ULTRASOUND-BASED NON-INVASIVE INTRACRANIAL PRESSURE

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LIST OF MAIN ABBREVIATIONS

ABP, arterial blood pressure
ABP$_d$, diastolic arterial blood pressure
ABP$_s$, systolic arterial blood pressure
ACA, anterior cerebral artery
ARI, autoregulation index
BMI, body-mass index
CBF, cerebral blood flow
CI, confidence interval
CO$_2$, carbon dioxide
CPP, cerebral perfusion pressure
CPP$_{opt}$, optimal cerebral perfusion pressure
CSF, cerebrospinal fluid
CT, computed tomography
CVR, cerebrovascular resistance
EEG, electroencephalogram
ETCO$_2$, end-tidal carbon dioxide concentration
FV, cerebral blood flow velocity
FV$_d$, diastolic cerebral blood flow velocity
FV$_s$, systolic cerebral blood flow velocity
GCS, Glasgow coma scale
HR, heart rate
ICA, internal carotid artery
ICH, intracranial hypertension
ICP, intracranial pressure
IQR, interquartile range
LP, lumbar puncture
MCA, middle cerebral artery
MRI, magnetic resonance imaging
MS, midline shift
NCCU, Neurosciences Critical Care Unit
nCPP, non-invasive cerebral perfusion pressure
nICP, non-invasive intracranial pressure
nICP$_{BB}$, non-invasive intracranial pressure based on the black box method
nICP$_{FVd}$, non-invasive intracranial pressure based on the diastolic cerebral blood flow velocity method
nICP$_{CrCP}$, non-invasive intracranial pressure based on the critical closing pressure method
nICP$_{PI}$, non-invasive intracranial pressure based on the pulsatility index method
NPV, negative predictive value
ONSD, optic nerve sheath diameter
OR, odds ratio

PaCO$_2$, partial pressure of carbon dioxide
PCA, posterior cerebral artery
PE, prediction error
PECO$_2$, pressure of expired carbon dioxide
PI, pulsatility index
PPV, positive predictive value
PRx, pressure reactivity index
R, correlation coefficient
R^2, coefficient of determination
REC, research ethics committee
RI, resistance index
ROC, receiver operating characteristic
rSCO$_2$, regional cerebral oxygen saturation
SAH, subarachnoid haemorrhage
SD, standard deviation
SDE, standard deviation of the error
TBI, traumatic brain injury
TCD, transcranial Doppler ultrasonography

SUMMARY

Intracranial pressure (ICP) is an important monitoring modality in the clinical management of several neurological diseases carrying the intrinsic risk of potentially lethal intracranial hypertension (ICH). Considering that the brain is in an enclosed compartment, ICH leads to brain hypoperfusion and eventually ischaemia followed by irreversible neuronal damage. Traumatic brain injury (TBI), for instance, is a condition in which ICH is strongly associated with unfavourable outcome and death.

Although ICP can guide patient management in neurocritical care settings, this parameter is not commonly monitored in many clinical conditions outside this environment. The invasive character of the standard methods for ICP assessment and their associated risks to the patient (like infections, brain tissue lesions, haemorrhage) contribute to this scenario. Such risks have prevented ICP assessment in a broad range of diseases like in patients with risk of coagulopathy, as well as in other conditions in which invasive assessment is not considered or outweighed by the risks of the procedure. Provided that knowledge of ICP can be crucial for the successful management of patients in many sub-critical conditions, non-invasive estimation of ICP (nICP) may be helpful when indications for invasive ICP assessment are not met and when it is not immediately available or even contraindicated.

Several methods for non-invasive assessment of ICP (nICP) have been described so far. Transcranial Doppler (TCD), for instance, is primarily a technique for diagnosing various intracranial vascular disorders such as emboli, stenosis, or vasospasm, but has been broadly utilised for non-invasive ICP monitoring due to its ability to detect changes in cerebral blood flow velocity derived from ICP variations. Moreover, TCD allows monitoring of these parameters as they may change in time.

Optic nerve sheath diameter ultrasonography (ONSD) is another non-invasive tool which gained interest in the last years. The optic nerve sheath is in continuous with the subarachnoid space, and when ICP increased, the diameter of ONSD enlarges proportionally to ICP.

The focus of this thesis is on the assessment, applications and development of ultrasound-based for nICP assessment in different clinical conditions where this parameter is relevant but in many circumstances not considered, including TBI and other neurological diseases

associated with impairment of cerebral blood flow circulation. As main results, ONSD and TCD-based non-invasive methods could replicate changes in direct ICP across time confidently, and could provide reasonable accuracy in comparison to the standard invasive techniques. These findings support the use of ultrasound based non-invasive ICP methods in a variety of clinical conditions requiring management of intracranial pressure and brain perfusion. More importantly, the low costs associated with nICP methods, ultrasound machines are widely available medical devices, could contribute to its widespread use as a reliable alternative for ICP monitoring in everyday clinical practice.

Chapter 1 . Background and Introduction

INTRACRANIAL PRESSURE MONITORING

The concept of intracranial pressure (ICP) was first described in 1783 by the Scottish anatomist Alexander Monro, who described the skull as a rigid structure containing incompressible brain and stated that a constant drainage of venous blood is required to allow continuous arterial supply (1,2). These assumptions were later confirmed in autopsy studies by George Kellie of Leith (3), whose findings were postulated as the Monro-Kellie doctrine. The doctrine was modified throughout the years with contributions of Vesalius (description of fluid-filled brain ventricles), François Magendie (establishment of the concept of cerebrospinal fluid – CSF (4)), George Burrows (reciprocal relationship between the volumes of CSF and blood (5)). However, it was Harvey Cushing in 1926 (6), who formulated the classic explanation of the doctrine: with an intact skull, the volume of the brain, blood, and CSF is constant; an increase in one component will cause a decrease in one or both of the other components.

On the basis of the Monro-Kellie doctrine, intracranial pressure can be described as the summation of at least four components, driven by different physiological mechanisms (7). The first component is associated with arterial blood inflow and volume of arterial blood. Most common phenomenon associated with this component is plateau wave of ICP. Second component of ICP is associated with venous blood outflow. Obstructions to the outflow of blood leads to elevation of ICP (like venous compression due to wrong head position, but also venous thrombosis). Third component is related with cerebrospinal fluid (CSF) circulation derangements, as commonly seen in 'acute hydrocephalus' after traumatic brain injury (TBI) or subarachnoid haemorrhage (SAH). In neurocritical care, this component is commonly eradicated by extraventricular drainage. Finally, the fourth component is related to increase in brain volume (oedema) or volume of contusion (like haematoma). Osmotherapy or surgical decompression is commonly used to eradicate this component. In clinical practice, it is important not only to monitor absolute value of ICP, but also to recognize which component is responsible for observed intracranial hypertension, as clearly different measures are appropriate for controlling different components (8).

ICP monitoring is one of the standard protocols that can guide patient management undergoing neurocritical care (9). In association with mean arterial blood pressure (ABP), ICP monitoring provides the knowledge of cerebral perfusion pressure (CPP = ABP - ICP),

interpreted as the main force maintaining cerebral blood flow (CBF). However, ICP/CPP are not commonly considered in many clinical conditions outside neurocritical care settings or in non-specialized centres. The invasiveness of the standard methods for ICP monitoring (epidural, subdural, intraparenchymal and intraventricular monitors) and their associated risks to the patient (infections, brain tissue lesions, haemorrhage) contribute to this scenario (Figure 1). They have prevented ICP monitoring in a broad range of diseases, like in patients with risk of coagulopathy, as well as in other conditions in which invasive monitoring is not considered or outweighed by the risks of the procedure. Another downside is related to costs and availability: invasive monitoring is an expensive technique, requires trained personnel and neurosurgical settings. Average cost of intraparenchymal microtransducer is US$ 600, additionally to US$ 6000-10000 for the display monitor (10), which makes it inaccessible in low to middle income regions. Provided that knowledge of ICP can be crucial for the successful management of patients in many sub-critical conditions, non-invasive estimation of ICP may be helpful when indications for invasive ICP monitoring are not met and when it is not immediately available or even contraindicated.

Several methods for non-invasive assessment of ICP have been described so far: transcranial Doppler ultrasonography (TCD) to measure cerebral blood flow velocity indices (11); skull vibrations (12); brain tissue resonance (13); transcranial time of flight (14); venous ophthalmodynamometry (15); optic nerve sheath diameter assessment (ONSD) (16); tympanic membrane displacement (17,18); otoacoustic emissions (19); magnetic resonance imaging (MRI) to estimate intracranial compliance (20); ultrasound-guided eyeball compression (21), and recordings of visual evoked potentials (22).

Most of these methods are better suited for one-point assessment of instant value of ICP rather than continuous monitoring. TCD, on the other hand, has been widely explored as a tool for non-invasive ICP monitoring (23–37) due to its ability to detect changes in CBF with ample time resolution

Figure 1.1. Example of extradural hemorrhage consequent to the insertion of invasive ICP

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography (TCD) technique is based on the phenomenon called Doppler effect, observed by the physicist Christian Andreas Doppler in the 19th century. This principle applied to imaging blood vessels was popularised by Reid and Spencer in the 1970's (38). The application of TCD in clinical practice was first described by Rune Aaslid and collaborators in 1982 (39) as a technique applying ultrasound probes for dynamic monitoring of CBF and vessel pulsatility in the basal cerebral arteries.

The Doppler effect states that when a sound wave with a certain frequency strikes a moving object, the reflected wave undergoes a change in frequency (the Doppler shift, f_d) directly proportional to the velocity of the reflector. When translated to medical applications, this principle has been applied to monitor erythrocyte motion inside an insonated blood vessel by measuring the difference in ultrasound frequencies between emission and reception (39). The equation derived from this principle is the basis for calculating cerebral blood flow velocity (FV, in cm/s) with TCD:

Equation 1.1

$$v = \frac{(c \times f_d)}{2 \times f_0 \times \cos\theta} \tag{1.1}$$

where c is the speed of the incident wave, f_0 is the incident pulse frequency, and θ is the angle of the reflector relative to the ultrasound probe (40).

TCD relies on pulsed wave Doppler to image vessels at various insonation depths. Received echoes generate an electrical impulse in the ultrasound probe and are processed to calculate f_d and v, yielding a spectral waveform with peak systolic velocity (FV$_s$) and end diastolic velocity (FV$_d$) values (Figure 2).
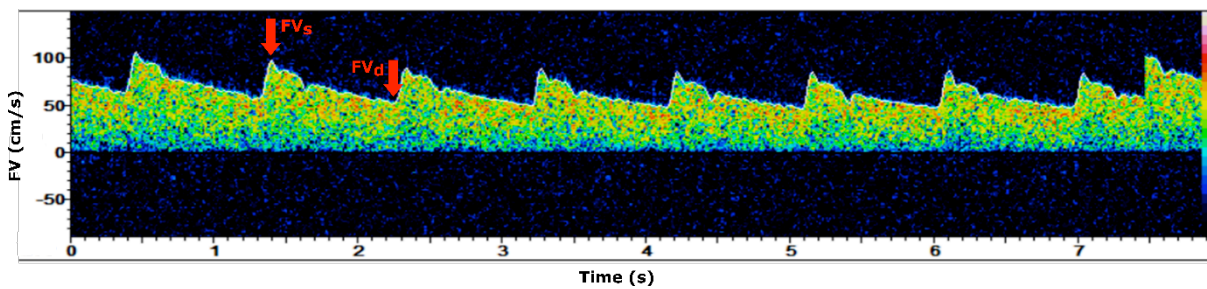
Figure 1.2. Representation of the systolic (FV$_s$) and diastolic (FV$_d$) components of the spectral cerebral blood flow (CBF) velocity (FV) waveform.

The use of low frequency ultrasound probes ($\leq$2 MHz) allows insonation of basal cerebral arteries through different acoustic windows in the skull. These are regions presenting thin bone layers, through which ultrasound waves can be transmitted. There are four acoustic windows: transtemporal, transforaminal, transorbital and submandibular (Figure 3). The transtemporal window is the most frequently used, anatomically located above the zygomatic edge between the lateral canthus of the eye and auricular pinna. It allows insonation of the circle of Willis, specifically middle (MCA), anterior (ACA), posterior cerebral arteries (PCA), and terminal internal carotid artery (ICA) (41). Artery insonation is subject to probe angle, depth and appropriate acoustic window. However, inadequate transtemporal windows have been reported in 10-20% of patients (42,43). This has been associated with patient age, female sex, and other factors affecting the bone thickness (44).
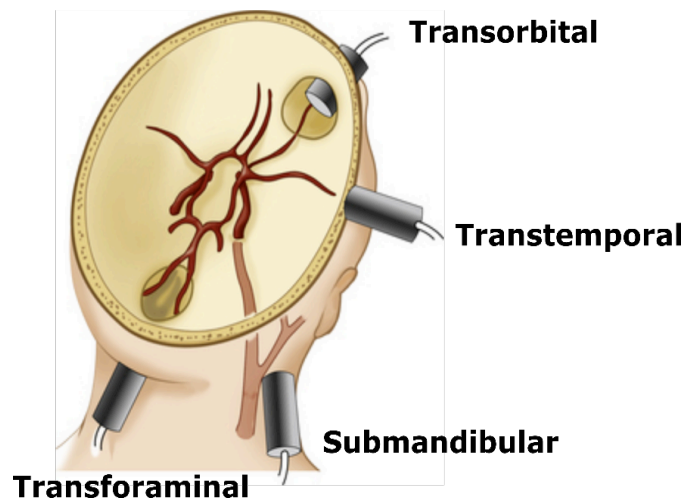
Figure 1.3. Schematic representation of the acoustic windows for transcranial Doppler ultrasonography.

In clinical practice, the MCA is the most frequently assessed artery. It is responsible for the greatest blood inflow to the brain (80%) (45,46), thus MCA measurement may represent the global blood flow. CBF represents the blood supply to the brain in a given period of time, and global changes in this parameter can be monitored continuously and non-invasively using TCD-derived FV (47). However, FV is only proportional to CBF when vessel cross-sectional area and angle of insonation are constant. The velocity detected by the probe as a fraction of the real velocity depends on the cosine of the angle of insonation (Equation 1.1). Consequently, at 0 angle, erythrocytes velocities are equal (cosine of $\theta = 1$), whereas at 90 degrees, no detection of velocity is possible. Anatomically, MCA insonation at the transtemporal acoustic window only allows signal capture at narrow angles (<30 degrees), which approximates the detected velocity of the true velocity (87% to 100%) (48).

Non-invasive estimation of ICP and CPP

TCD waveform analysis has been investigated as a technique for non-invasive estimation of ICP (nICP) and CPP (nCPP). TCD-derived nICP/nCPP methods are based on the relationship between ICP/CPP and indices derived from cerebral blood flow velocity.

Applications of TCD for nICP monitoring are conceivable if one considers the insonated compliant MCA as a biological pressure transducer, whose walls can be deflected by

transmural pressure (equivalent to CPP), modulating accordingly the FV pulsatile waveform (37).

Optic Nerve Sheath Diameter (ONSD) Ultrasonography for assessment of ICP

The optic nerve sheath is continuous with the meninges of the central nervous system and is encased with the subarachnoid membrane (Figure 3.4 and 3.5) (37,38). Cerebrospinal fluid (CSF), located in the subarachnoid space, accumulates in the optic nerve sheath thereby widening its diameter in the response to increased ICP and limited intracranial compliance.
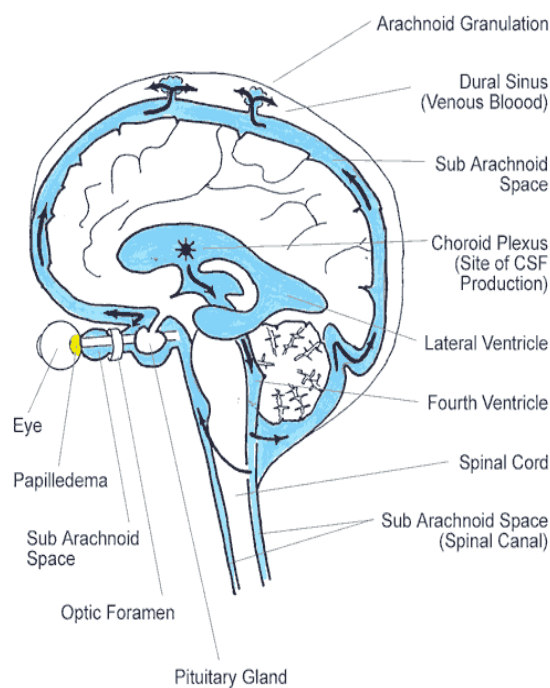
Figure 1.4. Schematic representation of cerebral spinal fluid circulation.
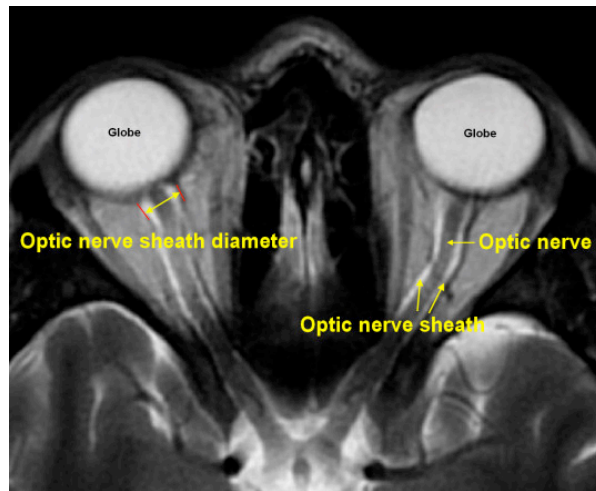
Figure 1.5. Magnetic Resonance imaging of the optic nerve and optic nerve sheath diameter.

Ultrasonography of ONSD has been shown to correlate with increased ICP (Figure 3.6) (37-40). Alternatively, ONSD measurements on MRI and CT are strongly correlated with increased ICP, but the relationship between optic nerve sheath diameter (ONSD) measured radiologically and simultaneously measured intracranial pressure (ICP) in patients with intracranial hypertension is not clear.

In this project, the changes of ONSD during recorded wave of ICP in NCCU will be analysed with ICP transducer in-situ. We intend to evaluate what is dynamics of ONSD changes in comparison to direct ICP monitoring in patients with intracranial hypertension in different clinical pathologies (traumatic brain injury, stroke, subarachnoid haemorrage).
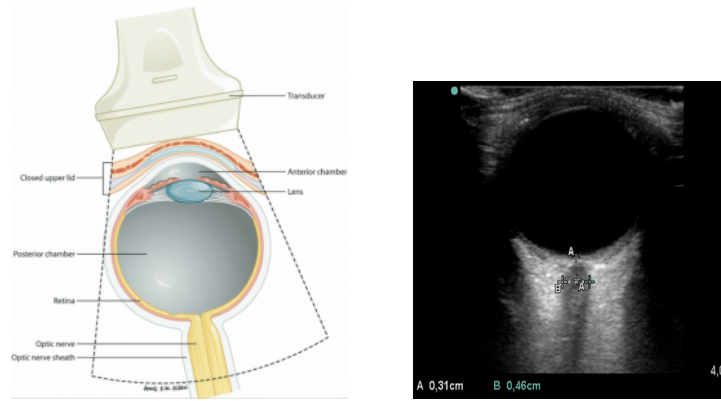
Figure 1.6. Measurement of ONSD with Ultrasound.

AIMS:

This project is organized into three general objectives:

OBJECTIVE 1. Evaluation of TCD-based methods versus invasive ICP

TCD-based, model-derived secondary indices offer readily available means for assessment and real-time monitoring of physiological and pathological processes, facilitating detection of onset of breakdown of homeostasis of cerebral and cerebrospinal circulation and estimation of ICP.

OBJECTIVE 2. To evaluate the dynamics of ICP versus ONSD methods

To determine the association between simultaneously obtained ONSD measured on CT, Ultrasound and ICP in patients with severe intracranial hypertension. In addition, to determine the ability of ONSD to discriminate between intracranial hypertension (ICP ≥20mmHg vs. ICP <20mmHg).

OBJECTIVE 3. To investigate the comparison and utilisation of both techniques

The last part of my project was concentrated on the comparison between TCD-based methods and OSND methods and on the study of an innovative system of non-invasive ICP monitoring

using a combination of these techniques and verifying their accuracy and feasibility in patients with intracranial hypertension.

OUTLINE OF THE THESIS

These general aims have been translated in a series of experiments, retrospective analyses and background studies which are presented in the subsequent chapters of this thesis.

Chapter 2 provides a further clinical background for the evaluation of non-invasive intracranial pressure in patients with traumatic brain injury, subarachnoidal haemorrage, and stroke. We describe the application of different techniques and methods to measure non-invasive ICP, through an historical description of the current available methods used in the experimental and clinical practice.

Chapter 3 describes in an experimental model of intracranial hypertension during infusion studies the accuracy of different non-invasive methods to assess ICP using TCD Ultrasonography.

Chapter 4 provides the clinical background for the intraoperative use of TCD and ONSD during surgery involving pneumoperitoneum and Trendenburg position highlighting the potential use of these techniques in the assessment of ICP during surgical procedures.

Chapter 5 introduces the use of Ultrasound based non-invasive ICP methods in the intraoperative settings and in particular the effects of prone position and of positive- end espiratory pressure on cerebral haemodynamics

Chapter 6 continues research in the intraoperative settings and in particular in patients undergoing Trendelenburg position and pneumoperitoneum. In particular, we tested the ability of non-invasive methods to assess changes in ICP during these procedures.

Chapter 7 describes in a multicenter pilot study, the application of non-invasive methods in brain injured patients and the ability of these methods to identify patients at risk of intracranial hypertension.

Chapter 8 introduces the role of ONSD in the assessment of intracranial hypertension in patients with traumatic brain injury.

Chapter 9 continues research into the role of ONSD and TCD in the estimation of ICP. In particular, we compared different Ultrasound based methods to assess the best estimator of ICP.

Chapter 10 describes the role of ONSD as predictor of increased intracranial pressure and impaired autoregualtion and the relationship between ONSD and mortality in TBI patients.

Chapter 11 explores the application of Ultrasound based non-invasive ICP methods in the pediatric population.

Chapter 12 provides a summary of our findings and the possible future applications of ultrasound based non-invasive ICP.

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Chapter 2 . Non-invasive assessment of intracranial pressure

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ABSTRACT

Background: Monitoring of intracranial pressure (ICP) is invaluable in the management of neurosurgical and neurological critically ill patients. Invasive techniques (ventriculostomy and microtransducers) are considered the gold standard in terms of reliability in the measurement of ICP but are associated with certain risks. Thus, the availability of a valid method to noninvasively detect ICP increase is of great utility for managing these patients. This review provides a comparative description of the different methods for non-invasive ICP measurement.

Brain imaging techniques, based on morphological changes associated with ICP increases: Magnetic Resonance, Computed Tomography, and optic nerve sheath diameter assessment; indirectly transmitted ICP caption: fundoscopy, timpanic membrane displacement; cerebral flow change detection: transcranial doppler, eyeball ophthalmic artery method; monitoring of metabolic alterations: Near Infrared Spectroscopy; neurophysiological registrations of functional activity: electroencephalography, visual Evoked Potentials, oto-acoustic emissions, time of flight method.

At present, none of the noninvasive techniques available are suitable enough to be used alone as a substitute for invasive monitoring. However, following the present analysis and considerations upon each technique, we propose a possible flowchart based on the combination of non-invasive techniques including continuous TCD and repetitive US measurements of ONSD, which can offer either a support in identifying the necessity for an invasive monitoring or a quite useful tool for patients where invasive ICP is contraindicated at all or unavailable.

INTRODUCTION

Intracranial hypertension (IH) is an important cause of secondary brain injury, and its association with poor outcome has been extensively demonstrated (1). Several conditions are associated with IH, which can be classified into extracranial (fever, increased abdominal pressure, increase of intra-thoracic pressure, venous obstruction, hypercarbia, hypoxia) and intracranial causes (hematoma, contusion, cerebrospinal fluid (CSF) alterations or edema) (revised in (2)). ICP monitoring is crucial in the management of neurocritical patients as clinical signs of IH are tardive and have a poor performance in predicting elevated ICP (3).

According to 'The Brain Trauma Foundation' guidelines (4), invasive ICP monitoring is indicated in all severe TBI patients in the following conditions: either positive brain CT findings (hematomas, contusion, swelling, herniation, or compressed basal cisterns), or normal brain CT if the patient is older than 40 years, or in presence of systolic blood pressure below 90 mmHg or in case of abnormal flexion or extension in response to pain.

The gold standard for ICP measurement is invasive monitoring through an intraventricular catheter; however, this technique is associated with certain risks (5).
Non-invasive estimation of ICP may be helpful when indications for invasive ICP measurement are not met or when ICP monitoring is not immediately available or even contraindicated, as in case of coagulopathy. Pathologic IH is defined when ICP rises persistently above 20-25 mmHg.

 The aim of this chapter is to review the current available modalities for non-invasive ICP measurement. We organized the various methods in categories, according to the physio-pathological mechanism used to detect ICP increase. In particular, we divided them in: *Brain imaging techniques*, (Magnetic Resonance (MR), Computed Tomography (CT), and Optic Nerve Sheet Diameter (ONSD assessment));*Indirectly transmitted ICP* (fundoscopy, timpanic membrane displacement (TMD)); *Cerebral Blood Flow change detection* (transcranial doppler (TCD), eyeball ophthalmic artery method); *Monitoring of metabolic alterations* (Near Infrared Spectroscopy (NIRS)); *Neurophysiological registrations of functional activity* (electroencephalography, (EEG) including visual Evoked Potential (VEP), otoacoustic emissions, time of flight (TOF) method).

ICP ESTIMATION THROUGH IMAGING

CT

A variety of CT findings have been considered for predicting elevated ICP: the midline shift, the size of sulci, the morphology of cisterns (6), and ventricles (7), intracerebral hematoma size, the presence of contusions or of subarachnoidal blood. However, none of these findings have demonstrated to be sufficiently reliable in assessing increased ICP (reviewed by (8)).

A normal brain CT at admission does neither exclude the risk of early ICH (9), nor the risk of following development of elevated ICP. Similar considerations were made regarding the predictive value of abnormal CT findings in the assessment of ICP (10). Some authors (11) attempted to create a CT based prediction model including ventricular size, sulci size, degree of transfalcine herniation, and gray/white matter differentiation, and they demonstrated that initial brain CT findings showed a linear, but ultimately non-predictive relationship with baseline ICP. This finding was also confirmed in another study based on the Marshall Brain CT classification (12) and by several other authors (6, 13-18).

In summary, brain CT is a valuable clinical tool for quickly diagnosing and managing patients presenting with clinical signs or symptoms of raised ICP. However, no Brain CT based criteria is sufficient, and this method has demonstrated high specificity but low sensitivity (11-14) with a high possibility of false-negatives (14, 16, 17).

MRI cerebrospinal fluid, volume accounting

The MRI based method to measure ICP takes advantage of the concept of intracranial elastance, derived from the exponential relationship between intracranial volume and pressure (19) (see figure 2.1).
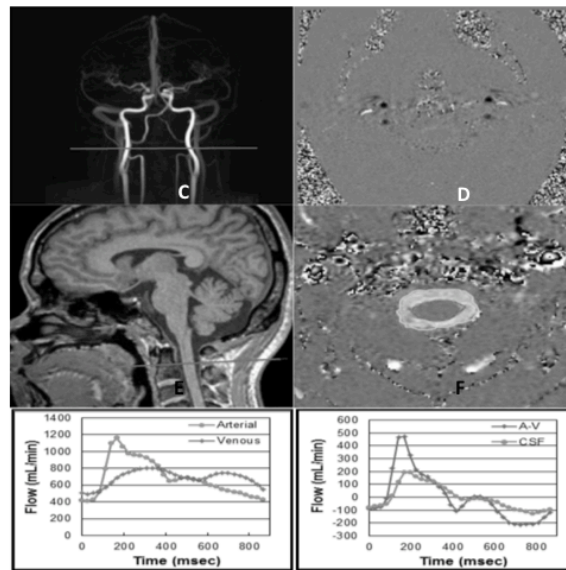
Figure 2.1. MRI method. A. *A blood vessel MRI scout image showing the location of the axial plane for blood flow measurement (horizontal line).* ***B.*** *A Phase Contrast MRI image of blood flow through that location of carotid arteries, vertebral arteries and jugular veins. Black pixels indicate arterial inflow and white are venous outflow.* ***C.*** *Anatomical mid-sagittal T1 weighted MR image showing the location of the axial plane used for CSF flow measurement (horizontal line).* ***D.*** *MRI images of the region of interest for CSF flow: the spinal canal (light grey) and the spinal cord (dark grey).* ***E-F.*** *MRI-based measurements of arterial inflow, venous outflow (E), and cerebrospinal fluid flow (F) used for derivation of the MRICP with derived waveforms of the total arterial inflow and venous outflow (E) and CSF flow and arterial minus venous (F) during the cardiac cycle (with permission from Alperin et al.).*

The pulsatility of blood flow with each cardiac cycle causes small fluctuation in intracranial volume, and the intracranial elastance is derived from the variation of these changes during the cardiac cycle. Thus, ICP value can be derived from the known relationship between ICP and elastance (20).

The accuracy of the MRI-based method was initially evaluated using a craniospinal flow-volume model, where the volume changes (ΔICV) could be determined independently from the method (21).

This technique offered high accuracy, reproducibility and good temporal response of non-steady flow measurement with the cine phase contrast technique (average maximum ΔICV value measured by MRI which within 5% of the value independently measured). Early evaluation of absolute ICP values of measurement reproducibility in human subjects

demonstrated a much larger measurement variability of 18% (22).

The relationship between time varying change in pressure was studied experimentally in animal model by Alperin et al. (22). The authors found a linear relationship between the amplitudes of the CSF pressure gradient measured by MRI and the amplitude of the invasively measured pulse pressure at three different levels of ICP.

Alperin et al. investigated the use of MR as a noninvasive method to assess intracranial elastance and pressure in patients with an invasive ICP measurement. From the ratio of pressure to volume change the elastance index was derived finding a very good correlation with invasive ICP ($r^2 = 0, 965$; $p < 0.005$) (22). Moreover, Muehlmann et al. (23) found a positive correlation (Spearman Q = 0.64, P = 0.01) between shunt valve opening pressure and MR-ICP in 15 shunt-treated hydrocephalus children without signs of shunt malfunction.

This method has been successfully applied for ICP assessment in patients with cerebral arteriovenous malformations (with assessment of blood and CSF dynamics as well) (24) and as a prognostic tool in patients with symptomatic hydrocephalus (25). Moreover, MR derived ICP method was successfully applied to demonstrate that severity of headaches in acute mountain sickness is correlated with the change in ICP between normoxia and hypoxia (26).

However, this method cannot be used for continuous monitoring or repeated assessment of ICP over time and it requires a careful selection of representative image slides and the choice of the representative blood vessels (27).

OPTIC NERVE SHEATH DIAMETER

Anatomy and physiology

The sheath enveloping the optic nerve is in continuity with the dura mater of the brain and the subarchnoidal interspace filled with CSF, accounting for a direct connection between the two compartments (28). As the ONS is distensible, CSF pressure variations influence the volume of ONSD with fluctuations in the anterior, retro-bulbar compartment, about 3 mm behind the

globe (29). There is a linear relationship between peri-optic CSF pressure and ICP (6, 30), and ONSD changes almost directly with ICP (29, 31), as during osmotic therapy (32) or following CO_2 variations (33).

Thus, ONSD for ICP detection based either on CT, MR or ultrasound, has been studied by several authors (figure 2).
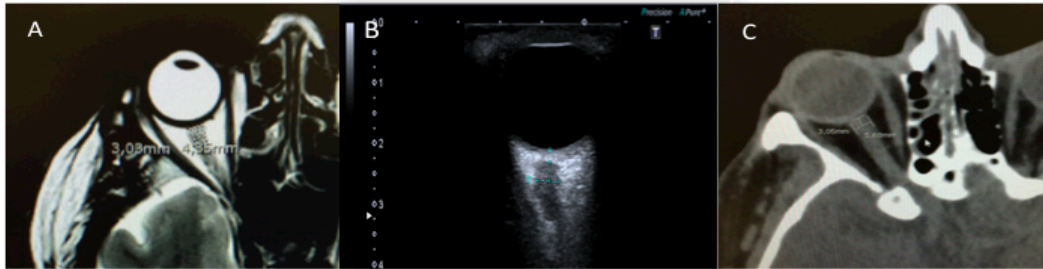

Figure 2.2. Measurement of ONSD. A: Methodology to measure ONSD on Magnetic Resonance. The axial proton density/T2-weighted turbo spin- echo fat-suppressed sequence is used to measure ONSD and optic nerve diameter **B:** Ultrasonographic picture of the optic nerve system. Caliper identifies the site of ONSD measurement 3 mm behind the retina. **C:** Computed Tomography image of the optic nerve sheath. Using electronic calipers ONSD is measured 3 mm behind and in a perpendicular vector with reference to the orbit.

ONSD and Ultrasound

Ultrasonography is a simple bedside tool, widely used in emergency units (34). Compared with CT and MR, ultrasound has low cost, high availability, does not need long acquisition times, does not require harmful patient transport and seems to have a high reproducibility of measures (29, 35, 36,37,38). However, due to its operator-dependency it should be combined with other clinical signs (37).

The cut-off value for normal ICP assessed with ONSD ranges from 4.8 to 6 mm. With exception of a study based on a very small sample size of TBI patients (38), all other studies found good correlation coefficents and good specificity and sensibility, demonstrating high accuracy for this method (as shown in table 2.1).

Ultrasound of the ONS has also been compared to findings of increased ICP on CT or MR, including the size of ventricle, basilar cistern, sulci, degree of transfalcine herniation, and gray/white matter differentiation (3, 39-41) and it appears much more reliable than these (42).

ONSD ranges from 4.84 to 6.4 mm in adult patients with radiological findings suggesting increased ICP and from 3.49 to 4.94 mm in patients with no radiological alterations, proving good sensitivity and specificity (table 2.1).

ONSD acquired with ultrasound has also been performed on children (29, 36): the upper limit of normality for children is considered 4.0 mm in infants aged less than 1 year, and 4.5 mm in elder children (36, 43, 44) with a rather good sensitivity (83%) despite a low and a specificity (38%) for predicting increased ICP .

ONSD in children has been investigated in different clinical scenarios associated with intracranial hypertension, such as acute hydrocephalus (44), intracranial lesions (39, 45) and liver failure (46); at present, there are no studies in the pediatric population which have compared ONSD values to direct ICP measurements.

Although this technique does not seem to be accurate enough to be used as a replacement for invasive ICP measuring methods, it has a good accuracy in recognizing normal from increased ICP.