Measuring Elevated Intracranial Pressure through Noninvasive Methods: A Review of the Literature

Helena Kristiansson, MD, Emelie Nissborg, MD,* Jiri Bartek, Jr, MD,†‡ Morten Andresen, MD,‡ Peter Reinstrup, MD, PhD,*§ and Bertil Romner, MD, PhD*‡*

Abstract: Elevated intracranial pressure (ICP) is an important cause of secondary brain injury, and a measurement of ICP is often of crucial value in neurosurgical and neurological patients. The gold standard for ICP monitoring is through an intraventricular catheter, but this invasive technique is associated with certain risks. Intraparenchymal ICP monitoring methods are considered to be a safer alternative but can, in certain conditions, be imprecise due to zero drift and still require an invasive procedure. An accurate noninvasive method to measure elevated ICP would therefore be desirable. This article is a review of the current literature on noninvasive methods for measuring and evaluating elevated ICP. The main focus is on studies that compare noninvasively measured ICP with invasively measured ICP. The aim is to provide an overview of the current state of the most common noninvasive techniques available. Several methods for noninvasive measuring of elevated ICP have been proposed: radiologic methods including computed tomography and magnetic resonance imaging, transcranial Doppler, electroencephalography power spectrum analysis, and the audiological and ophthalmological techniques. The noninvasive methods have many advantages, but remain less accurate compared with the invasive techniques. None of the noninvasive techniques available today are suitable for continuous monitoring, and they cannot be used as a substitute for invasive monitoring. They can, however, provide a reliable measurement of the ICP and be useful as screening methods in select patients, especially when invasive monitoring is contraindicated or unavailable.

Key Words: intracranial pressure, non invasive/noninvasive, MRI/magnetic resonance imaging, CT/computed tomography, EEG/electroencephalography, TCD/transcranial Doppler, tympanic membrane displacement, otoacoustic emissions, distorsion product otoacoustic emissions, optic nerve sheath diameter

(*J Neurosurg Anesthesiol* 2013;25:372–385)

Assessment of the intracranial pressure (ICP) is crucial in many neurological and neurosurgical patients. Clinical signs of elevated ICP, such as headache, altered level of consciousness, and vomiting, are considered to be nonspecific and unreliable predictors of the condition. Elevated ICP, defined as ICP $\geq$ 20 mm Hg, is an important cause of secondary brain injury and may be associated with a poor outcome. Conditions where ICP monitoring may be of value include a wide range of disorders, including traumatic brain injury (TBI), intracerebral hemorrhage, subarachnoid hemorrhage (SAH), hydrocephalus, benign intracranial hypertension, meningitis, stroke, acute liver failure, etc.[1,2]

The gold standard for continuous ICP monitoring is an intraventricular catheter connected to an external pressure transducer.[3] This method has been shown to be the most accurate and low-cost method available for ICP monitoring, and it can also be used for therapeutic cerebrospinal fluid (CSF) drainage and administration of drugs.[4] However, the procedure is invasive, and it is at times complicated by infection, hemorrhage, malfunction, obstruction, and malpositioning.[3] Infection rates in the wide range of 1% to 20% have been reported[5–7] and 2 relatively new meta-analyses found hemorrhagic complications in 6% to 7% of patients.[8,9] There are also situations where intraventricular catheters cannot be placed, because of hemostasis abnormalities, severe brain swelling with compressed ventricles, or the lack of available neurosurgeons.[2] In many units, intraparenchymal ICP monitors are used as a first-line monitoring method and are considered to be safe and of comparable technical and clinical quality to the intraventricular measurements.[10] The intraparenchymal monitors still require an invasive procedure and cannot be recalibrated once inserted, which can make the measurements imprecise due to a zero drift.[11,12] Considered to be less accurate, subdural and epidural devices are rarely used in neurosurgical practice,[13] whereas lumbar measurements of CSF pressure are frequently used by neurologists.

Because of the above-mentioned drawbacks with the invasive methods, an accurate noninvasive method to

Received for publication October 16, 2012; accepted April 17, 2013.
From the *Department of Neurosurgery; §Department of Intensive and Perioperative Care, University Hospital of Lund, Lund; †Department of Clinical Neuroscience, Section for Neurosurgery, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; and ‡Department of Neurosurgery, Copenhagen University Hospital Rigshospitalet, Denmark.
H.K. and E.N. shared first authorship.
The authors have no funding or conflicts of interest to disclose.
Reprints: Jiri Bartek Jr, MD, Department of Clinical Neuroscience, Section for Neurosurgery, Karolinska University Hospital, Karolinska Institutet, Karolinskavägen, 17176 Stockholm, Sweden (e-mail: jiri.bartek@karolinska.se).

measure ICP has long been looked for. Several methods for noninvasive measuring of ICP have been proposed such as computed tomography (CT), magnetic resonance imaging (MRI), transcranial Doppler (TCD), electroencephalography (EEG), and the audiological and ophthalmological techniques.

The aim of this review was to provide an overview of the current state of the most common noninvasive techniques available for measuring ICP. The main focus was on studies that compare these methods with invasively obtained ICP.

METHODS

This is a general review of the literature on noninvasive methods for estimating ICP. The review is based on a selection of articles listed in PubMed, with no limits imposed on the date of publication, by searching specific keywords. The first search was carried out in March 2012 and the last in December 2012. A search using the medical subject headings (MeSH) and free-text terms, "intracranial pressure" in combination with "non invasive" or "noninvasive," was performed. The results of this search provided a total of 496 articles. On the basis of these results, the most commonly described noninvasive methods for estimating elevated ICP were identified. Additional specific keywords with respect to these methods were then included in the search strategy: "intracranial pressure" in combination with "non invasive" or "noninvasive" and "diagnostic imaging," "MRI," "magnetic resonance imaging," "tomography x-ray computed," "computed tomography," CT, EEG, "transcranial doppler", TCD, Doppler, "tympanic membrane displacement," "otoacoustic emissions," "distortion product otoacustic emissions," "optic nerve sheath diameter," "NIRS," "Near infrared spectroscopy," "NPi," and "Neurological Pupil index." Only articles published in English were reviewed. Abstracts were independently assessed by the 2 first authors (E.N. and H.K.). All articles regarding noninvasive estimations of elevated ICP were selected and reviewed in their entirety. Differences in the selection were resolved by consensus between all authors. Finally, to eliminate the possibility of missed articles, the reference lists of the included articles were manually reviewed, and an additional selection of studies was made.

NONINVASIVE TECHNIQUES FOR ICP MEASUREMENTS

CT

CT is a commonly used tool to evaluate the intracranial state in neurological and neurosurgical patients. An initial CT scan is—in combination with clinical symptoms and signs—often used as a first guide to diagnosis and subsequent management of these patients. A variety of CT findings have been suggested to be predictive of elevated ICP, including abnormal morphology of cisterns and ventricles, midline shift, hematoma, subarachnoid blood, size of sulci, and gray/white matter differentiation. Results regarding which of these parameters to use and how well they correlate to ICP are inconclusive.[14] Abnormal basal cisterns have been suggested to be one of the main parameters correlating with increased ICP.[15–18] Toutant et al[16] found that 74% of patients with absent basal cisterns had an ICP exceeding 30 mm Hg. Similar results were reported by Eisenberg et al,[15] who found that abnormal cisterns were associated with a 3-fold increased risk of elevated ICP. However, Kouvarellis et al[17] emphasized that normal basal cisterns do not exclude the presence of increased ICP. In their study of 57 children with severe TBI, 40% of the children with normal cisterns had at least 1 episode of ICP $\geq$ 20 mm Hg and 15% had an average ICP of $\geq$ 20 mm Hg.

Studies conducted on patients with acute head injury and a normal CT scan show a risk of elevated ICP from 0% to 88%.[14] Attempts have been made to measure ICP from multiple CT scan using different scoring systems.[18,19] In a complex model using 39 checkpoints, Mizutani et al[18] showed that 80% of predicted ICP were within the range of invasively measured ICPs $\pm$ 10 mm Hg for ICP < 30 mm Hg, whereas a large discrepancy between the measured and predicted ICPs was found for ICP > 40 mmHg. In a more simplified model, using only 5 parameters, Miller et al[19] concluded in their results that a predictive model could not be obtained. However, a linear relationship between the change in CT and the change in ICP was demonstrated opening up for the possibility of creating a predictive model.

Because of these results, a CT scan can indicate the presence of high ICP with high specificity but low sensitivity. It must therefore be emphasized that a normal CT scan cannot exclude the presence of an elevated ICP as there is a high possibility of false-negative results.

CT is a noninvasive method based on x-rays and therefore associated with the risks of exposure to ionizing radiation. This is of particular importance in children requiring repeated measurements as they have a greater susceptibility to radiation and a longer life expectancy.[20,21]

From the authors' perspective, a CT scan is a valuable clinical asset, which helps to guide neurologists and neurosurgeons to quickly and effectively diagnose possible pathology in patients presenting with clinical signs or symptoms of raised ICP. Furthermore, in this patient category, a CT usually helps in deciding which management strategy to choose. Nevertheless, caution is advised, as a normal CT does not exclude raised ICP, and the clinician should always have this in mind while treating patients with suspected rise in ICP.

MRI

The MRI-based techniques to measure ICP use the relationship between intracranial compliance and pressure.[22,23] The exponential pressure-volume curve (Fig. 1) first introduced by Marmarou et al[24] shows that when the initial ICP is low, a small given volume will cause a small pressure change due to the compliance of the brain. When the initial pressure increases, compliance is reduced, and the same given volume will cause a larger pressure change. By measuring the intracranial volume and

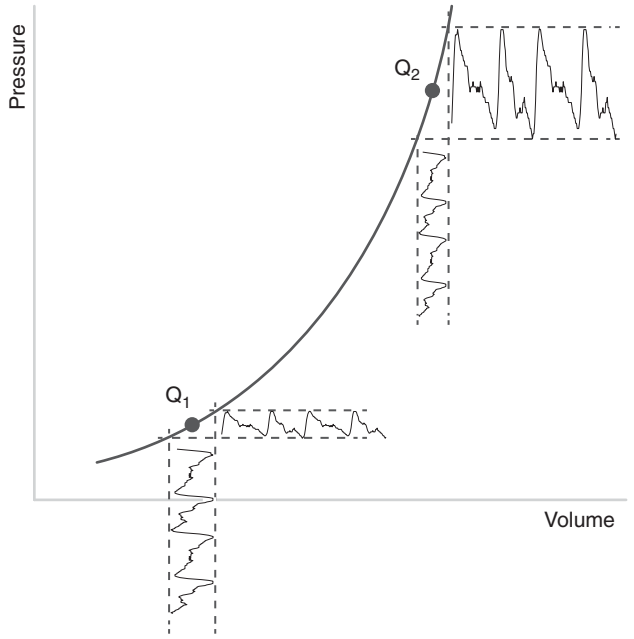

FIGURE 1. The pressure-volume curve describes the nonlinear relationship between rising volume and intracranial pressure. At high volumes the compensatory reserve is diminished, and even small increases in volume causes marked increases in pressure.

pressure fluctuations that occur during each cardiac cycle, a method has been proposed to calculate intracranial elastance. Elastance is defined as the ratio of $\Delta P/\Delta V$, the inverse of compliance. The volume change, ΔV, is derived from phase-contrast MRI measurements of arterial, venous, and CSF flows that occur in and out of the cranial vault during each cardiac cycle. The pressure change, ΔP, is derived from the CSF velocities, which are calculated from velocity-encoded MRI images. A mean ICP value is derived through the linear relationship between elastance and ICP.[22] In an attempt to implement this method clinically, Alperin et al[22] found a strong correlation ($r = 0.98$ $P < 0.005$) between the MRI-derived elastance index and the invasively obtained ICP measurements.

Marshall et al[25] have examined the variability of the parameters described by Alperin and colleagues,[22,26–29] and found a modest to poor repeatability. They note that care is required when selecting image planes because of interindividual variation in vasculature anatomy, that the difference between the arterial inflow and the venous outflow is small, which makes the method very sensitive to errors during measurement, and that the method is sensitive to heart-rate changes leading to intraindividual variations between the repeated measurements. The authors therefore concluded that caution is required when interpreting isolated examinations. Dhoondia[30] have come up with a technique to overcome the difficulties with variations in heart rate; however, this function is not available on clinical MRI systems.[25]

In a recent study of 28 patients, Zhang et al[23] correlated cine phase-contrast MRI-derived CSF peak flow velocity measured in the aqueduct of the midbrain with ICP obtained from lumbar puncture. In 22 patients, a craniocaudal CSF flow was found, which correlated well with ICP ($r = 0.69$, $P < 0.01$). In the remaining 6 patients, a cranial CSF flow was found and no correlation with ICP could be established.

From the authors' perspective, MRI has the same clinical applications as a CT with regards to identifying and managing pathology responsible for raised ICP. Nevertheless, being costly and time consuming, CT is instead the preferred diagnostic modality—especially in emergency situations. We also believe that the MRI technique may be able to provide an indirect measurement of the ICP, but, at the present time, MRI-derived measurements of ICP are not sufficiently reliable. In addition, the technique is cumbersome and cannot be recommended for clinical use.

TCD

The TCD technique for monitoring cerebral hemodynamics was introduced by Aaslid et al[31] in 1982. By using a low-frequency–pulsed Doppler of 2 MHz over the acoustic window regions—where the skull bone is thin—or at the foramen magnum, it is possible to measure flow velocities in the basal cerebral arteries. A broad spectrum of usage scenarios for TCD have been proposed, including detection of vasospasm in SAH, detection of cerebral embolization, and arterial stenoocclusive disease, evaluation of collateral circulation, evaluation of recanalization, cerebrovascular autoregulation, detection of cerebral circulatory arrest, and for measuring ICP.[32,33] The American Society of Neuroimaging's Practice Guidelines Committee has developed standardized guidelines for TCD performance.[34,35]

TCD Technique and ICP

In 1987, Klingelhöfer and colleagues[36,37] first described a relationship between increasing ICP and decreasing TCD-derived flow velocities and an increase in the Pourcelot index or resistance index (RI), defined as $RI = (FV_{peak\ sys} - FV_{end\ dia})/(FV_{peak\ sys})$. Since then, different approaches have been attempted, in order to find the "ultimate" TCD variable to define the relationship to ICP.[38] The Gosling pulsatility index (PI), defined as $PI = (FV_{peak\ sys} - FV_{end\ dia})/(FV_{mean})$,[39] first introduced in the 1970s, is currently the most commonly used formula. The indices are based on the change that occurs in the TCD-derived pulse curve when the intracranial hemodynamic changes. As ICP increases, the diastolic flow velocity is more reduced compared with the systolic flow velocity, resulting in an increased pulse peak between the diastole and the systole and hence in the PI and RI (Fig. 2). Flow velocity values derived from TCD are dependent on the angle of insonation. A main advantage with PI and RI are that they are ratios, derived from the difference between the systolic and diastolic velocities, and thus are not affected by the angle of insonation.[40] Several authors have supported the notion that PI is a reflection of distal cerebrovascular

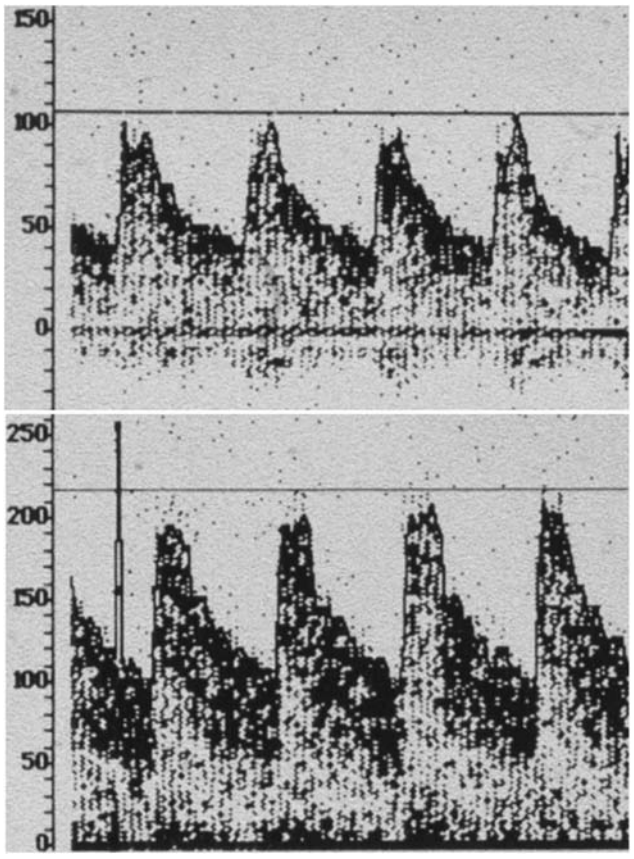

FIGURE 2. Graphical representation of the effect of changes in intracranial pressure (ICP) on the transcranial Doppler waveform appearance. The top waveform is an example of a normal pulsatility index (PI) of roughly 0.7, and ICP of 5 to 10 mm Hg. The bottom waveform is an example of a moderately raised ICP with PI 1.2.

resistance (CVR).[41,42] However, this interpretation has been disputed. In a rabbit study, Czosnyka et al[43] showed that a decrease in CVR in 2 different situations, hypercapnia and decreased cerebral perfusion pressure (CPP), produced different PI responses, such as a decrease and an increase in PI, respectively. Furthermore, in 2012, de Riva et al[44] showed an increase in PI both during ICP sequences with plateau waves (vasodilation and CVR decrease) and during hypocapnia (vasoconstriction and CVR increase), and, therefore, they concluded that PI could not be interpreted as an index of CVR alone.

TCD Versus Invasive Techniques

In a study of 10 head-injured patients in 1993, Homburg et al[45] correlated the TCD-derived PI with invasively obtained ICP and suggested that Doppler monitoring may replace the former invasive ICP monitoring. Since then, several authors have tried to investigate the direct correlation between TCD-derived indices and invasively obtained ICP values.[44–52] The obtained correlation coefficients from the studies comparing PI with ICP vary between 0.36 and 0.94 (Table 1). Most of these studies support the use of TCD as a predictor of ICP; however, doubts have been raised with respect to its reliability and to what extent the method is applicable in clinical practice. Eight of these studies[44,46–52] found a positive linear correlation between PI and ICP, whereas the study by Homburg et al[45] found an exponential correlation. The aim, currently, is to find an equation that adequately and reliably describes ICP as a function of the TCD findings. However, 5 of these studies describe correlation coefficients derived from equations that calculate PI from ICP, that is, PI as a function of ICP, which must be considered to be a limitation of these studies.[44,45,47–48,52] Another difference between the studies is that some of them used repeated measurements from each patient,[49–51] whereas others used a single measurement from each patient.[46,47,52] To be able to use PI in clinical practice, it must be shown how well the PI-derived ICP can predict the actual ICP. Bellner et al[49] was the only group that made a statistical prediction. They found that the ICP value predicted from the PI was within $\pm$ 4.2 mm Hg of the actual ICP, with a 95% confidence interval, in the ICP range of 5 to 40 mm Hg. In an attempt to investigate 3 previously described equations for estimating ICP from TCD measurements,[49,53,54] Brandi et al[55] compared the ICP estimated by TCD with invasively obtained ICP in

TABLE 1. Correlations Between PI and Invasively Obtained ICP in all Studies Investigating the Direct Correlation Between TCD-derived PI and Invasively Obtained ICP

References	Study Size (Measurements)	Patient Group	Results
Homburg et al[45]	10 (58)	TBI	$r = 0.82$ ($P < 0.001$)
Moreno et al[47]	125 (125)	TBI	$r = 0.83$ ($P < 0.0001$)
Rainov et al[52]	29 (29)	Hydrocephalus	$r = 0.37$ ($P < 0.075$)
Bellner et al[49]	81 (658)	Various intracranial disorders*	$r = 0.94$ ($P < 0.0001$)
Voulgaris et al[48]	37 (165)	TBI	$r = 0.64$ ($P < 0.0001$)
Figaji et al[51]	34 (275)	TBI children	$r = 0.36$ ($P = 0.038$)
Gura et al[46]	52 (52)	TBI	Day 1: $r = 0.57$ ($P < 0.0001$) Day 3: $r = 0.53$ ($P < 0.0001$) Day 5: $r = 0.78$ ($P < 0.0001$)
Behrens et al[50]	8 (35)	NPH	$r = 0.47$ ($P < 0.01$)
de Riva et al[44]	51	TBI	$r = 0.70$

*Subarachnoid hemorrhage, severe head injury, spontaneous intracerebral hemorrhage, other neuological disorders.
ICP indicates intracranial pressure; NPH, normal pressure hydrocephalus; PI, pulsatility index; TBI, traumatic brain injury.

45 TBI patients. The equation proposed by Bellner et al[49] ($ICP = 10.972 \times PI - 1.284$) proved to be the superior, with a median ICP difference, ± 2-fold SD −3.2 ± 12.6 mm Hg, between the measured and invasively obtained ICP values.

A novel technique by Ragauskas et al[56] is based on a 2-depth TCD technique for simultaneous measurement of flow velocities in the intracranial and extracranial segments of the ophtalmic artery made before, during, and after the application of small pressure steps to the tissue surrounding the eyeball. This technique was tested in patients with invasive ICP pressure monitors, and, on comparison, this technique showed a low mean systematic error and a low SD of the paired recordings of invasive and noninvasive ICPs. The limitations of this technique are that it can only be applied on individuals with healthy eyes and orbits and that it has an upper ICP pressure range of 25 mm Hg.

TCD as a Predictor of Outcome

Ract et al[57] correlated early TCD measurements in TBI patients, with outcome, evaluated 3 months later by using the Glasgow Outcome Score (GOS),[58] defined as GOS: 1: good recovery, 2: moderate disability, 3: severe disability, 4: vegetative state, and 5: dead. Outcome was significantly ($P < 0.006$) poorer, median GOS 3 (range, 1 to 5), in a group with abnormal ($FV_{mean} < 30$ cm/s, $FV_{dia} < 20$ cm/s, $PI > 1.4$) TCD compared with median GOS 1 (range, 1 to 2) in a group with normal TCD. These findings suggest that TCD might have an important role in early management of TBI. In line with this, Moreno et al[47] correlated PI with outcome, measured as a 6-month follow-up by using the GOS, in patients suffering from severe TBI. $PI < 1$ measured within the first 24 hours predicted good outcome in 71% of the patients and $PI > 1.56$ predicted poor outcome in 83% of the patients. The mortality rate was 100% in patients with a $PI > 2.3$. Even in a pediatric cohort of 36 children (mean age 7 ± 4 y), with moderate or severe head trauma, Trabold et al[59] found a significant association between abnormal TCD ($FV_{end\ dia} < 25$ cm/s or $PI > 1.31$ or no-flow/backflow) on admission and outcome at discharge.

TCD in a Pediatric Population

As the cerebral hemodynamics is considered to be different in children, it is important to validate the use of TCD in children and to learn the differences of TCD in children.[60] The mean flow velocities and PI have been shown to vary with sex and age in healthy children between 2 and 19 years of age.[61] Other factors, suggested to influence the hemodynamics, are open or closed fontanels and patent ductus arteriosus.[62] In addition, physiological ICP is lower in children and they have a lower threshold for elevated ICP, varying with age.

Two relatively new articles have been published studying the direct correlation of TCD and invasively obtained ICP in children with severe TBI.[51,63] In a study of 34 patients, 275 simultaneous measurements of TCD, ICP, and CPP were performed. As only a weak relationship between the TCD-derived PI and invasively obtained ICP was found, the authors concluded that PI is not a reliable indicator of ICP in children with severe TBI.[51] In contrast, Melo et al[63] performed TCD on admission in 117 patients with severe TBI who later received intraparenchymal pressure transducers. They found that by using validated TCD thresholds ($FV_{end\ dia} < 25$ cm/s or $PI > 1.31$ or no-flow/backflow) the method had a 94% sensitivity in identifying patients who later developed intracranial hypertension ($ICP \geq 20$ mm Hg for > 10 min). They concluded that TCD is an excellent first-line examination to identify children in need of invasive ICP monitoring.

The use of TCD in childhood hydrocephalus has been more extensively investigated.[38,64–67] As clinical signs and radiologic findings in hydrocephalus in children are variable and unreliable,[64–66] TCD could provide a valuable tool to the subsequent management of these children.[62] However, none of the articles found were based on the direct correlation between ICP and the TCD-derived indices. Quinn et al[66] examined 63 children with symptoms of blocked ventriculoperitoneal shunts and found that 32 children who later required shunt revision had significantly higher PI values compared with the ones who did not require shunt revision. After the surgery, a reduction in the PI values was seen. Similar results have been reported in several studies on TCD in hydrocephalic children.[38,64,67] Hanlo et al[65] found an average decrease in the Doppler indices following shunt implantation, although it could not be demonstrated in all cases, and the authors thereby concluded that the present Doppler indices are currently inadequate for clinical use.

Limitations of the TCD Technique

The main limitation of TCD is the reliability of the values obtained, as they are affected by different operator-dependent factors, for example, the capability to locate an acoustic window and to obtain a strong pulse signal with the accurate depth and the angle of insonation.[42] The level of reproducibility has therefore been questioned, and the usefulness of TCD at smaller clinics, where the operators get limited practice, seems to be a limitation. In a study of repeated measurements in 20 healthy subjects, Baumgartner et al[68] found a good intraobserver reproducibility. This was also reported by Maeda et al,[69] who in addition showed a good interobserver reproducibility. Shen et al[42] reported a high level of interobserver agreement but concluded that a lack of regular practice during an 8-week break reduced the accuracy. In accordance with this, McMahon et al[70] found that interobserver reproducibility was better among experienced operators than among inexperienced and concluded that it is essential that operators are well trained. A minimum number of 25 to 50 TCD studies under supervision have been recommended.[71] All of the above-mentioned studies were performed on healthy adult volunteers.

Another main limitation is that inadequate temporal windows—where no or insufficient Doppler signals can be obtained—are found in 10% to 15% of all individuals. This

is due to bone thickness and is particularly found in elderly women.[32] In younger subjects, the temporal bone windows are larger and more accessible for TCD recordings.[61]

Flow velocities and therefore the TCD-derived pulse curve and PI are influenced by different physiological and pathologic conditions.[49,72] These include variations in pCO_2,[73] hematocrit, arterial blood pressure (ABP), arterial stenosis, the level of consciousness,[74] and microangiopathy in diabetes.[75] In addition, sedation will affect cerebral blood flow on the basis of the type of anesthetic used. PI should never be interpreted without the consideration of these factors. This is of particular importance when examining TBI patients in the emergency care unit, where alterations in these parameters, for example, a low hematocrit and a low pCO_2 during hyperventilation, are commonly found. Because of the vasoconstricting effect of a low pCO_2, high PI values will be obtained.[61] Consequently, PI may, under these circumstances, not be an accurate predictor of ICP.

TCD provides a snapshot of the cerebrovascular state. Blood flow velocities and PI have, however, been shown to fluctuate in patients suffering from head injury.[45,76] Venkatesh et al[76] showed greater variability in cerebral blood flow velocities in patients suffering from SAH compared with healthy volunteers. Homburg et al[45] suggested a state of "vascular instability" finding that PI values varied in patients during the unconscious phase to return to resemble PI of healthy individuals again after 3 to 4 days. Continuous monitoring with TCD would therefore be desirable, and trials have been made using head devices with fixed Doppler probes.[76,77] The continuous monitoring is problematic to use in clinical practice as it is hard to fixate and stabilize the right angles of the probes, which make the method prone to artifacts, especially during the movement of the patient.[77]

Studies conducted on TCD and PI use different cutoff values for PI. It is desirable that standardized cutoff values be obtained.[57] Normative reference data showed that PI might be higher in boys aged between 15 and 19 years compared with girls in the same age group and compared with boys in the younger age groups.[61]

It has been argued whether PI reflects ICP or CPP better. We found that 5 of the studies conducted on TBI made a direct comparison of PI with both ICP and CPP, 2 of them finding a better correlation between PI and CPP,[44,48] and 3 of them finding a better correlation between PI and ICP.[46,47,49] Zweifel et al[78] recently evaluated the association between the TCD-derived PI and ICP and CPP in a cohort of 209 head-injured patients. They analyzed the prospectively collected ABP, ICP, and cerebral blood flow velocities obtained by TCD. They showed that the 95% prediction interval of ICP values for a given PI was $> \pm 15$ mm Hg and for CPP $> \pm 25$ mm Hg. On that basis, the diagnostic value of the PI for direct noninvasive assessment of ICP and CPP is limited.

Further development of the technique is in process. New approaches to identify additional TCD waveform features, for example, changes of the slopes and angles of the pulse curve, in order to find a better correlation with an elevated ICP, a low CPP, or a decreased cerebral blood flow have been proposed with promising results.[79,80]

From the authors' perspective, the TCD technique has come a long way since being discovered in the 1980s, and it is now successfully being applied for vasospasm detection at intensive care units around the world. With regard to ICP monitoring, it is believed to be the most promising noninvasive technique.

TCD is useful in brain trauma situations as an initial screening tool to identify patients with elevated ICP.[79,80] An advantage of TCD in the emergency care setting is that it is noninvasive, easily accessible, and can be rapidly and repeatedly performed bedside, offering real-time measurements of the cerebrovascular state. Ract et al[79,80] investigated the use of TCD to identify patients at risk for secondary brain injury before invasive ICP measurements could be obtained. They concluded that early TCD goal–directed therapy improved early management in head-injured patients.

Although TCD-derived ICP-targeted therapy may be of use in the initial management of brain trauma situations, the authors believe that replacing continuous invasive ICP monitoring by frequent TCD-derived ICP values is still not clinically applicable. The current limitations of the TCD technique—mainly due to different operator-dependent factors and different physiological and pathologic conditions of the patient—still need to be overcome.

Furthermore, we believe that the focus for the future should be on isolating an equation that reliably describes ICP as a function of TCD findings. To be able to use PI in clinical practice, it must be shown how well the PI-derived ICP can predict the actual ICP. At present, PI is not able to accurately show the absolute "true" ICP but to a larger extent reveals the *changes* in ICP.

EEG

A novel technique is based on EEG power spectrum analysis, recently evaluated by Chen et al[81] on 62 patients with central nervous disorders. By using self-designed software, EEG power spectrum analysis was conducted and an intracranial pressure index (IPI) was automatically calculated, whereas CSF pressure was measured by a lumbar puncture. The results have shown a significant negative correlation between IPI and ICP ($r = -0.849$, $P < 0.01$) leading the authors to conclude that IPI obtained from EEG analysis is correlated with ICP.

From the authors' perspective, the EEG technique is not suited for the emergency setting, and, despite the available preliminary results, the technique needs to be further investigated and refined before being put to any clinical use.

Audiological Techniques

Audiological techniques for measuring ICP are based on the close relationship between the CSF pressure and the cochlear fluid pressure. ICP is transmitted to the cochlear fluid pressure through connecting channels, the main one being the cochlear aqueduct. This relationship

makes it possible to detect variations in ICP through measurements of the dynamic changes in the ear.

Tympanic membrane displacement (TMD) was the first proposed audiological method for assessing ICP noninvasively. The technique is based on the measurements of the resulting TMD in response to the elicitation of the acoustic reflex.[82] The acoustic reflex is elicited through sound stimulation. This induces the stapedius muscle to contract, which in turn causes a movement of the stapes. Stapes rests on the oval window where its position is determined by the cochlear fluid pressure and, hence, the CSF pressure. A variation in the cochlear fluid pressure therefore induces different movements of the stapes and, consequently, changes the direction of the tympanic membrane movement. High cochlear fluid pressure causes an inward-directed movement of the tympanic membrane, low cochlear fluid pressure causes an outward movement, and normal cochlear fluid pressure causes a bidirectional movement of the membrane. This movement is measured as the mean volume displacement (V_{mean} [nL]) in the external ear meatus, using a computer-based instrumentation.[82] Reid et al[83] examined 58 patients with various neurological disorders using TMD. In 17 of these patients, they compared their obtained TMD values with invasively obtained ICP and found that TMD categorized 76% correctly and 13% incorrectly as to whether ICP was high or normal. They concluded that TMD could be a useful tool to classify ICP as normal or raised, although it was not possible to obtain an absolute ICP value. Samuel et al[84] made repeated TMD measurements in 8 hydrocephalic children with shunt malfunction and found a good intraindividual reproducibility of the obtained values. They also compared their TMD values with invasively obtained ICP values and found a significant correlation with a correlation coefficient of -0.94. Shimbles et al[85] also found a significant correlation ($r = -0.57$) between TMD values and invasively obtained ICP in patients with hydrocephalus. However, they found that the predictive limits of the linear regression were too wide, approximately $\pm$ 25 mm Hg, to make a clinically useful measurement of ICP. Although consistent with previous studies,[83,84] it is suggested that serial TMD recordings could be used to find a change in ICP if an individual baseline value has previously been obtained.

There are certain limitations with the TMD method, one of them being that with an absent stapedial reflex, there will be no displacement of the membrane. Absent stapedial reflex is found in the brainstem or middle-ear dysfunction and also due to muscle relaxants and sedation, which is used in some neurointensive care units.[84] A patent cochlear aqueduct is also crucial.[83] As anatomic studies show varying results regarding the incidence of closed aqueducts,[86,87] the patency needs to be tested. This test, along with other pretests, makes the total testing time longer, approximately 45 to 60 minutes, and requires an experienced audiologist to obtain valid results.[84]

Another method to measure ICP noninvasively is based on otoacoustic emissions (OAEs). Evoked otoacoustic emissions (EOAEs), first recorded by Kemp[88] in 1978, are sounds reemitted by the inner ear in response to external acoustic stimuli and can be recorded by microphones in the external meatus. As mentioned earlier, increased cochlear fluid pressure leads to a change in the position of the stapes. This in turn gives a modification of the middle ear's conduction of the sounds.[89] One type of EOAEs, commonly analyzed in these methods, is distortion product otoacoustic emissions (DPOAEs), evoked by a pair of primary tones. In attempts to investigate the effect of increased ICP, modulated by posture changes, on DPOAEs, significant phase-shift changes were found for low frequencies, 750 to 1500 Hz.[90–92] Buki et al[89] reported a significant linear regression between invasively obtained ICP and DPOAE phase shift measured in degrees, with a correlation coefficient of 0.77.

One limitation with the use of OAEs is the large intersubject variability, and, as for TMD, an individual baseline measurement is required.[89] When the baseline measurement is performed, the method is suited to use in long-term screening when changes in ICP could be expected.[91]

Another limitation with EOAEs is that it cannot be applied on patients with sensorineural or conductive hearing loss.[93] An alternative measurement of cochlear microphonic potentials, which are less influenced by hearing loss, has recently been shown to be proportional to DPOAEs and ICP changes[90,93] and may therefore be a promising alternative for the future.

From the authors' perspective, although promising and relatively simple to use, TMD and OAE are still the unreliable techniques in a clinical setting, primarily because of the need for a baseline measurement to make any reliable follow-up measurements. In addition, the quality of measurements can easily be influenced by factors such as sedatives, intersubject variability, etc. Further research and improvement of the technique needs to be conducted before it can be considered clinically applicable.

Ophtalmological Techniques

Ophthalmoscopic examination has become a routine clinical examination when there is a suspicion of elevated ICP.[94] There are several signs indicating elevated ICP, mainly swelling of the optic disc, blurred margins, and elevated borders of the nerve head.[95] These are, however, late signs of elevated ICP, and papillary edema is an uncommon event in patients with acute ICP elevation. To this end, a normal papilla does not exclude the presence of high ICP.[94]

Additional noninvasive methods to assess ICP by applying techniques examining the eye have been extensively examined in recent years. The optic nerve is a part of the central nervous system, and its nerve sheath is continuous with the dura mater of the brain. The subarachnoid compartment surrounding the optic nerve contains CSF and communicates with the subarachnoid space of the brain.[96] Increased ICP has been shown to be transmitted to the subarachnoid compartment of the nerve, causing expansion of the optic nerve sheath and

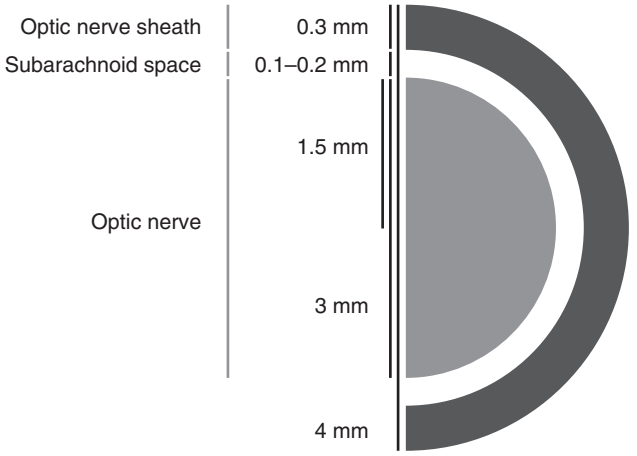

FIGURE 3. The optic nerve surrounded by the subarachnoid space and the optic nerve sheath.

thereby an increase in the optic nerve sheath diameter (ONSD), shown schematically in Figure 3.[97] Ultrasonography is a widely studied technique for noninvasive measuring of elevated ICP measuring the ONSD. The measurements are being performed using a 5 to 10.5 MHz probe, placed over the upper temporal eyelid.[98] The anterior region of the optic nerve sheath, just behind the eyeball, has been proposed to be more sensitive to changes in pressure compared with the posterior parts. Therefore, measurements made 3 mm behind the globe have been suggested to be the most optimal for ONSD evaluation.[97] The technique has shown to be quick and easily learned, even by ultrasound novices,[99,100] with a high intraobserver and interobserver reliability.[101,102] Several studies have been made on the direct correlation between ONSD and invasively measured ICP, obtaining correlation coefficients between 0.46 and 0.74 (Table 2).[103–109] Most of these studies have emphasized on the possible clinical use of ONSD as a noninvasive indicator of ICP due to their results.[103,105–109] Using different cutoff values, varying between 4.8 and 5.9 mm, when the ONSD is considered to indicate raised ICP, we found that 7 of the 8 studies showed sensitivity and specificity values in a range of 74% to 96% and 74% to 100%, respectively (Table 3).[103,105–110] The remaining study found a sensitivity of 36% and a specificity of 38% using a cutoff value of 6.0 mm and thereby concluded the method to be unreliable because of poor accuracy.[104]

MRI is an alternative way to demonstrate increased ONSD. This technique has been proposed to provide more precise measurements of the ONSD compared with ultrasonography.[111] However, MRI measurements have other drawbacks; they are expensive, time consuming, and have a limited availability. Two studies, made in 2008, correlated MRI-derived ONSD measurements with invasively obtained ICP.[112,113] Geeraerts et al[112] made a retrospective analysis of the ONSD on T2-weighted sequence MRI, with simultaneously invasively obtained ICP. In line with the majority of the ultrasound studies, they found a significant positive correlation between the ONSD and invasively obtained ICP, with a correlation coefficient of 0.71. An even better correlation coefficient of 0.88 was found by Watanabe et al,[113] which is the highest obtained correlation coefficient among all the ONSD studies, including the ultrasound studies. They used thinner slices (3.5 vs. 4.0 mm) and a smaller slice gap (0.3 vs. 5.0 mm) in their images, compared with Geeraerts et al,[112] which may have contributed to this higher precision.

Even if the overall results remain positive, there are certain limitations with the ONSD techniques. The ONSD and its expansion have been shown to vary among humans in postmortem studies, the diameter varying between 2.1 and 4.8 mm.[97] Similar results have been shown in healthy individuals, with variations between 2.2 and 4.9 mm.[107,114] This interindividual variation makes cutoff values hard to define. As it has been shown that the

TABLE 2. Correlations Between ONSD and Invasively Obtained ICP in all Studies Investigating the Direct Correlation Between ONSD and Invasively Obtained ICP

References	Study Size (Measurements)	Patient Group	Modality	Results
Geeraerts et al[106]	31	TBI	US	0.74 ($P < 0.0001$)
Kimberly et al[108]	15 (38)	Various*	US	0.59 ($P < 0.0005$)
Soldatos et al[107]	32 (32)	TBI	US	0.68 ($P = 0.002$)
Geeraerts et al[105]	37 (78)	Various†	US	0.71 ($P < 0.0001$)
Moretti et al[109]	63 (94)	SAH and ICH	US	0.70 ($P < 0.0001$)
Strumwasser et al[104]	10 (114)	TBI	US	Unilateral HI 0.68 ($P = 0.02$) Bilateral HI 0.46 ($P = 0.01$)
Rajajee et al[103]	65 (536)	Various‡	US	0.73 ($P < 0.0001$)
Watanabe[113]	12 (12)	Various§	MRI	0.88 ($P = 0.0036$)
Geeraerts et al[112]	38 (45)	TBI	MRI	0.71 ($P < 0.0001$)

*Traumatic injuries, spontaneous intracerebral hemorrhages.
†TBI, SAH, intracranial hematoma, stroke.
‡SAH, TBI, ICH, ischemic stroke, brain tumor.
§Chronic subdural hematoma, hygroma.
HI indicates head injury; ICH, intracerebral hemorrhage; ICP, intracranial pressure; MRI, magnetic resonance imaging; ONSD, optic nerve sheath diameter; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; US, ultrasonography.

TABLE 3. Cutoff Values for ONSD

References	Study Size (Measurements)	Patient Group	Modality	Cutoff (mm)	Sensitivity (%)	Specificity (%)
Geeraerts et al[106]	31	TBI	US	5.9	87	94
Kimberly et al[108]	15 (38)	Various*	US	5.0	88	93
Soldatos et al[107]	32 (32)	TBI	US	5.7	74	100
Geeraerts et al[105]	37 (78)	Various†	US	5.9	95	79
Moretti et al[109]	63 (94)	SAH and ICH	US	5.2	93	74
Strumwasser et al[104]	10 (114)	TBI	US	6.0	36	38
Bäuerle et al[101]	10	BIH	US	5.8	90	84
Rajajee et al[103]	65 (536)	Various‡	US	4.8	96	94
Watanabe[113]	12 (12)	Various§	MRI	6.0	x	x
Geeraerts et al[112]	38 (45)	TBI	MRI	5.8	90	92

*Traumatic injuries, spontaneous intracerebral hemorrhages.
†TBI, SAH, intracranial hematoma, stroke.
‡SAH, TBI, ICH, ischemic stroke, brain tumor.
§Chronic subdural hematoma, hygroma.
BIH indicates benign intracranial hypertension; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; ONSD, optic nerve sheath diameter; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; US, ultrasonography.

ONSD increases with age, a need for age-specific cutoff values in children has also been suggested.[115] Another important limitation is that the ONSD technique cannot be used in patients suffering from ocular trauma and pathologies of the optic nerve, such as tumor, inflammation, sarcoidosis, and hemorrhage, where the ONSD is suspected to be altered by other reasons.[116]

A promising new method for noninvasive measurement of ICP was described in 2011 by Chen et al.[117] The method uses a pupillometer for measuring the Neurological Pupil index (NPi, values 0 to 5, with 3 to 5 being normal), which shows an inverse relationship with ICP. The pupillometer measures pupil size and pupil reactivity.

After investigating 134 patients with subdural and epidural hematomas, as well as SAH and intracerebral hemorrhage, they were able to identify pupillary abnormalities close to 16 hours before peak ICP levels were achieved. In addition, they were able to show a significantly higher ICP in patients with 1 or more occurrences of abnormal pupil reactivity, and in patients with nonreactive pupils, compared with patients with a normal NPi.

From the authors' perspective, the main strength of the method is the introduction of an objective quantification of pupil size and reactivity. Further research needs to be conducted to determine its practical relevance to clinical practice and whether neurosurgical interventions guided by NPi improves patient outcome.

Overall, ophthalmologic examinations are valuable first-line clinical methods used as screening tools in cases suspected of having raised ICP. Nevertheless, it is important to keep in mind that an apparently normal papilla does not exclude raised ICP. Regarding ONSD, even though the technique has shown to have a high degree of interobserver reliability, the technique's multiple limitations make it unreliable for clinical use.

Near-Infrared Spectroscopy (NIRS)

Another noninvasive method, with the potential for assisting in the treatment of patients with TBI, is the use of NIRS for detecting changes in the cerebral blood volume, brain tissue oxygenation, and cerebral blood flow.[118] NIRS works in the near-infrared spectrum where a low absorptivity of light allows for deep-tissue penetration. The method detects changes in deoxyhemoglobin and oxyhemoglobin concentrations, which are quantified by measuring variations in the absorption of near-infrared light.

Cerebrovascular pressure reactivity index (PRx) describes a linear correlation between the slow waves of ABP and ICP[119] and has been shown to correlate with the long-term patient outcome. Positive values are associated with a poor outcome, whereas negative values are associated with increased survival in patients with head injury.[119–121] In addition, PRx values allow for the definition of the optimal cerebral perfusion pressure (CPP_{OPT}), which is the CPP, where PRx reaches its lowest value compared with CPP. CPP_{OPT} was associated with a better outcome in the patients, where it could be evaluated.[122] Although a prognostic index such as PRx has obvious benefits, it is limited by the requirement of invasive ICP measurements.

NIRS monitoring makes it possible to calculate the hemoglobin volume index (HVx), which is a correlation between ABP and relative total hemoglobin,[123] and the total hemoglobin index (THx).[122] Consequently, both are NIRS-estimated cerebrovascular reactivity indices. The coupling from HVx/THx to PRx and ICP exists in the form of a linear correlation coefficient between THx and PRx of 0.56.[122] However, on the basis of CPP_{OPT} values calculated from PRx and THx, respectively, the authors found a significant correlation between $CPP_{OPT\text{-}PRx}$ and $CPP_{OPT\text{-}THx}$ ($r = 0.74$).

The method is currently limited by the availability of NIRS equipment, and the fact that the parameter of interest for the individual patient (CPP_{OPT}) takes several hours of monitoring to obtain, and can only be reliably measured in about 50% of patients.[122] As NIRS allows for the calculation of different indices, which subsequently correlate with PRx, the technique remains an area of interest for the future. At present NIRS does not

TABLE 4. Characteristics of Available Methods for Noninvasive Measurements of ICP

	Operator Dependent	Interindividual Variability	Time Consuming	Performed Bedside	Suitable in Emergency Setting
Computed tomography	No?	No	No	No	Yes
Magnetic resonance imaging	Yes	Yes	Yes	No	No
Transcranial Doppler	Yes	Yes	No	Yes	Yes
Electroencephalography			Yes	Yes	No
Audiological techniques					
Tympanic membrane displacement	Yes	Yes	Yes	Yes	No
Otoacoustic emissions	Yes	Yes	Yes	Yes	No
Ophtalmological techniques					
Ophtalmoscopic examination	Yes	Yes	No	Yes	Yes, however, late sign of high ICP
Optic nerve sheath diameter	No	high	No with sonography Yes with magnetic resonance imaging	Yes	Yes with sonography
Pupillometry	No	Yes	No	Yes	Yes
Near-infrared spectroscopy	Yes	Yes	Yes	Yes	No

ICP indicates intracranial pressure.

allow for the estimation of absolute values of ICP nor the detection of changes in ICP.

NONINVASIVE TECHNIQUES AND ANESTHESIA

In theory, estimations of ICP with CT, the MRI, ophthalmological, and acoustic techniques should be rather unaffected whether or not sedatives or anesthestics are used. For obvious reasons, this is not the case for the nICP techniques using EEG and TCD. Estimating ICP from EEG is based on an identification of slow high-voltage waves.[124] Most anesthetics promote formation of delta or slow waves hampering the identification of a high ICP.

TCD-ICP uses the PI, which is the correlation between the systolic, diastolic, and the mean flow velocity. In patients with or without intracranial pathology, who are anesthetized with volatile anesthetics, the anesthetic in itself—depending on the CO_2 level—has a direct effect on the cerebral arteries and consequently on the PI. When the patients are given anesthesia using sevoflurane, the PI is increased by 16% in them.[125] Furthermore, PI increases in response to increased positive end-expiratory pressure.[126] One reason for the increased PI is the lowering of the mean flow velocity, which is a general effect of the volatile anesthetics, propofol, thiopenthal, and some morphines. Nitrous oxide and ketamine have the opposite effect on the mean flow velocity.[127] All these studies have been performed on patients with or without intracranial pathology, and, to our knowledge, no one has studied the effect of anesthetics on the PI in patients with intracranial pathology.

Dealing with a multitraumatized patient with brain trauma increases the risk of raised ICP due to progressive intracranial bleeding, brain edema, or increase in cerebral blood volume. The anesthetic procedure might promote—as well as hide—such a development, as clinical evaluation is impossible. In such cases, frequent noninvasive ICP measurements would be desirable. Measurements with CT, MR, and EEG are not possible, leaving ONSD and auditory TMD techniques as possible options, as TCD is difficult to interpret in this scenario. ONSD and TMD techniques are theoretically not influenced by anesthesia and should reflect ICP changes.

FUTURE ASPECTS

The technical and software development will improve the noninvasive ICP techniques, but obtaining an exact ICP value is difficult with the current techniques—with pros and cons of the currently available techniques summarized in Table 4. The CT-based and MRI-based techniques will only give an estimation of the ICP at the investigation time. CT does not always reflect the actual ICP, making pure imaging methods inappropriate in the future.[128] The present TCD method will be improved by attempts to automatically detect the supreme signal with the fastest flow velocity in the middle cerebral artery and such a system has been presented, even though it has not been put on the market yet. Such equipment will eliminate the disparity seen between different investigators.[129] However, it will still be an indirect technique, which in most cases can discriminate between the high-pressure and low-pressure situations, but will most probably never be used in the treatment of patients with brain trauma, as a much higher precision is required.

CONCLUSIONS

Monitoring of ICP is invaluable in clinical practice. However, invasive ICP monitoring is cumbersome, not always available, associated with risks, and can be contraindicated. Noninvasive methods have therefore been proposed. Several of the noninvasive methods could be valuable as screening methods for elevated ICP, especially when invasive monitoring is contraindicated or unavailable. For the methods to be implemented in clinical practice, normative cutoff values are still required. Because of

interindividual variability, these cutoff values are hard to obtain. The noninvasive methods share many advantages; however, these methods also have the common significant disadvantage of not being as accurate as the invasive techniques. Their reproducibility has been questioned as the methods are affected by different operator-dependent factors. A certain margin of error can be accepted if the methods are only to be used as screening methods; however, a high sensitivity is crucial, as a false-negative result could lead to fatal consequences in patients with acute elevated ICP. In patients with longer follow-up periods, such as hydrocephalus and idiopathic intracranial hypertension, the possibility of obtaining individual baseline values can overcome the difficulty with interindividual variability. This makes the noninvasive methods potentially suitable for long-term follow-up in these patients.

To further assess the noninvasive techniques' applicability as predictors of intracranial hypertension, large-scale clinical trials are needed.

REFERENCES

1. Miller JD, Becker DP, Ward JD, et al. Significance of intracranial hypertension in severe head injury. *J Neurosurg*. 1977;47:503–516.
2. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry*. 2004;75:813–821.
3. Online TBI guidelines 2010 [online]. Available at: www.braintrauma.org/coma-guidlines. Accessed May 14.
4. Citerio G, Andrews PJ. Intracranial pressure. Part two: clinical applications and technology. *Intensive Care Med*. 2004;30:1882–1885.
5. Hoefnagel D, Dammers R, Ter Laak-Poort MP, et al. Risk factors for infections related to external ventricular drainage. *Acta Neurochir (Wien)*. 2008;150:209–214; discussion 214.
6. Holloway KL, Barnes T, Choi S, et al. Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. *J Neurosurg*. 1996;85:419–424.
7. Anderson RC, Kan P, Klimo P, et al. Complications of intracranial pressure monitoring in children with head trauma. *J Neurosurg*. 2004;101:53–58.
8. Binz DD, Toussaint LG III, Friedman JA. Hemorrhagic complications of ventriculostomy placement: a meta-analysis. *Neurocrit Care*. 2009;10:253–256.
9. Bauer DF, Razdan SN, Bartolucci AA, et al. Meta-analysis of hemorrhagic complications from ventriculostomy placement by neurosurgeons. *Neurosurgery*. 2011;69:255–260.
10. Koskinen LO, Olivecrona M. Clinical experience with the intraparenchymal intracranial pressure monitoring Codman Micro-Sensor system. *Neurosurgery*. 2005;56:693–698; discussion 693-698.
11. Poca MA, Sahuquillo J, Arribas M, et al. Fiberoptic intraparenchymal brain pressure monitoring with the Camino V420 monitor: reflections on our experience in 163 severely head-injured patients. *J Neurotrauma*. 2002;19:439–448.
12. Gelabert-Gonzalez M, Ginesta-Galan V, Sernamito-Garcia R, et al. The Camino intracranial pressure device in clinical practice. Assessment in a 1000 cases. *Acta Neurochir (Wien)*. 2006;148:435–441.
13. Smith M. Monitoring intracranial pressure in traumatic brain injury. *Anesth Analg*. 2008;106:240–248.
14. Rosenberg JB, Shiloh AL, Savel RH, et al. Non-invasive methods of estimating intracranial pressure. *Neurocrit Care*. 2011;15:599–608.
15. Eisenberg HM, Gary HE Jr, Aldrich EF, et al. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. *J Neurosurg*. 1990;73:688–698.
16. Toutant SM, Klauber MR, Marshall LF, et al. Absent or compressed basal cisterns on first CT scan: ominous predictors of outcome in severe head injury. *J Neurosurg*. 1984;61:691–694.
17. Kouvarellis AJ, Rohlwink UK, Sood V, et al. The relationship between basal cisterns on CT and time-linked intracranial pressure in paediatric head injury. *Childs Nerv Syst*. 2011;27:1139–1144.
18. 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.
19. Miller MT, Pasquale M, Kurek S, et al. Initial head computed tomographic scan characteristics have a linear relationship with initial intracranial pressure after trauma. *J Trauma*. 2004;56:967–972; discussion 972-963.
20. Pauwels EK, Bourguignon MH. Radiation dose features and solid cancer induction in pediatric computed tomography. *Med Princ Pract*. 2012;21:508–515.
21. Krille L, Zeeb H, Jahnen A, et al. Computed tomographies and cancer risk in children: a literature overview of CT practices, risk estimations and an epidemiologic cohort study proposal. *Radiat Environ Biophys*. 2012;51:103–111.
22. Alperin NJ, Lee SH, Loth F, et al. 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.
23. Zhang B, Li SB. Cine-PC MR in assessment of cerebrospinal fluid velocity in the aqueduct of the midbrain correlated with intracranial pressure—initial study. *Med Hypotheses*. 2012;78:227–230.
24. Marmarou A, Shulman K, LaMorgese J. Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. *J Neurosurg*. 1975;43:523–534.
25. Marshall I, MacCormick I, Sellar R, et al. Assessment of factors affecting MRI measurement of intracranial volume changes and elastance index. *Br J Neurosurg*. 2008;22:389–397.
26. Alperin N. MR-intracranial compliance and pressure: a method for noninvasive measurement of important neurophysiologic parameters. *Methods Enzymol*. 2004;386:323–349.
27. Alperin N, Kulkarni K, Loth F, et al. Analysis of magnetic resonance imaging-based blood and cerebrospinal fluid flow measurements in patients with Chiari I malformation: a system approach. *Neurosurg Focus*. 2001;11:1–10.
28. Alperin N, Vikingstad EM, Gomez-Anson B, et al. Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. *Magn Reson Med*. 1996;35:741–754.
29. Raksin PB, Alperin N, Sivaramakrishnan A, et al. Noninvasive intracranial compliance and pressure based on dynamic magnetic resonance imaging of blood flow and cerebrospinal fluid flow: review of principles, implementation, and other noninvasive approaches. *Neurosurg Focus*. 2003;14:1–8.
30. Dhoondia HAN. Improved MR-intracranial pressure (MR-ICP) measurement using a new data acquisition technique. *Intl Soc Mag Reson Med*. 2003;1:793.
31. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg*. 1982;57:769–774.
32. Tsivgoulis G, Alexandrov AV, Sloan MA. Advances in transcranial Doppler ultrasonography. *Curr Neurol Neurosci Rep*. 2009;9:46–54.
33. Saqqur M, Zygun D, Demchuk A. Role of transcranial Doppler in neurocritical care. *Crit Care Med*. 2007;35:S216–S223.
34. Alexandrov AV, Sloan MA, Tegeler CH, et al. Practice standards for transcranial Doppler (TCD) ultrasound. Part II. Clinical indications and expected outcomes. *J Neuroimaging*. 2012;22:215–224.
35. Alexandrov AV, Sloan MA, Wong LK, et al. Practice standards for transcranial Doppler ultrasound: part I—test performance. *J Neuroimaging*. 2007;17:11–18.
36. Klingelhofer J, Conrad B, Benecke R, et al. Intracranial flow patterns at increasing intracranial pressure. *Klin Wochenschr*. 1987;65:542–545.

37. Klingelhofer J, Conrad B, Benecke R, et al. Evaluation of intracranial pressure from transcranial Doppler studies in cerebral disease. *J Neurol*. 1988;235:159–162.
38. Hanlo PW, Peters RJ, Gooskens RH, et al. Monitoring intracranial dynamics by transcranial Doppler—a new Doppler index: trans systolic time. *Ultrasound Med Biol*. 1995;21:613–621.
39. Gosling RG, King DH. Arterial assessment by Doppler-shift ultrasound. *Proc R Soc Med*. 1974;67:447–449.
40. Michel E, Zernikow B. Gosling's Doppler pulsatility index revisited. *Ultrasound Med Biol*. 1998;24:597–599.
41. McQuire JC, Sutcliffe JC, Coats TJ. Early changes in middle cerebral artery blood flow velocity after head injury. *J Neurosurg*. 1998;89:526–532.
42. Shen Q, Stuart J, Venkatesh B, et al. Inter observer variability of the transcranial Doppler ultrasound technique: impact of lack of practice on the accuracy of measurement. *J Clin Monit Comput*. 1999;15:179–184.
43. Czosnyka M, Richards HK, Whitehouse HE, et al. Relationship between transcranial Doppler-determined pulsatility index and cerebrovascular resistance: an experimental study. *J Neurosurg*. 1996;84:79–84.
44. de Riva N, Budohoski KP, Smielewski P, et al. Transcranial Doppler Pulsatility Index: what it is and what it isn't. *Neurocrit Care*. 2012;17:58–66.
45. Homburg AM, Jakobsen M, Enevoldsen E. Transcranial Doppler recordings in raised intracranial pressure. *Acta Neurol Scand*. 1993;87:488–493.
46. Gura M, Elmaci I, Sari R, et al. Correlation of pulsatility index with intracranial pressure in traumatic brain injury. *Turk Neurosurg*. 2011;21:210–215.
47. Moreno JA, Mesalles E, Gener J, et al. Evaluating the outcome of severe head injury with transcranial Doppler ultrasonography. *Neurosurg Focus*. 2000;8:1–7.
48. Voulgaris SG, Partheni M, Kaliora H, et al. Early cerebral monitoring using the transcranial Doppler pulsatility index in patients with severe brain trauma. *Med Sci Monit*. 2005;11: CR49–CR52.
49. Bellner J, Romner B, Reinstrup P, et al. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). *Surg Neurol*. 2004;62:45–51; discussion 51.
50. Behrens A, Lenfeldt N, Ambarki K, et al. Transcranial Doppler pulsatility index: not an accurate method to assess intracranial pressure. *Neurosurgery*. 2010;66:1050–1057.
51. Figaji AA, Zwane E, Fieggen AG, et al. Transcranial Doppler pulsatility index is not a reliable indicator of intracranial pressure in children with severe traumatic brain injury. *Surg Neurol*. 2009;72:389–394.
52. Rainov NG, Weise JB, Burkert W. Transcranial Doppler sonography in adult hydrocephalic patients. *Neurosurg Rev*. 2000;23:34–38.
53. Edouard AR, Vanhille E, Le Moigno S, et al. Non-invasive assessment of cerebral perfusion pressure in brain injured patients with moderate intracranial hypertension. *Br J Anaesth*. 2005;94: 216–221.
54. Schmidt EA, Czosnyka M, Gooskens I, et al. Preliminary experience of the estimation of cerebral perfusion pressure using transcranial Doppler ultrasonography. *J Neurol Neurosurg Psychiatry*. 2001;70:198–204.
55. Brandi G, Bechir M, Sailer S, et al. Transcranial color-coded duplex sonography allows to assess cerebral perfusion pressure noninvasively following severe traumatic brain injury. *Acta Neurochir (Wien)*. 2010;152:965–972.
56. Ragauskas A, Matijosaitis V, Zakelis R, et al. Clinical assessment of noninvasive intracranial pressure absolute value measurement method. *Neurology*. 2012;78:1684–1691.
57. Ract C, Le Moigno S, Bruder N, et al. Transcranial Doppler ultrasound goal-directed therapy for the early management of severe traumatic brain injury. *Intensive Care Med*. 2007;33: 645–651.
58. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480–484.
59. Trabold F, Meyer PG, Blanot S, et al. The prognostic value of transcranial Doppler studies in children with moderate and severe head injury. *Intensive Care Med*. 2004;30:108–112.
60. Chiron C, Raynaud C, Maziere B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med*. 1992;33:696–703.
61. Brouwers PJ, Vriens EM, Musbach M, et al. Transcranial pulsed Doppler measurements of blood flow velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy children and adolescents in relation to age and sex. *Ultrasound Med Biol*. 1990;16:1–8.
62. Udomphorn Y, Armstead WM, Vavilala MS. Cerebral blood flow and autoregulation after pediatric traumatic brain injury. *Pediatr Neurol*. 2008;38:225–234.
63. Melo JR, Di Rocco F, Blanot S, et al. Transcranial Doppler can predict intracranial hypertension in children with severe traumatic brain injuries. *Childs Nerv Syst*. 2011;27:979–984.
64. Westra SJ, Lazareff J, Curran JG, et al. Transcranial Doppler ultrasonography to evaluate need for cerebrospinal fluid drainage in hydrocephalic children. *J Ultrasound Med*. 1998;17:561–569.
65. Hanlo PW, Gooskens RH, Nijhuis IJ, et al. Value of transcranial Doppler indices in predicting raised ICP in infantile hydrocephalus. A study with review of the literature. *Childs Nerv Syst*. 1995;11:595–603.
66. Quinn MW, Pople IK. Middle cerebral artery pulsatility in children with blocked cerebrospinal fluid shunts. *J Neurol Neurosurg Psychiatry*. 1992;55:325–327.
67. Sanker P, Richard KE, Weigl HC, et al. Transcranial Doppler sonography and intracranial pressure monitoring in children and juveniles with acute brain injuries or hydrocephalus. *Childs Nerv Syst*. 1991;7:391–393.
68. Baumgartner RW, Mathis J, Sturzenegger M, et al. A validation study on the intraobserver reproducibility of transcranial color-coded duplex sonography velocity measurements. *Ultrasound Med Biol*. 1994;20:233–237.
69. Maeda H, Etani H, Handa N, et al. A validation study on the reproducibility of transcranial Doppler velocimetry. *Ultrasound Med Biol*. 1990;16:9–14.
70. McMahon CJ, McDermott P, Horsfall D, et al. The reproducibility of transcranial Doppler middle cerebral artery velocity measurements: implications for clinical practice. *Br J Neurosurg*. 2007;21:21–27.
71. Martin NA, Thomas KM, Caron M. Transcranial Doppler—techniques, application, and instrumentation. *Neurosurgery*. 1993; 33:761–764.
72. Prunet B, Asencio Y, Lacroix G, et al. Noninvasive detection of elevated intracranial pressure using a portable ultrasound system. *Am J Emerg Med*. 2012;30:936–941.
73. Markwalder TM, Grolimund P, Seiler RW, et al. Dependency of blood flow velocity in the middle cerebral artery on end-tidal carbon dioxide partial pressure—a transcranial ultrasound Doppler study. *J Cereb Blood Flow Metab*. 1984;4:368–372.
74. Manno EM. Transcranial Doppler ultrasonography in the neurocritical care unit. *Crit Care Clin*. 1997;13:79–104.
75. Lee KY, Sohn YH, Baik JS, et al. Arterial pulsatility as an index of cerebral microangiopathy in diabetes. *Stroke*. 2000;31: 1111–1115.
76. Venkatesh B, Shen Q, Lipman J. Continuous measurement of cerebral blood flow velocity using transcranial Doppler reveals significant moment-to-moment variability of data in healthy volunteers and in patients with subarachnoid hemorrhage. *Crit Care Med*. 2002;30:563–569.
77. De Salles AA, Manchola I. CO2 reactivity in arteriovenous malformations of the brain: a transcranial Doppler ultrasound study. *J Neurosurg*. 1994;80:624–630.
78. Zweifel C, Czosnyka M, Carrera E, et al. Reliability of the Blood Flow Velocity Pulsatility Index for assessment of intracranial and cerebral perfusion pressures in head injured patients. *Neurosurgery*. 2012;71:237–239.
79. Aggarwal S, Brooks DM, Kang Y, et al. Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure

using transcranial doppler ultrasonography. *Liver Transpl*. 2008;14:1048–1057.
80. Hu X, Glenn T, Scalzo F, et al. Intracranial pressure pulse morphological features improved detection of decreased cerebral blood flow. *Physiol Meas*. 2010;31:679–695.
81. Chen H, Wang J, Mao S, et al. A new method of intracranial pressure monitoring by EEG power spectrum analysis. *Can J Neurol Sci*. 2012;39:483–487.
82. Marchbanks RJ. Measurement of tympanic membrane displacement arising from aural cardiovascular activity, swallowing, and intra-aural muscle reflex. *Acta Otolaryngol*. 1984;98:119–129.
83. Reid A, Marchbanks RJ, Bateman DE, et al. Mean intracranial pressure monitoring by a non-invasive audiological technique: a pilot study. *J Neurol Neurosurg Psychiatry*. 1989;52:610–612.
84. 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.
85. Shimbles S, Dodd C, Banister K, et al. Clinical comparison of tympanic membrane displacement with invasive ICP measurements. *Acta Neurochir Suppl*. 2005;95:197–199.
86. Bachor E, Byahatti S, Karmody CS. The cochlear aqueduct in pediatric temporal bones. *Eur Arch Otorhinolaryngol*. 1997; 254(suppl 1):S34–S38.
87. Tekdemir I, Aslan A, Ersoy M, et al. A radiologico-anatomical comparative study of the cochlear aqueduct. *Clin Radiol*. 2000;55: 288–291.
88. Kemp DT. Stimulated acoustic emissions from within the human auditory system. *J Acoust Soc Am*. 1978;64:1386–1391.
89. Buki B, Avan P, Lemaire JJ, et al. Otoacoustic emissions: a new tool for monitoring intracranial pressure changes through stapes displacements. *Hear Res*. 1996;94:125–139.
90. Sakka L, Thalamy A, Giraudet F, et al. Electrophysiological monitoring of cochlear function as a non-invasive method to assess intracranial pressure variations. *Acta Neurochir Suppl*. 2012;114:131–134.
91. Voss SE, Horton NJ, Tabucchi TH, et al. 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.
92. Buki B, Chomicki A, Dordain M, et al. Middle-ear influence on otoacoustic emissions. II: contributions of posture and intracranial pressure. *Hear Res*. 2000;140:202–211.
93. Buki B, Giraudet F, Avan P. Non-invasive measurements of intralabyrinthine pressure changes by electrocochleography and otoacoustic emissions. *Hear Res*. 2009;251:51–59.
94. Steffen H, Eifert B, Aschoff A, et al. The diagnostic value of optic disc evaluation in acute elevated intracranial pressure. *Ophthalmology*. 1996;103:1229–1232.
95. Frisen L. Swelling of the optic nerve head: a staging scheme. *J Neurol Neurosurg Psychiatry*. 1982;45:13–18.
96. Killer HE, Laeng HR, Flammer J, et al. Architecture of arachnoid trabeculae, pillars, and septa in the subarachnoid space of the human optic nerve: anatomy and clinical considerations. *Br J Ophthalmol*. 2003;87:777–781.
97. Hansen HC, Helmke K. The subarachnoid space surrounding the optic nerves. An ultrasound study of the optic nerve sheath. *Surg Radiol Anat*. 1996;18:323–328.
98. Shah S, Kimberly H, Marill K, et al. Ultrasound techniques to measure the optic nerve sheath: is a specialized probe necessary? *Med Sci Monit*. 2009;15:MT63–MT68.
99. Potgieter DW, Kippin A, Ngu F, et al. Can accurate ultrasonographic measurement of the optic nerve sheath diameter (a non-invasive measure of intracranial pressure) be taught to novice operators in a single training session? *Anaesth Intensive Care*. 2011;39:95–100.
100. Major R, Girling S, Boyle A. Ultrasound measurement of optic nerve sheath diameter in patients with a clinical suspicion of raised intracranial pressure. *Emerg Med J*. 2011;28:679–681.
101. Bauerle J, Lochner P, Kaps M, et al. Intra- and interobsever reliability of sonographic assessment of the optic nerve sheath diameter in healthy adults. *J Neuroimaging*. 2012;22:42–45.
102. Ballantyne SA, O'Neill G, Hamilton R, et al. Observer variation in the sonographic measurement of optic nerve sheath diameter in normal adults. *Eur J Ultrasound*. 2002;15:145–149.
103. Rajajee V, Vanaman M, Fletcher JJ, et al. Optic nerve ultrasound for the detection of raised intracranial pressure. *Neurocrit Care*. 2011;15:506–515.
104. Strumwasser A, Kwan RO, Yeung L, et al. Sonographic optic nerve sheath diameter as an estimate of intracranial pressure in adult trauma. *J Surg Res*. 2011;170:265–271.
105. Geeraerts T, Launey Y, Martin L, et al. Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. *Intensive Care Med*. 2007;33: 1704–1711.
106. Geeraerts T, Merceron S, Benhamou D, et al. Non-invasive assessment of intracranial pressure using ocular sonography in neurocritical care patients. *Intensive Care Med*. 2008;34: 2062–2067.
107. Soldatos T, Karakitsos D, Chatzimichail K, et al. Optic nerve sonography in the diagnostic evaluation of adult brain injury. *Crit Care*. 2008;12:1–7.
108. Kimberly HH, Shah S, Marill K, et al. Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. *Acad Emerg Med*. 2008;15:201–204.
109. Moretti R, Pizzi B, Cassini F, et al. Reliability of optic nerve ultrasound for the evaluation of patients with spontaneous intracranial hemorrhage. *Neurocrit Care*. 2009;11:406–410.
110. Bauerle J, Gizewski ER, Stockhausen KV, et al. Sonographic assessment of the optic nerve sheath and transorbital monitoring of treatment effects in a patient with spontaneous intracranial hypotension: case report. *J Neuroimaging*. 2013;23:237–239.
111. Lagreze WA, Lazzaro A, Weigel M, et al. Morphometry of the retrobulbar human optic nerve: comparison between conventional sonography and ultrafast magnetic resonance sequences. *Invest Ophthalmol Vis Sci*. 2007;48:1913–1917.
112. Geeraerts T, Newcombe VF, Coles JP, et al. Use of T2-weighted magnetic resonance imaging of the optic nerve sheath to detect raised intracranial pressure. *Crit Care*. 2008;12:1–7.
113. Watanabe A, Kinouchi H, Horikoshi T, et al. Effect of intracranial pressure on the diameter of the optic nerve sheath. *J Neurosurg*. 2008;109:255–258.
114. Skoloudik D, Herzig R, Fadrna T, et al. Distal enlargement of the optic nerve sheath in the hyperacute stage of intracerebral haemorrhage. *Br J Ophthalmol*. 2011;95:217–221.
115. Shofty B, Ben-Sira L, Constantini S, et al. Optic nerve sheath diameter on MR imaging: establishment of norms and comparison of pediatric patients with idiopathic intracranial hypertension with healthy controls. *AJNR Am J Neuroradiol*. 2012;33:366–369.
116. Soldatos T, Chatzimichail K, Papathanasiou M, et al. Optic nerve sonography: a new window for the non-invasive evaluation of intracranial pressure in brain injury. *Emerg Med J*. 2009;26: 630–634.
117. Chen JW, Gombart ZJ, Rogers S, et al. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the Neurological Pupil index. *Surg Neurol Int*. 2011;2:1–7.
118. Ghosh A, Elwell C, Smith M. Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth Analg*. 2012;115: 1373–1383.
119. Czosnyka M, Smielewski P, Kirkpatrick P, et al. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery*. 1997;41:11–17; discussion 17-19.
120. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med*. 2002;30:733–738.
121. Zweifel C, Lavinio A, Steiner LA, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. *Neurosurg Focus*. 2008;25:1–8.
122. Zweifel C, Castellani G, Czosnyka M, et al. Noninvasive monitoring of cerebrovascular reactivity with near infrared spectroscopy in head-injured patients. *J Neurotrauma*. 2010;27:1951–1958.

123. Lee JK, Kibler KK, Benni PB, et al. Cerebrovascular reactivity measured by near-infrared spectroscopy. *Stroke*. 2009;40:1820–1826.
124. Munari C, Calbucci F. Correlations between intracranial pressure and EEG during coma and sleep. *Electroencephalogr Clin Neurophysiol*. 1981;51:170–176.
125. Molnar C, Settakis G, Sarkany P, et al. Effect of sevoflurane on cerebral blood flow and cerebrovascular resistance at surgical level of anaesthesia: a transcranial Doppler study. *Eur J Anaesthesiol*. 2007;24:179–184.
126. Werner C, Kochs E, Dietz R, et al. [The effect of positive end expiratory pressure on the blood flow velocity in the basal cerebral arteries during general anesthesia]. *Anasth Intensivther Notfallmed*. 1990;25:331–334.
127. Fodale V, Schifilliti D, Conti A, et al. Transcranial Doppler and anesthetics. *Acta Anaesthesiol Scand*. 2007;51:839–847.
128. Winkler F, Kastenbauer S, Yousry TA, et al. Discrepancies between brain CT imaging and severely raised intracranial pressure proven by ventriculostomy in adults with pneumococcal meningitis. *J Neurol*. 2002;249:1292–1297.
129. Staalso JM, Edsen T, Romner B, et al. Transcranial Doppler velocimetry in aneurysmal subarachnoid haemorrhage: intra- and interobserver agreement and relation to angiographic vasospasm and mortality. *Br J Anaesth*. 2013;110:577–585.