same patient is extremely suggestive of increased ICP, although there are occasional exceptions, 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, and SVPs were recently demonstrated to be in phase with the ICP. SVPs are not observed in about 10% of normal patients; so their absence is generally not interpretable, but several studies have suggested that SVPs are only present when the ICP is normal.

However, a recent prospective study found that the sensitivity of the presence of SVPs for normal ICP was 94%, 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. 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. 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. In contrast, the presence of SVPs indicates that the IOP is close to the central retinal venous pressure. 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 (R²=0.109) leading to poor accuracy. 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. 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). The expansion has been shown to be reversible, at least in the acute setting. 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. Several studies have demonstrated that enlargement of the optic nerve sheath is strongly associated with increased ICP in emergency department and neurocritical care patients. Similarly, the optic nerve sheath has been shown to be enlarged in patients with IIH compared with controls.

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). 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. 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. 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.\(^2^6\) 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.\(^2^7\)

**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 cmH\(_2\)O) 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.\(^2^8\) 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.\(^2^9\)

**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.\(^3^0\)
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textit{et al.} in the early 1980s found a relatively strong relationship ($R^2=0.7$) between ICP and the N\textsubscript{2} latency of the visual evoked potential (VEP).\textsuperscript{35,36} No ophthalmic examination appears to have been performed to rule out ophthalmic disease that could affect the VEP, but the strong intrapatient correlations with ICP were quite remarkable.\textsuperscript{35} More recent studies, however, have suggested that high variability in normal subjects limits the ability of VEP to predict ICP.\textsuperscript{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.\textsuperscript{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 mmH2O (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 (R²=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 intervention 43 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 an 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 (R²=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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{51}

As emphasized by Horton in a recent editorial on the results of the Idiopathic Intracranial Hypertension Treatment Trial,\textsuperscript{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**


## Table

Approaches to the non-invasive assessment of cerebrospinal fluid pressure

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