

KAUNAS UNIVERSITY OF TECHNOLOGY

YASIN HAMARAT

INVESTIGATION OF TRANSORBITAL
DOPPLER TECHNOLOGY FOR
NON-INVASIVE INTRACRANIAL PRESSURE
AND CEREBRAL AUTOREGULATION
MONITORING

Doctoral Dissertation
Technological sciences, Measurement Engineering (T 010)

2020, Kaunas

The entire research work was accomplished during the period of 2015–2019 at the Health Telematics Science Institute of Kaunas University of Technology.

The doctoral dissertation was supported by the Research Council of Lithuania (LMT) and the Agency for Science, Innovation and Technology (MITA) for scientific visits.

Scientific supervisor:

Arminas Ragauskas, Prof., DSc., FBC, FLSHD (Kaunas University of Technology, Technological Sciences, Measurement Engineering – T 010)

Doctoral dissertation has been published in:

<http://ktu.edu>

Editor:

Armandas Rumšas (Publishing Office “Technologija”)

ACKNOWLEDGMENTS

It is a pleasure to express my gratitude to those who made this thesis possible. First and foremost, I thank my thesis supervisor Arminas Ragauskas, Prof., DSc., FBC, FLSHD, for inspiring and supporting me throughout my journey. It has been an honor to be his first international Ph.D. student. This work would have not been possible without his constant mentoring, advice, encouragement, exchange of ideas and discussions through studies. In particular, whenever there were any obstacles to overcome, he dedicated time to go over my problems for as long as it took to get them completely resolved. Thank You for giving me the freedom to explore and the support to succeed. His guidance helped me during all the time of research and writing of this thesis. I could never have imagined having a better advisor and mentor for my Ph.D. study. I am immensely grateful for his support at both the professional and personal level.

I would like to thank brilliant doctors at Vilnius Republic University Hospital, in Vilnius University Hospital Santaros Klinikos, at Texas Medical Center at Baylor College of Medicine affiliate hospitals (Baylor Saint Luke's Medical Center, or Baylor Clinics), at the Department of Neurosurgery of Kantonsspital Aarau, at the Department of Neurology and at the Eye Clinic of the Hospital of the Lithuanian University of Health Sciences. I would also especially like to thank Aidanas Preikšaitis, MD, Saulius Ročka, MD, Prof., Vaidas Matijošaitis, MD, Assoc. Prof., for the generously provided anonymous data of their patients.

I would also like to thank Vytautas Petkus, DSc., Gediminas Daubaris, DSc., Rolandas Žakelis, DSc., Laimonas Bartušis, DSc., Solventa Krakauskaitė, DSc., Vilma Putnynaitė MSc., Mantas Deimantavičius, MSc., for their continuous support, enthusiasm, dedication, passion, their help throughout this writing process, for reminding me how to be a good person and researcher. At Kaunas University of Technology, I would like to thank the Doctoral School, the international office and the human resources office. I would also like to thank all of my friends who are all over the world for always being there for me.

Closest to my heart, I would like to thank my family for pushing me throughout my life. Mom, Dad, Ersin, you all inspire me to work hard and accomplish my dreams. I would also like to thank my daughters, Alisija Nazlı and Eva Burcu, for reminding me that life exists outside of the lab. Above all I would like to thank my wife Laura for her love and constant support, for all the late nights and early mornings, and for keeping me sane over the past few months. Especially thank You for being extremely supportive to me throughout this entire process as You have made countless sacrifices to help me get to this point. But, most of all, thank You for being my best friend. I owe you everything. "When he closes one door he opens another door" as You say always, thank You.

TABLE OF CONTENTS

ABBREVIATIONS	7
INTRODUCTION	10
1. INTRACRANIAL PRESSURE MONITORING.....	16
1.1. ANALYSIS OF INVASIVE INTRACRANIAL PRESSURE MONITORING METHODS	16
1.1.1. Lumbar puncture (LP)	16
1.1.2. External ventricular drain (EVD)	16
1.1.3. Microtransducer ICP monitoring devices.....	17
1.1.4. Conclusions	19
1.2. ANALYSIS OF NON-INVASIVE INTRACRANIAL PRESSURE MONITORING METHODS	19
1.2.1. Fluid dynamics approaches	20
1.2.2. Ophthalmic methods.....	25
1.2.3. Otic approaches	27
1.2.4. Electrophysiologic methods	29
1.2.5. Others	29
1.2.6. Conclusions	30
2. LOCATION OF THE INTERNAL CAROTID ARTERY AND OPHTHALMIC ARTERY SEGMENTS FOR NON-INVASIVE INTRACRANIAL PRESSURE MEASUREMENT AND MONITORING.....	33
2.1. Introduction	33
2.2. Methods	34
2.2.1. Patient eligibility.....	34
2.2.2. Standard protocol approval, registration, and patient consent.....	34
2.2.3. Data collection.....	35
2.2.4. Statistical analysis.....	36
2.3. Results	37
2.4. Discussion.....	44
2.5. Conclusions	46

3. GRAPHICAL AND STATISTICAL ANALYSIS OF THE OCULOCARDIAC REFLEX DURING NON-INVASIVE INTRACRANIAL PRESSURE MEASUREMENT.....	47
3.1. Introduction	47
3.2. Materials and methods.....	48
3.2.1. Equipment and measurement technique	48
3.2.2. Subjects and settings.....	50
3.2.3. Data processing.....	50
3.2.4. Statistical analysis.....	51
3.3. Results	52
3.4. Discussion.....	56
3.5. Conclusions	58
4. NON-INVASIVE CEREBROVASCULAR AUTOREGULATION ASSESSMENT USING THE VOLUMETRIC REACTIVITY INDEX	59
4.1. Introduction	59
4.2. Materials and methods.....	61
4.2.1. Non-invasive cerebrovascular autoregulation assessment.....	61
4.2.2. Data processing.....	62
4.3. Results	65
4.4. Discussion.....	69
4.5. Limitations.....	71
4.6. Conclusions	71
5. NON-INVASIVE CONTINUOUS INTRACRANIAL PRESSURE MONITORING	72
5.1. Introduction	72
5.2. Methods	75
5.2.1. Derivation of blood flow velocity parameter used for the ICP _{non-inv} monitoring	75
5.2.2. Clinical material	77
5.2.3. ICP monitoring and data sampling	77
5.2.4. Novel non-invasive cerebral autoregulation monitoring by using OA... ..	78
5.2.5. Statistical analysis.....	80
5.3. Results	80

5.3.1. Patient No. 1	80
5.3.2. Patient No. 2	83
5.3.3. Patient No. 3	86
5.3.4. Patient No. 4	89
5.3.5. Patient No. 5	92
5.3.6. Patient No. 6	95
5.3.7. Patient No. 7	98
5.3.8. Novel non-invasive cerebral autoregulation monitoring using OA.....	101
5.4. Discussion.....	103
5.5. Conclusions	104
5.6. Source of errors	112
GENERAL CONCLUSIONS.....	114
REFERENCES	116
LIST OF PUBLICATIONS.....	133

ABBREVIATIONS

AAMI	Association for the Advancement of Medical Instrumentation
ABP	Arterial Blood Pressure
ACA	Anterior Communicating Artery
AUC	Area Under Curve
BA	Basilar Artery
BFV	Blood Flow Velocity
BFVd	Diastolic Blood Flow Velocity
BFVm	Mean Blood Flow Velocity
BFVP	Blood Flow Velocity Parameter
BFVs	Systolic Blood Flow Velocity
BHR	Baseline Heart Rate
CA	Cerebrovascular Autoregulation
CBF	Cerebral Blood Flow
CBFV	Cerebral Blood Flow Velocity
CI	Confidence Interval
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CVR	Cerebrovascular Resistance
CW	Circle of Willis
DAI	Diffuse Axonal Injury
DBI	Diffuse Brain Injury
ECG	Electrocardiogram
EEG	Electroencephalography
EOA	Extracranial Segment of the Ophthalmic Artery
EVD	External Ventricular Drain

FCA	Front Cerebral Artery
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Score
HDT	Head Down Tilt
HR	Heart Rate
HTG	High Tension Glaucoma
HUT	Head Up Tilt
HVs	Healthy Volunteers
IBV	Intracranial Blood Volume
ICA	Internal Carotid Artery
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IOA	Intracranial Segment of the Ophthalmic Artery
IOP	Intraocular Pressure
LD	Lateral Decubitus
LP	Lumbar Puncture
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MHR	Mean Heart Rate
MRI	Magnetic Resonance Imaging
Mx	Pearson's Correlation Coefficient between Cerebral Blood Flow and Arterial Blood Pressure
nICP	Non-invasive Intracranial Pressure
NIRS	Near Infrared Spectroscopy
OA	Ophthalmic Artery
OAE	Otoacoustic Emissions
OCR	Oculocardiac Reflex
OCT	Optical Coherence Tomography

ONSD	Optic Nerve Sheath Diameter
PCA	Posterior Communicating Artery
PCA	Posterior Cerebral Artery
Pe	Externally Applied Pressure
PI	Pulsatility Index
PRx	Pressure Reactivity Index
RNFL	Retinal Nerve Fiber Layer
SD	Standard Deviation
SDH	Subdural Hematoma
TBI	Traumatic Brain Injury
TCA	Transcranial Acoustic
TCD	Transcranial Doppler
TMD	Tympanic Membrane Displacement
TRA	Tissue Resonance Analysis
UT	Ultrasonic Transducer
VA	Vertebral Artery
VEP	Visual Evoked Potentials
VRx	Volumetric Reactivity Index

INTRODUCTION

Relevance of the research

The skull consists of the cranium and the mandible. The cranium has three contents which are brain, cerebrospinal fluid (CSF), and blood. An increase in one means a decrease in one or both of the remaining two because of the rigid structure of the cranium (Mokri, 2001; Popovic, Khoo, & Lee, 2009). Intracranial pressure (ICP) is the cerebrospinal fluid pressure inside the cranium and is usually expressed in millimeters of mercury. An extended definition of ICP is the pressure around the brain caused by cerebrospinal fluid or blood. Some factors, such as age, body posture, etc., affect the normal range of ICP, and ICP is maintained in a narrow range, specifically, 5–15 mmHg, in healthy supine adults, 3–7 mmHg in children, and 1.5–6 mmHg in term infants (Raboel, Bartek, Andresen, Bellander, & Romner, 2012; Smith, 2008). Cerebral autoregulation (CA) is the mechanism that regulates and maintains the cerebral blood flow (CBF) constant across a range of cerebral perfusion pressures by dilating and constricting arterioles (Yang & Liu, 2017). Lassen described the origin of CA as the triphasic curve consisting of the lower limit, the plateau and the upper limit. In healthy adults, the limits of cerebral autoregulation are between 50 and 150 mmHg for cerebral perfusion pressure (CPP) or 60 and 160 mmHg for mean arterial pressure (MAP) (Lassen, 1959).

$$CPP = MAP - ICP \quad (1)$$

here, CPP is the cerebral perfusion pressure, MAP represents the mean arterial pressure, and ICP stands for intracranial pressure.

ICP is clinically important in neurological and neurosurgical diseases. Even secondary brain injuries that were caused by elevated ICP take place in minutes. For example, a raised ICP is associated with poor outcomes of traumatic brain injuries (TBI). Therefore, reliable and rapid monitoring of ICP is crucial for the patients who have suffered TBI. According to the World Health Organization, more than 5 million people die as a result of trauma yearly. About 2.8 million people sustain TBI each year in the United States. Every 15 seconds, someone suffers TBI in the United States. The direct medical and indirect costs of TBI are calculated as more than \$60 billion a year in the United States (BrainFacts, 2018). In Europe, about 2.5 million people suffer TBI annually. The yearly cost of TBI exceeds €100 million in Europe. 69 million (95% CI 64 to 74 million) individuals suffer TBI each year worldwide (Hutchinson *et al.*, 2019). TBI is the leading cause of death and permanent disability in young adults.

An ICP monitor is needed to diagnose elevated ICP since clinical evaluation alone is not enough to determine raised ICP. Therefore, an ICP monitor is recommended for TBI patients when the risk of intracranial hypertension and

abnormal admission head computed tomography (CT) exists (Brain Trauma Foundation, 2007). The aggressive care including an ICP monitor for patients with TBI can improve the outcome of patients (Alali *et al.*, 2013; Farahvar *et al.*, 2012; Gerber, Chiu, Carney, Hartl, & Ghajar, 2013; Stein, Georgoff, Meghan, Mirza, & El Falaky, 2010; Talving *et al.*, 2013), it is also cost-effective even for older patients (Whitmore *et al.*, 2012).

There are several techniques that can be used to monitor ICP, but the best results are obtained when clinical examination, brain imaging and an ICP monitor are used together (Le Roux, 2016). Two invasive techniques – intraparenchymal and intraventricular methods – are common in clinical practice. The intraventricular method with ventriculostomy (EVD) is considered as the gold standard in monitoring ICP. EVD is also preferred since it can be used for treatment. Several factors play a major role when choosing whichever ICP monitoring method is fit for the patient; those factors are pathology, presence of coagulopathy, device accuracy, ease of insertion, cost, reliability, and bedside setting.

Today, elevated ICP is treated mainly for two reasons: to prevent herniation and to preserve CBF (Le Roux, 2016). In clinical practice, several ICP thresholds are used: 14.7 mmHg (Nourallah *et al.*, 2018), 15 mmHg (Marshall, Smith, & Shapiro, 1979; Saul & Ducker, 1982), 20 mmHg (Marmarou, Saad, Aygok, & Rigsbee, 2005; Miller *et al.*, 1977), 25 mmHg (Ratanalert *et al.*, 2004) and 35 mmHg (Chambers, Treadwell, & Mendelow, 2001). An individualized threshold of ICP can be set based on patient characteristics, pathology and physiological parameters. Multimodal monitoring including ICP monitoring and CA monitoring can be used to determine the ICP threshold based on clinical and CT findings for the favorable outcome (Le Roux, 2016).

Maintaining the optimal patient-specific cerebral blood flow through the brain is essential for a better outcome for TBI patients. Cerebral perfusion needs to be kept within certain limits to protect the brain (including the eye) from functional damage. A normal brain autoregulates the cerebral blood flow regardless of any changes in the blood pressure or CPP. Homeostatic mechanisms are usually lost in the case of a head trauma; therefore, brain becomes susceptible to blood pressure changes. When cerebral autoregulation is impaired, an increase in the arterial blood pressure leads to an increase in the cerebral blood flow and intracranial hyperperfusion. In this concept, arterial blood pressure (ABP) acts as the input, and intracranial pressure (ICP) acts as the output, i.e., ABP is the action and ICP is the reaction (**Fig. I.1**).

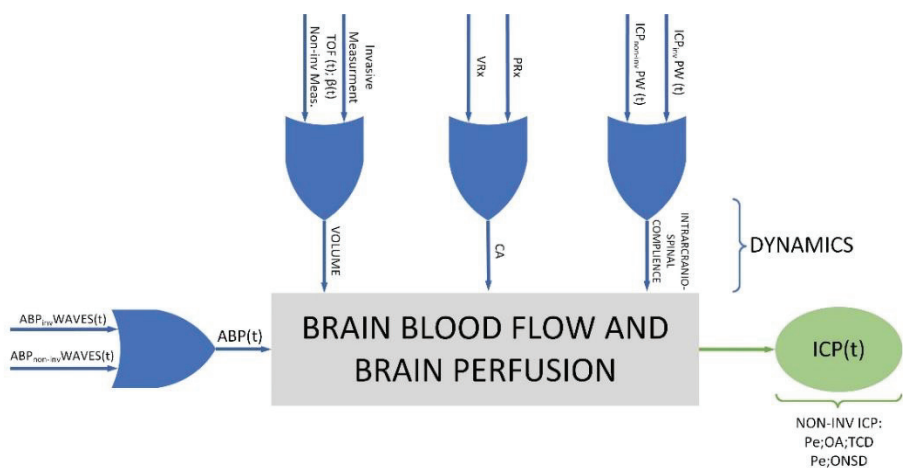


Fig. I.1. Concept of the optimal brain blood flow and brain perfusion. ABP – arterial blood pressure, CA – cerebral autoregulation, ICP – intracranial pressure, Pe – externally applied pressure, OA – ophthalmic artery, TCD – transcranial Doppler, ONSD – optic nerve sheath diameter

Several methodologies have described non-invasive ICP monitoring, yet none of them are denoted by clinically acceptable accuracy. Therefore, ICP monitoring remains an invasive procedure which needs a burr hole to introduce a transducer-coupled probe into the brain parenchyma or ventricles. All the invasive ICP monitoring methods are considerably complex, expensive and suffer from a high risk of misplacement, bleeding, hemorrhage, infection, and injury. Beside these, invasive ICP monitoring methods can be used in specific patients' groups, such as brain tumors, hydrocephalus, idiopathic intracranial hypertension, severe TBI, etc.

A new approach in non-invasive ICP monitoring is needed. This non-invasive ICP monitoring device should be used in a wider group of patients than invasive ICP monitoring. The novel non-invasive absolute value ICP snapshot measurement (Ragauskas & Daubaris, 1995; Ragauskas, Daubaris, & Dziugys, 1999) device has a high level of accuracy and precision (Krakauskaite *et al.*, 2016). Therefore, this methodology can be suitable for long-term monitoring, but there are safety and technological problems which still need to be addressed before using it in the clinical practice. The safety problem is the incidence of the oculocardiac reflex, and the technological problem is the location of IOA and EOA. Thus, this dissertation shall focus on solving those problems and on using the adapted new non-invasive ICP monitoring device in clinical trials.

Scientific-technological problem and research hypothesis

The scientific-technological problem: *in which way and by which means is it possible to monitor the intracranial pressure continuously and non-invasively by using a non-invasive absolute value ICP snapshot measurement device; can this non-invasively monitored data be used in the non-invasive cerebrovascular autoregulation assessment?*

The research hypothesis was raised after the formulation of the scientific-technological problem: *it is possible to monitor ICP continuously and non-invasively by adapting a non-invasive absolute value ICP snapshot measurement device which has clinically acceptable accuracy and precision and to address the problem of safety, if needed, as well as to use the collected non-invasive monitoring data to assess the cerebrovascular autoregulation in patients with TBI.*

Aim and tasks of the research

The aim of the research is to assess the possibility of adaption of the non-invasive ICP absolute value snapshot measurement system to continuous ICP and CA monitoring by performing prospective and retrospective studies, to address the technical and safety problems that may occur during non-invasive continuous ICP monitoring.

The following tasks have been formulated to achieve the aim of this research:

1. To analyze and review the existing literature on intracranial pressure monitoring methods; to investigate the possibilities for continuous intracranial pressure monitoring.
2. To carry out a prospective and retrospective study of patients with high tension glaucoma and healthy volunteers: to analyze the location and position of the internal carotid artery and the ophthalmic artery as a technical problem for the operator of a transcranial Doppler.
3. To carry out a retrospective study of neurological and ophthalmological (glaucoma) patients as healthy volunteers: to analyze the oculocardiac reflex as a safety problem for patients and volunteers during continuous ICP monitoring.
4. To carry out the prospective comparative clinical study of patients with a traumatic brain injury; to compare real time invasive and non-invasive cerebrovascular autoregulation indexes calculated from invasive intracranial pressure, invasive arterial blood pressure and non-invasive intracranial blood volume monitoring data.
5. To carry out a prospective clinical study of non-invasive ICP monitoring for patients with a severe traumatic brain injury; to compare the obtained results

with the invasive ICP monitoring system by accuracy, precision, diagnostic sensitivity, and specificity.

Scientific novelty

For the first time, the incidence of the oculocardiac reflex was analyzed during non-invasive ICP snapshot measurement which uses external gradual pressure up to 48 mmHg. As a result, a very low incidence of the oculocardiac reflex was found.

The new methodology is suggested for the continuous monitoring of ICP that is based on literature analysis and the accumulated data from a prospective study on glaucoma patients and healthy volunteers. According to this methodology, the edge of the internal carotid artery shall be used as the reference depth. Then, the intracranial segment of the ophthalmic artery can be found simultaneously with the extracranial segment of the ophthalmic artery. The new methodology also suggests the possible location of those arteries based on literature analysis. Another finding of this study is that the ultrasonic transducer's angle for the edge of the internal carotid artery is different from the angle of the intracranial segment of the ophthalmic artery and the extracranial segment of the ophthalmic artery.

The new scientific data obtained during a prospective study on patients with TBI is that non-invasive ICP monitoring is possible by using a non-invasive absolute value ICP snapshot measurement device. As a result of this study, a strong correlation was found between non-invasive ICP monitoring and invasive ICP monitoring. The accuracy, precision, sensitivity and specificity of non-invasive ICP monitoring were found to be **0.99** (95% CI = 0.90 to 0.91), **0.91** (95% CI = 0.90 to 0.91), **0.87** (95% CI = 0.85 to 0.89) and **0.91** (95% CI = 0.90 to 0.93), respectively.

Structure of the dissertation

This dissertation consists of an introduction, five main chapters, a conclusion, a list of references, and a list of scientific publications.

In Chapter One of the dissertation, invasive intracranial pressure monitoring and non-invasive intracranial pressure monitoring were discussed, and the advantages and disadvantages of the current clinical methodologies were highlighted. The necessity of a novel non-invasive ICP monitoring method with high accuracy and precision is expressed in this chapter.

In Chapter Two of the dissertation, the result of the prospective and retrospective study on a patient with high tension glaucoma and healthy volunteers revealed a new methodology for the monitoring and measurement of ICP. With this methodology, reliable ICP monitoring and snapshot measurement is possible.

In Chapter Three of the dissertation, the incidence of the evoked oculocardiac reflex was analyzed in patients with neurological and ophthalmological (glaucoma) diseases and healthy volunteers.

In Chapter Four of the dissertation, a prospective comparative clinical study was performed in order to compare non-invasive cerebrovascular autoregulation and invasive cerebrovascular autoregulation. The non-invasive ultrasonic volumetric reactivity index showed a strong correlation with the pressure reactivity index.

In Chapter Five of the dissertation, a prospective study was performed on patients with TBI in order to compare non-invasive ICP monitoring with invasive ICP monitoring. This chapter presents such findings as accuracy, precision, sensitivity and specificity of the non-invasive ICP monitoring method.

The total volume of this dissertation is 136 pages. There are 61 figures, 13 tables and 198 references in the text.

Funding of research

This prospective study of the location of the internal carotid artery and the ophthalmic artery segments for non-invasive intracranial pressure measurement and monitoring was supported by the European Social Fund under the Global Grant project *Evidence Based Glaucoma Diagnostic and Treatment Methods Employing Innovative Non-Invasive Measurement of Intracranial Pressure and Eye Blood Flow Parameter*, Grant number VP1-3.1-SMM-07-K-03-080.

The prospective studies whose data were used for this retrospective OCR analysis received financial support from the European Commission's Seventh Framework Programme project *BrainSafe* (grant No. 232545), Lithuanian-Swiss Programme project *BrainCare* (grant No. CH-3SMM-01/06), the European Social Fund under the Global Grant measure (grant No. VP1-3.1-SMM-07-K-03-080), and the National Space Biomedical Research Institute via NASA NCC9-58 and the Center for Space Medicine, Baylor College of Medicine.

1.INTRACRANIAL PRESSURE MONITORING

1.1.ANALYSIS OF INVASIVE INTRACRANIAL PRESSURE MONITORING METHODS

1.1.1.Lumbar puncture (LP)

The lumbar puncture (LP), also known as the spinal tap, is a medical technique in which a needle is inserted into the spinal canal, between L3 and L4 or L4 and L5 vertebra in order to investigate the intrathecal environment (**Fig. 1.1.**). Quincke introduced this procedure to collect the cerebrospinal fluid (CSF) for diagnostic testing and the measurement of a column of water that reflects the intraspinal pressure (Quincke, 1891; Zhang *et al.*, 2017). LP is the simplest and long-standing invasive ICP measurement method (Wiegand & Richards, 2007). However, LP is not strictly an ICP measurement but also determination of drugs or contrast material in the spinal canal. Researchers showed that LP accuracy is 0.75 mm Hg, and SD = 2.1 mm Hg, compared to the parenchymal ICP measurement (Lenfeldt, Koskinen, Bergenheim, Malm, & Eklund, 2007).

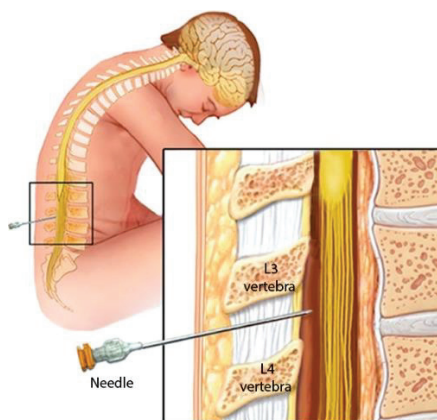


Fig. 1.1. Illustration of lumbar puncture (spinal tap) (adapted from Mayo foundation for medical education and research)

Kashif *et al.* mentioned that the LP procedure is not recommended when ICP is suspected to be high because of the brain herniation risk (Kashif, Verghese, Novak, Czosnyka, & Heldt, 2012).

1.1.2.External ventricular drain (EVD)

The external ventricular drain (EVD), also known as intraventricular monitoring devices, is one of the most common and important invasive techniques

in the neurological intensive care unit (**Fig. 1.2.**). This technique was originally described as a highly accurate tool for monitoring ICP since intraventricular catheters are considered as the gold standard (Brain Trauma Foundation, 2007). In addition to ICP monitoring, EVD can be used for the therapeutic relief of elevated ICP via CSF drainage. EVD appears to be beneficial in various types of acquired brain injury, such as intracranial hemorrhage with intraventricular extension, subarachnoid hemorrhage, traumatic brain injury, bacterial meningitis, as well as intracranial hypertension and raised ICP (Zhang *et al.*, 2017). There are several disadvantages of EDV including infection due to the invasive nature of the device, low reading due to leakage, injuries due to incorrect placement, etc.

Regarding to the Association for the Advancement of Medical Instrumentation (AAMI), ICP monitoring devices should provide an accuracy of ± 2 mmHg in the range of 0–20 mmHg and feature a maximum error that cannot exceed 10% in the range of 20–100 mmHg (Andrews *et al.*, 2008). As a matter of fact, that is tolerated up to 4–5 mmHg in the worldwide clinical practice. **Table 1.1.** shows the results of the clinical studies of ICP measuring instruments of various manufacturers (Citerio *et al.*, 2004; Lang, Beck, Zimmermann, Seifert, & Raabe, 2003; Lescot *et al.*, 2011).

1.1.3. Microtransducer ICP monitoring devices

Microtransducer devices which use catheters to measure ICP when placed within the brain parenchyma can be divided into fiberoptics (Camino), electrical impedance (Codman ‘Microsensor’) and pneumatic sensors (Spiegelberg pressure sensor) (Raboel *et al.*, 2012; Wiegand & Richards, 2007). These devices offer comparable results with intraventricular catheters, are minimally invasive, and have a minimal baseline drift even if placed for a few days. They have become the standard procedure to measure ICP accurately by neurosurgical teams worldwide (Luerssen, 1997).

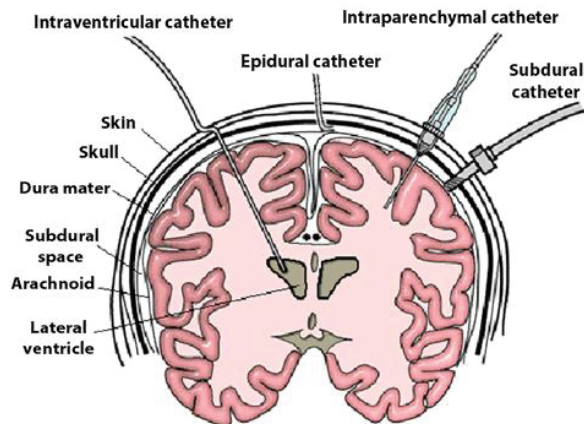


Fig. 1.2. Devices for invasive ICP monitoring (adapted from Medgadget, n.d.)

Epidural ICP monitoring does not provide the necessary accuracy for the routine/clinical use (**Fig. 1.2.**). Epidural pressure sensors do not require drilling into the dura matter, which gives a low probability of infection. However, the accuracy and precision of measurements are low as well. The dura matter is relatively inelastic and does not fully transfer the CSF pressure to the epidural pressure sensor. One report showed that an epidural Camino sensor considerably overestimated ICP with a mean of about 9mmHg, extending to almost 30mmHg (Bruder *et al.*, 1995). Another study showed a marginal difference in the mean ICP of 12.7 ± 1.5 mmHg, but comparable parameters of pulsatile ICP, such as the mean ICP wave amplitude of 3.7 ± 1.7 mmHg and the mean ICP wave latency of 0.28 ± 0.02 , were observed (Eide, 2008).

Subdural ICP monitoring can be done via two principal methods (**Fig. 1.2.**). The first method is based on fluid continuity between the subdural space and an externally placed transducer, such as the Leeds screw (Coroneos, McDowall, Gibson, Pickerodt, & Keaney, 1973) and the Richmond screw (Johnston & Rowan, 1974). The second method depends on the pressure sensor fitted under the dura matter to measure pressure changes directly at the brain surface (Barlow, Mendelow, Lawrence, Barlow, & Rowan, 1985). Subdural ICP monitoring is denoted by a low infection possibility as well as accuracy of ICP measurement. The catheter can be clogged with air bubbles, blood clots, or brain tissue pieces. Subdural ICP monitoring is noticeably less reliable when ICP is elevated (Gupta & Bhatia, 2007; Wiegand & Richards, 2007; Zhang *et al.*, 2017).

Intraparenchymal ICP monitoring catheters are inserted through a support bolt or a burr hole (**Fig. 1.2.**). Intraparenchymal devices have a lower complication rate, a lower infection rate, and no chance of catheter occlusion or leakage, which means that they are the most reliable devices in the daily practice. However, the accuracy in Intraparenchymal ICP monitoring is lower than EVD, also, other issues involve the high expense of the procedure and the inability to calibrate the device once it has been placed. Intraparenchymal catheters are usually placed in the right frontal region at depths of approximately 2 cm (Zhang *et al.*, 2017). Yet, when employing this method, it is not possible to release CSF and to control ICP with it. Intraparenchymal and intraventricular monitors are the standard choice.

It is worth noting that some (but not all) microtransducers (Neurovent – P sensor, Spiegelberg sensor, and Codman sensor) are compatible with magnetic resonance imaging (MRI) without any danger to the patient (Raboel *et al.*, 2012; Shellock, 2002; Stendel *et al.*, 2003).

The implantation of invasive ICP monitoring sensors into the intracranial medium takes about 7 minutes, but the total procedure with preparation takes more than 30 minutes. This procedure can only be carried out in a neurological intensive care unit, thus the arrival to this unit takes additional time as well. Time is very important in the case of a brain injury. In the case of a severe traumatic brain injury, ICP is one of the critically important parameters in the ‘golden’ hour period which is

the first hour after a traumatic brain injury has occurred. Another important time frame is the duration of brain blood flow disturbance which causes neurons in the brain to die after 3–10 minutes. Thus, it is necessary to develop a technology which non-invasively measures the absolute value of ICP with errors in the tolerance range of less than 10 minutes to provide diagnostic benefits.

1.1.4. Conclusions

ICP monitoring is essential in the patients' management when ICP is elevated. The therapy based on the management of raised ICP results in a better outcome of the patient. **Table 1.1.** shows the advantages and disadvantages of invasive ICP monitoring methods. Despite the strengths of all the non-invasive ICP monitoring methods, the invasive ICP monitoring methods remain the gold standard, especially intraventricular drain.

Table 1.1. Advantages and disadvantages of invasive ICP monitoring (Popovic *et al.* 2009)

Method	Advantages	Disadvantages
Intraventricular catheter	Provides 'true' global ICP Allows for CSF drainage and drug delivery <i>In-vivo</i> calibration through an external pressure sensor	Infections Difficult insertion
Epidural Catheter	Ease of insertion Minimal risk of infection	Low accuracy
Lumbar CSF pressure	Extracranial procedure Can be performed ambulatorily	May not reflect ICP Dangerous if ICP is high
Catheter-tip microtransducer (subdural or Intraparenchymal)	Rare complications during the procedure Low risk of infection Can be made with permanent implants	Drift of the transducer output over time <i>In-vivo</i> calibration not possible Inaccurate if Intraparenchymal gradients exist

1.2. ANALYSIS OF NON-INVASIVE INTRACRANIAL PRESSURE MONITORING METHODS

There have been various invasive ICP monitoring methods in use for a long time. They require opening the skull and carry such risks as bleeding, infection, and damage to the brain tissue, thus a non-invasive ICP (nICP) monitoring system with the clinically acceptable accuracy is needed. A nICP monitoring method needs to be developed because of several reasons including, but not limited to, the consideration that there should be no risk of complications encountered in invasive ICP monitoring, such as hemorrhage, bleeding and infection; nICP monitoring is expected to provide long-term monitoring of ICP without having to insert a new device every time, it eliminates or minimizes the need for a neurological intensive care unit and a neurosurgeon.

1.2.1.Fluid dynamics approaches

1.2.1.1. Magnetic resonance imaging (MRI)

MRI can be used to measure ICP non-invasively. This method uses the well-established relationship between ICP and volume (Alperin, Lee, Loth, Raksin, & Lichtor, 2000). During the cardiac cycle, the pulsatile arterial, venous, and CSF flow in and out of the brain was measured by using motion-sensitive MRI (Raboel *et al.*, 2012). The MR imaging-based ICP measurements in the healthy subjects were 4–12 mm Hg, which is within the normal pressure range of 3–15 mm Hg as observed in 1,033 healthy subjects (Alperin *et al.*, 2000).

MRI could have a role in the diagnosis and evaluation of several chronic disorders associated with the increased ICP values. The main disadvantages of this method are the running cost; besides, it is not flexible and portable.

1.2.1.2. Cerebral blood flow velocity (CBFV) monitoring

CBFV is related to both cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR). When ICP is elevated, CPP is decreased, and CVR is increased due to the compression of the cerebrovascular system. Monitoring of the arterial blood pressure (ABP) and the blood flow velocity in the cerebral arteries can be used to calculate ICP estimation. Unfortunately, many monitoring methods based on this technique require various types of empirical parameters or invasive ICP measurement values (Mourad *et al.*, 2005; Popovic *et al.*, 2009; Schmidt *et al.*, 2003; Xu, Kasproicz, Bergsneider, & Hu, 2010). Kashif proposed a simplified monitoring model based on CBFV and ABP (Kashif, 2011). The advantages of this monitoring method are that there is no requirement for the calibration or invasive ICP for training before estimating the nICP value. There is time delay since CBFV and ABP need to be detected, which then serve as input to the model. This can influence the real-time prediction for critical/serious patients.

1.2.1.3. Near-infrared spectroscopy (NIRS)

NIRS can detect changes in the cerebral blood volume (CBV), brain tissue oxygenation, and cerebral blood flow (CBF). The deep tissue penetration and the low absorptivity form are the reasons for choosing NIRS as the nICP monitoring device (Narayan *et al.*, 2018). The variability of absorptivity is used to quantify changes in the concentrations of deoxyhemoglobin and oxyhemoglobin (Khan, Shallwani, Khan, & Shamim, 2017). This method is suitable for continuous detection of changes in CBV (Zweifel, Castellani, Czosnyka, Carrera, *et al.*, 2010). Several hours of monitoring are needed to obtain the necessary parameters for individual patient nICP monitoring, and then the value can only be reliably measured in about 50% cases of recording (Zhang *et al.*, 2017).

1.2.1.4. Transcranial time-of-flight

Ultrasonic transcranial time-of-flight was developed as a brain physiological monitoring technology (Ragauskas & Daubaris, 1995). The transmission time of the ultrasound wave and its (potentially multiple) echoes on their path through the cranium reflects the corresponding distance when using known ultrasound propagation velocities in various tissues (e.g., bone, brain, or CSF) (Petkus, Ragauskas, & Jurkonis, 2002; Popovic *et al.*, 2009; Zhang *et al.*, 2017). The dimensions of the cranium or its structures are measured from the transfer time of the ultrasound transcranial time-of-flight; either the incident ultrasound wave is calculated by using two transducers located on the opposite walls of the cranium, or a single transducer generates the incident wave and measures the echo wave from the contralateral wall of the cranium (Popovic *et al.*, 2009; Zhang *et al.*, 2017). However, the measurement of the quantitative relationship between the cranial diameter and ICP is not reproducible because ICP-induced changes in the cranium diameter are very small compared to the inter-individual variability of skull sizes, shapes and thicknesses (Petkus *et al.*, 2002). The nICP monitoring by the transcranial time-of-flight method has had little validation for the clinical use, and the accuracy of this method still remains unclear. This method is not reliable since the angles and locations of the transducer placement influence ICP measurement.

1.2.1.5. Transcranial Doppler ultrasonography (TCD)

In 1982, Aaslid *et al.*, introduced transcranial Doppler (TCD) for monitoring cerebral hemodynamics (**Fig. 1.3.**). Since then, TCD has become an attractive tool to assess the cerebrovascular tree (Hamarat *et al.*, 2017). TCD can be used for the detection of vasospasm and cerebral embolization, cerebral autoregulation, the detection of cerebral circulatory arrest, traumatic brain injury, circulatory arrest, and non-invasive monitoring of ICP. TCD measures the red cell flow velocity in real time in order to estimate the ICP value. However, nearly all non-invasive ICP assessment approaches based on TCD are correlation-based or model-based; therefore, the absolute value of ICP cannot be measured because patient-specific calibration is required for such measurement methods (Hamarat *et al.*, 2017).

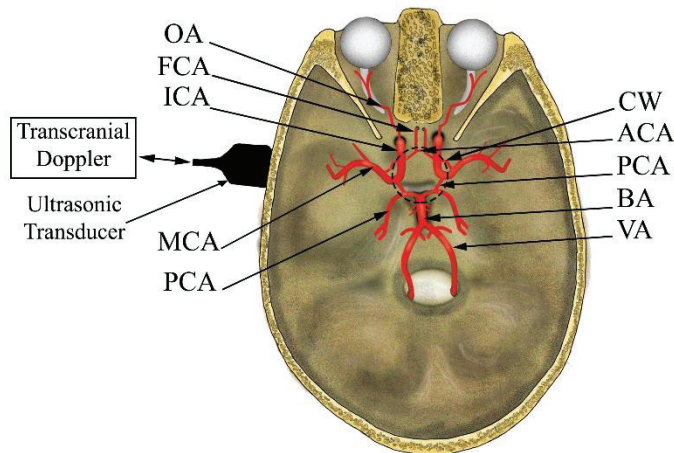


Fig. 1.3. Schematic view of transcranial Doppler ultrasonography and circle of Willis (adapted from Hemodynamics AG 2018). OA – ophthalmic artery, FCA – front cerebral artery, ICA – internal carotid artery, CW – circle of Willis, ACA – anterior communicating artery, PCA – posterior communicating artery, BA – basilar artery, MCA – middle cerebral artery, VA – vertebral artery, PCA – posterior cerebral artery

The brain and the surrounding structures are fed with blood. The circle of Willis, or the circulus arteriosus, is formed by the anastomosis of the two internal carotid arteries with the two vertebral arteries (**Fig. 1.3.**). The anterior communicating, anterior cerebral, internal carotid, posterior communicating, posterior cerebral, and basilar arteries are all part of the circle of Willis. The circle of Willis combines six main brain arteries into a single general pool, and may redistribute the blood flow to all these brain arteries (by supplying blood to the whole brain) even if three brain-feeding (vertebral and internal carotid) arteries close. The cortical and central branches arise from the circle and further supply the brain.

TCD can be used to measure CBF non-invasively in the middle, front and back cerebral arteries as well as in the middle carotid arteries and their branch, eye arteries (**Fig. 1.3.**). The middle cerebral artery (MCA) is most commonly used for TCD measurements. The Doppler instrument operates at 2 MHz, whereas the angles and locations of the transducer can be adjusted to obtain the highest quality signal.

There is a negative correlation between a brain injury and the blood flow velocity in the middle brain arteries. The decrease in the blood flow velocity causes the ICP increase due to the reduced blood flow through the brain. An increase of ICP is paralleled with the increased pulsatility index (PI), which is a parameter of the relative blood flow velocity (Bellner *et al.*, 2004; Voulgaris *et al.*, 2005). The difference between systolic and diastolic BFV, divided by the mean BFV, is equal to PI.

$$PI=(BFVs-BFVd)/BFVm \quad (2)$$

here, PI – pulsatility index, BFVs – systolic blood flow velocity, BFVd – diastolic blood flow velocity, BFVm – mean blood flow velocity.

The active surface of the transducer is layered with an ultrasound gel and then pressed against the thin temporal bone. By changing the locations and angles of the transducer, MCA can be found for the evaluation of PI.

The arterial blood pressure method was invented more than 100 years ago, and it was directly comparable with the external pressure which was applied to the brachial artery. Therefore, there is no need for calibration. The novel method based on this fundamental principle for non-invasive absolute value ICP measurement was invented by Prof. Arminas Ragauskas from the Health Telematics Science Institute of Kaunas University of Technology (Bartusis, 2015) (**Fig. 1.4.**). To obtain a reliable non-invasive ICP measurement with the presently discussed method, the operator must manually find the correct depths of the intracranial (IOA) and extracranial (EOA) segments of the ophthalmic artery (OA) by using a multi-depth TCD (Hamarat *et al.*, 2017). OA is used as a pressure sensor. The pressure is applied externally with a pressure cuff to the eye and its surrounding tissues. Since the eye and its surrounding tissues are incompressible, the gradually applied external pressure is transferred to EOA (Hamarat *et al.*, 2018). The applicable accuracy, precision, diagnostic sensitivity and the specificity of the non-invasive ICP measurement method have been shown by clinical studies (Ragauskas *et al.*, 2012; Ragauskas *et al.*, 2014).

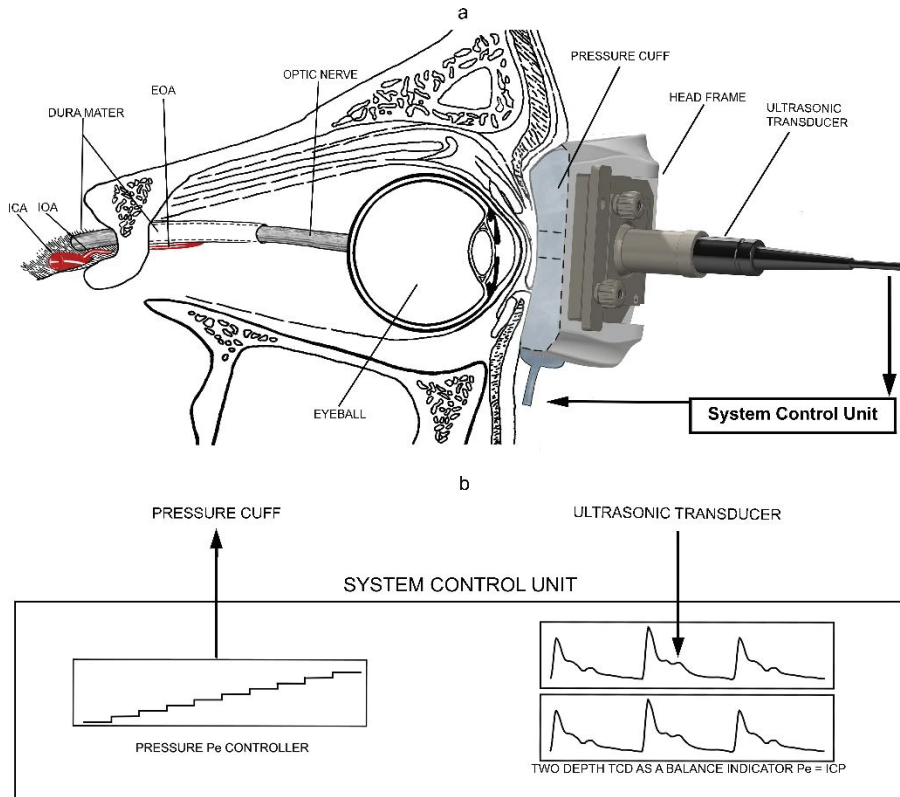


Fig. 1.4. Schematic representation of non-invasive intracranial pressure (ICP) monitoring equipment (adapted from Hamarat *et al.*, 2018). (a) Relevant orbit and brain anatomy in contact with the ICP measurement device. (b) Block diagram of the system control unit. ICA – internal carotid artery; IOA – intracranial part of the ophthalmic artery; EOA – extracranial part of the ophthalmic artery; TCD – transcranial Doppler; P_e – external pressure applied to the ocular globe

The ophthalmic artery (OA) is the first branch of the larger internal carotid artery (ICA), and it consists of two segments: (1) the intracranial ophthalmic artery (IOA) which is located in the intracranial compartment and is affected by ICP, (2) the extracranial ophthalmic artery (EOA) which is located in the orbit and is affected by the external pressure. The dura matter is a thick membrane made of elongated fibroblasts and copious amounts of collagen fibrils; it does not transfer the CSF since it is relatively inelastic. IOA and EOA are separated by the dura matter. By using TCD, the blood flow parameters are measured in both IOA and EOA simultaneously. Various blood flow parameters equalize in both IOA and EOA when ICP is equal to the externally applied pressure. Physiological parameters including the blood vessel diameter and ABP do not affect the result of ICP

measurement because TCD measurements of BFV are performed in the same artery but in different segments (Bartusis *et al.*, 2012).

1.2.2.Ophthalmic methods

1.2.2.1. Spontaneous venous pulsations (SVPs)

SVPs consist of subtle, rhythmic variations in the central retinal vein caliber seen on the optic disc (Jacks and Miller 2003). The pulsations are in fact caused by the pressure gradient variation which is the differences between the intraocular and CSF pulse pressures as the retinal vein traverses the lamina cribosa (Bruce, 2014; Zhang *et al.*, 2017). SVPs are absent in 10% of the ‘normal’ people; therefore, their absence is not interpretable (Levin, 1978). Thus, SVPs do not indicate an increased ICP; some studies even suggested that SPVs are present when ICP is normal (Jacks & Miller, 2003; Levin, 1978).

Venus ophthalmodynamometry. The pressure within the central retinal vein depends on ICP (Baumann, 1925). Venus ophthalmodynamometry is a technique to measure the pressure within the central retinal vein. When applying this method, the presence of SPVs is the indication that intraocular pressure (IOP) is close to the central retinal vein pressure. External pressures are applied in order to increase IOP until the collapsing of the central retinal vein. External pressure is added to the baseline IOP in order to measure the venous outflow pressure which closely correlates with ICP. However, this method is unsuitable for continuous ICP monitoring since it requires dilated pupils, a physician skilled in eye examinations, and patient collaboration (Zhang *et al.*, 2017).

1.2.2.2. Optical coherence tomography (OCT)

OCT can be an effective method for distinguishing papilledema nerves from normal nerves, and it can be used for quantitative analysis and monitoring of the retinal nerve fiber layer (RNFL) in papilledema (Bruce, 2014; Zhang *et al.*, 2017). However, there are several limitations of this method in the clinical use. For example, when disk edema is severe, automated algorithms of OCT fail (Bruce, 2014), and, unless ICP is extremely high, disc edema is generally very slow (Zhang *et al.*, 2017).

1.2.2.3. Optic nerve sheath diameter (ONSD)

The optic nerve sheath, which is part of the central nervous system, is surrounded by the dura sheath and CSF (Khan *et al.*, 2017; Raboel *et al.*, 2012). Therefore, when an increased ICP is observed, the sheath expands (Geeraerts, Merceron, Benhamou, Vigue, & Duranteau, 2008). By transocular ultrasound, ONSD changes can be visualized (**Fig. 1.5.**). This method can be compared to papilledema measurement with OCT, but ONSD expansion occurs within seconds of the acute rise of ICP (Geeraerts *et al.*, 2008).

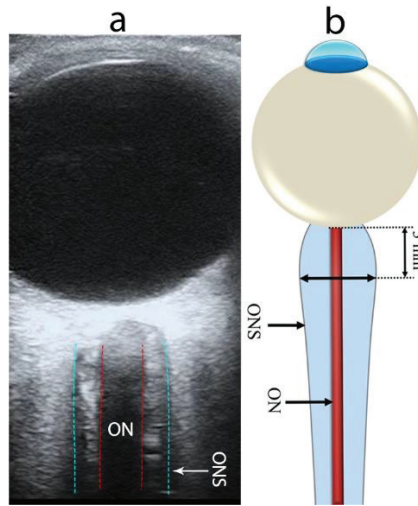


Fig. 1.5. Measurement of Optic nerve sheath diameter: (a) sonography of the optic nerve and the optic nerve sheath, (b) schematic representation of the optic nerve and the optic nerve sheath. ON – optic nerve, ONS – optic nerve sheath. (Fig. 5b is adapted from Nelson, Mulugeta, & Myers, 2014).

When ICP increases by >20 mmHg, there is an increase of the ONSD estimated range between 4.5 and 5.5 mm (Ballantyne, O'Neill, Hamilton, & Hollman, 2002; Geeraerts *et al.*, 2007, 2008; Kimberly & Noble, 2008; Kristiansson *et al.*, 2013). One of the biggest studies with ONSD concluded that an ONSD of >4.8 mm corresponded to an ICP of >20 mmHg with the sensitivity of 96% and the specificity value of 94% (Rajajee, Vanaman, Fletcher, & Jacobs, 2011).

ONSD measurement is quick, efficient, and easy to apply. However, there are several disadvantages of this method including, but not limited to, the fact that ONSD measurement is a point-in-time/snapshot assessment instead of continuous ICP monitoring, and also several conditions including tumors, inflammation, or Grave's diseases can affect the measurement result. Therefore, ONSD measurement can be used as a screening method when invasive ICP monitoring capabilities are not available (Khan *et al.*, 2017; Raboel *et al.*, 2012).

1.2.2.4. Pupillometry

Quantitative pupillometers can measure subtle changes/constriction in the pupillary light response (Bruce, 2014; Zhang *et al.*, 2017). The pupil diameter decreases by 34% in the 'normal' individuals and by 20% in patients with a head trauma (Bruce, 2014; Rosenberg, Shiloh, Savel, & Eisen, 2011; Taylor *et al.*, 2003). The 10% reduction of the pupillary size was associated with an ICP of >20 mmHg (Bruce, 2014; Taylor *et al.*, 2003). However, pupillometry measurements can be affected by certain medical, ocular, and non-ICP related neurological conditions,

various medications, the emotional state of the individual, and the time of day (Fountas *et al.*, 2006).

1.2.3. Otic approaches

1.2.3.1. Tympanic membrane displacement (TMD)

TMD can be measured during the acoustic middle-ear reflex. The cochlear aqueduct, the normal middle ear pressure, and the intact stapedial reflex are required in this approach (Zhang *et al.*, 2017). TMD is based on the communication between CSF and the perilymph via the perilymphatic duct (**Fig. 1.6.**). Acoustic stimulation of the stapedial reflex with 1000 Hz causes movement of the tympanic membrane, which is correlated to ICP (Gwer *et al.*, 2013; Raboel *et al.*, 2012). Thus, the tympanic membrane is displaced by these pressure waves. Specific TMD changes, such as outward or inward motions, are indicative of a high or low ICP (Gaihede, Felding, & Elbrond, 1995; Gwer *et al.*, 2013). Due to the membrane's flexibility, CSF and perilymph communicate through the cochlear aqueduct, and elevated ICP is directly transmitted to the stapes footplate, thus changing its initial position and thereby affecting the direction and magnitude of displacement of the eardrum in response to the sound (Popovic *et al.*, 2009; Zhang *et al.*, 2017). TMD has some limitations, yet it may serve as useful non-invasive ICP monitoring for the patients in whom ICP has already been established by other means (Bruce, 2014; Zhang *et al.*, 2017).

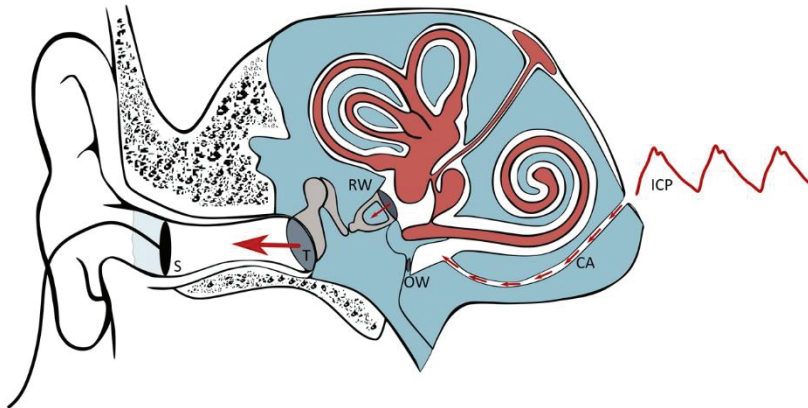


Fig. 1.6. Schematic illustration of TMD method. ICP – ICP input signal, CA – cochlear aqueduct, OW – oval window, RW – round window, T – tympanic membrane also known as eardrum, S – sensor (adapted from Evensen, Paulat, Prieur, Holm, & Eide, 2018)

1.2.3.2. Otoacoustic Emissions (OAE)

The basis of OAE measurement is similar to that of ONSD (**Fig. 1.7.**). CSF is continuous with the perilymphatic space as in the subarachnoid space subtle changes in ICP can be transmitted to the middle ear (Narayan *et al.*, 2018).

Acoustic signals, which are vibrations, enter through the outer ear and reach the middle ear to vibrate the eardrum. Vibrations are transmitted through the ossicles which consist of three tiniest bones: the hammer, the anvil, and the stirrup. Then, vibrations reach the cochlea which is filled with liquid. Inside the cochlea, there are specialized cells known as hair cells. The hair cells turn the fluid vibrations into electrical nerve impulses. Human brain perceives these nerve impulses as sound. The hair cells movement introduces additional weak vibration that is transmitted backward through the middle ear. These weak vibrations which are generated in the ear are a response to an acoustic signal; they called otoacoustic emission (Meyerson, Avan, & Buki, 2003).

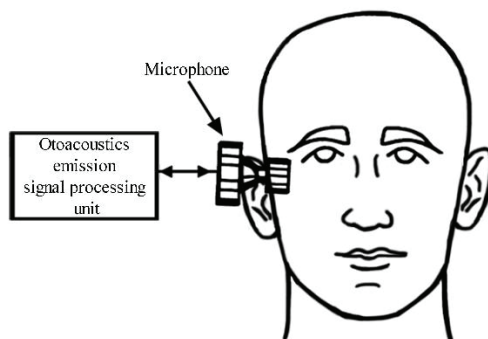


Fig. 1.7. Schematic illustration of otoacoustic emission method (adapted from Meyerson *et al.*, 2003)

In the healthy ear, ICP is equal to the pressure within the cochlea. Any fluctuation in ICP is transferred into the fluid of the cochlea, which results in a change of the stirrup's position and tension. These changes affect the mechanism of otoacoustic emission. Therefore, ICP can be estimated by analyzing the otoacoustic emission signal. OAE has some limitations, such as intersubject variability. Like TMD, OAE can be a useful non-invasive ICP monitoring method for patients in whom ICP has already been established by other means.

1.2.3.3. Transcranial Acoustic Signals

Transcranial acoustic signals (TCA) are generated by an earbud like device which is placed in the right outer ear channel. TCA signals are sent through the ear and picked up along with head-generated sounds by an earbud like device which is placed in the left outer ear channel (Levinsky, Papyan, Weinberg, Stadheim, & Eide, 2016). This method is based on the properties of the intracranial structure, unlike TMD and OAE methods which are based on extra-cranial organs/structure being connected to the intracranial compartment measurements (Bershad *et al.*, 2014; Levinsky *et al.*, 2016; Popovic *et al.*, 2009; Schmutzhard *et al.*, 2013). The method of TCA signals estimates static and pulsatile invasive ICP non-invasively with fairly

good accuracy. Further studies are required to validate this method for continuous nICP monitoring.

1.2.4. Electrophysiologic methods

Visual Evoked Potentials (VEP) are well known to provide information about visual acuity, diseases of the optic nerve and chiasm, color blindness, or other problems of vision (York, Pulliam, Rosenfeld, & Watts, 1981). York *et al.* analyzed each positive and negative peak of the visually evoked response and its relationship to ICP (York *et al.*, 1981). The first positive wave following the stimulus is set as P1, and the first negative wave is set as N1. The following waves are labeled sequentially, i.e., P2, N2, and P3, N3. Studies suggested a close relationship between the elevation of ICP and the increased latency of the N2 wave of VEP (York *et al.*, 1981; York, Legan, Benner, & Watts, 1984; Zhao, Zhou, & Zhu, 2005). VEP is not a fully developed method for ICP continuous monitoring as there are some limitations, such as neurophysiological expertise and the visual function of the patient (Zhang *et al.*, 2017).

The electroencephalography (EEG) method is based on electroencephalographic VEP. It uses a few optical EEG electrodes to record the electrical activity of the brain (Rosenfeld, Watts, & York, 1986). In 2007, this method was improved by Wu *et al.* who investigated the relationship between ICP and the third positive wave of VEP recorded with high density electrode arrays. Unfortunately, the ICP measurement by using EEG is sensitive and cumbersome for practical use in an emergency room, an intensive care unit or a neurosurgery department (Zhang *et al.*, 2017).

1.2.5. Others

Skull vibrations. The cranium can move with the dura matter in relation to the ICP fluctuation. This method is based on the measurement of changes in the natural frequency of the skull bone and frequency response spectrum (Mick, 1991, 1992). The frequency response spectrum detected by a sensor is analyzed and compared to the exciting spectrum by an analyzer (Mick, 1991). The viscoelasticity of the human skull and the dura matter have a major impact on this method.

Brain tissue resonance. The soft tissue and the fluid of the brain produce characteristic vibration and mechanical resonant responses following the heartbeat. Tissue resonance analysis (TRA) can be used to characterize the patterns of vibration and the mechanical resonance of various body organs and tissues (Zhang *et al.*, 2017). A nICP monitoring and measurement device based on TRA was developed by Michaeli & Rappaport (2002).

Jugular vein. Gentle pressure on the neck over the jugular veins results in ICP rise (Wilson 2016). This method described by Allocca (1980) is based on occluding the jugular vein for a short period of time (c. 5 seconds) and measuring non-

invasively, with a Hall sensor or an ultrasound transducer, the blood flow in the occluded jugular vein upstream (Zhang *et al.*, 2017; Popovic *et al.*, 2009). This method is simple and can easily be made portable and field deployable. However, there are some limitations including the additional increase of ICP by this method as it might provoke dangerous complications in patients (Popovic *et al.*, 2009).

1.2.6. Conclusions

Non-invasive ICP monitoring methods that are available for clinical use have many advantages against invasive ICP monitoring methods, such as a low infection rate and long-term monitoring. However, they suffer from several drawbacks including low accuracy and precision. Non-invasive ICP monitoring methods are in the exploratory phase since they are not sufficiently accurate and easy to use (Zhang *et al.*, 2017). All non-invasive methods mentioned in this thesis are summarized in **Table 1.2**.

Table 1.2. Comparison of non-invasive ICP monitoring methods (adapted from Popovic *et al.*, 2009 and Zhang *et al.*, 2017)

	Method	Continuous monitoring	Accuracy	Skill	Cost of Technology	Time consumption	Bedside setting	Emergency setting
FLUID DYNAMICS APPROACHES	Magnetic resonance imaging (MRI)	No	Not validated	Expert	High	Yes	No	No
	Transcranial Doppler ultrasonography (TCD)	No	±10–15 mmHg	Expert	Moderate	No	Yes	Yes
	Cerebral blood flow velocity (CBFV)	No	±1.5 mmHg	Low	Moderate	Yes	Yes	No
	Near-infrared spectroscopy (NIRS)	Yes (for cerebral blood volume)	Not validated	Low	Moderate	Yes	Yes	No
	Ultrasound time of flight	Yes	±9 mmHg	Low	Moderate	No	Yes	No
	Spontaneous venous pulsations (SVPs)	No	Not validated	Moderate	Moderate	No	No	No
OPHTHALMIC METHODS	Venous ophthalmodynamometry	No	±3–5 mmHg	Expert	Low	Yes	Yes	No
	Optical coherence tomography of retina	No	Not validated	Expert	Moderate	Yes	No	No
	Optic nerve sheath diameter assessment (ONSD)	No	±5–10 mmHg	Moderate/High	Moderate	No with sonography; yes with magnetic resonance	Yes	Yes with sonography
	Pupillometry	No	Not validated	Low	Low	No	Yes	Yes

Table 1.2. (Continued)

	Method	Continuous monitoring	Accuracy	Skill	Cost of Technology	Time consumption	Bedside setting	Emergency setting
OTIC APPROACHES	Sensing tympanic membrane displacement (TMD)	No	$\pm 15-20$ mmHg	Moderate	Low	Yes	Yes	No
	Analyzing otoacoustic emissions (OAE)/ acoustic measure	No	$\pm 15-20$ mmHg	Moderate	Low	Yes	Yes	No
	Transcranial acoustic (TCA) signals	Possible	± 5 mmHg	Moderate	Moderate	No	Yes	No
ELECTROPHYSIOLOGIC METHODS	Visual-evoked Potentials (VEP)	No	Not validated	Expert	Low	Yes	Yes	No
	Electroencephalography (EEG)	Possible	Not validated	Moderate	Moderate	Yes	Yes	No
OTHERS	Skull vibrations	No	Not validated	Expert	Low/moderate	Yes	No	No
	Brain tissue resonance	No	Not validated	Expert	Moderate	No	Yes	No
	Jugular vein	No	Not validated	Expert	Low/moderate	Yes	No	No

2. LOCATION OF THE INTERNAL CAROTID ARTERY AND OPHTHALMIC ARTERY SEGMENTS FOR NON-INVASIVE INTRACRANIAL PRESSURE MEASUREMENT AND MONITORING

2.1. Introduction

Intracranial pressure (ICP) monitoring is clinically important to many neurological diseases (Akman-Demir, Serdaroglu, & Tasci, 1999; Bradley, 2000; Doherty & Forbes, 2014) and some neurosurgical conditions (Andrews *et al.*, 2008; Brain Trauma Foundation, 2007; Padayachy, Figaji, & Bullock, 2009). ICP measurement has clinical importance in ophthalmology when assessing the progress of glaucoma disease (Berdahl, Allingham, & Johnson, 2008; Berdahl, Fautsch, Stinnett, & Allingham, 2008; Siaudvytyte *et al.*, 2014), in nephrology during hemodialysis sessions (Lin *et al.*, 2008) and even in gynecology during laparoscopic surgeries (Ozturk, 2011).

Transcranial Doppler (TCD) was introduced by Aaslid in 1982 for rapid, non-invasive, real time monitoring of the cerebrovascular function (Aaslid, Markwalder, & Nornes, 1982). TCD is a non-invasive, non-ionizing, inexpensive, portable and safe technique (Naqvi, Yap, Ahmad, & Ghosh, 2013). TCD is based on a pulsed Doppler transducer for the assessment of intracerebral blood flow (Cardim *et al.*, 2016). Methods based on TCD can estimate ICP non-invasively via blood flow velocity parameters that are obtained from the cerebral arteries. However, nearly all of those methods are correlation-based or model-based. As patient-specific calibration is required, therefore, the absolute value of the ICP cannot be measured for such measurement methods.

A novel non-invasive absolute ICP snapshot measurement method based on TCD which does not require patient-specific calibration has been developed (Ragauskas, Daubaris, Dziugys, Azelis, & Gedrimas, 2005). The operator must manually find the correct depths of the intracranial (IOA) and extracranial (EOA) segments of the ophthalmic artery (OA) by using a multi-depth TCD to make a reliable non-invasive snapshot measurement of the ICP with this method. Clinical studies have shown applicable accuracy, precision, diagnostic sensitivity and specificity of the non-invasive ICP measurement method (Ragauskas *et al.*, 2012; Ragauskas *et al.*, 2014).

Normally, the ophthalmic artery is the first branch of the larger internal carotid artery (ICA) (Michalinos *et al.*, 2015). The pulse wave shape in OA is different from that in the ICA. Therefore, it is easy to distinguish OA from ICA via TCD spectral patterns (Bathala, Mehndiratta, & Sharma, 2013). There are some published results of OA anatomical studies (Erdogmus & Govsa, 2006; Hayreh & Dass, 1962; Jimenez-Castellanos, Carmona, Castellanos, & Catalina-Herrera, 1995). The following summarizes the results of these studies:

1. The distance between the point where OA pierces the dura matter up to the OA branching point from ICA is individual. The range of IOA distances from ICA is 0.5–9.5 mm. The depths of the selected IOA segment with no overlap/cross the area of the dura matter should be 3–5 mm away from the edge of ICA.

2. The range of OA which extends from the apex of the orbit up to the dura matter is 3.9–7.0 mm. In order to choose the correct depth of the extracranial segment of OA, the depth of the selected EOA segment with no overlap/cross the area of the dura matter and with a high probability that the OA segment would be in the intraorbital part should be 8–12 mm away from IOA.

There are several publications focusing on the depths of ICA and OA measured by TCD from the external surface of the closed eyelid. According to Naqvi *et al.*, the depth of ICA is 65–80 mm, and the depth of OA is 45–55 mm (Naqvi *et al.*, 2013). Alexandrov *et al.* found that the ICA depth is 58–65 mm (Alexandrov *et al.*, 2007); Kassab *et al.* determined OA depth of 40–60 mm (Kassab *et al.*, 2007). Therefore, generally, literature agrees on ICA depth between 58 and 80 mm (Alexandrov *et al.*, 2007; Hu *et al.*, 1995; Kassab *et al.*, 2007; Naqvi *et al.*, 2013), whereas the depth of OA is between 40 and 60 mm (Hu *et al.*, 1995; Kassab *et al.*, 2007; Naqvi *et al.*, 2013). However, these publications show a possible depth range of ICA and OA, and none of the sources mentions either the depth ranges of the edge of ICA or the depth range of IOA and EOA, which would be advantageous to the operator who locates the IOA and EOA segments before the non-invasive ICP snapshot measurement can be initiated.

The main aim of this study was to carry out a prospective and then retrospective study of patients with high tension glaucoma and healthy volunteers: to analyze the location and position of the internal carotid artery and the ophthalmic artery as a technical problem for the operator of a transcranial Doppler.

2.2. Methods

2.2.1. Patient eligibility

The prospective study was conducted at the Eye Clinic at the Hospital of the Lithuanian University of Health Sciences and the Health Telematics Science Institute of Kaunas University of Technology between July 2013 and March 2016. The retrospective study was conducted at the Health Telematics Science Institute of Kaunas University of Technology between March 2016 and March 2017.

Patients with high tension glaucoma (HTG) and healthy volunteers (HVs) who were undergoing non-invasive intracranial pressure snapshot measurement were selected. The exclusion criteria were as follows: younger than 18 years, pregnant or nursing women, subjects with uncontrolled systemic diseases, and subjects with a history of allergy to local anesthetics, orbital/ocular trauma or other diseases.

2.2.2. Standard protocol approval, registration, and patient consent

The protocol of the prospective study was approved by the Kaunas Regional Bioethics Committee (Registration No. BE – 2 – 41). The patients' written consent

was obtained in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194).

2.2.3. Data collection

The TCD examination was conducted with a *BNS ICP 3* (Boston Neuroscience, Waltham, MA, USA) device, and the following parameters were used: ultrasound probe central frequency of 2 MHz, sample volume size equal to 3 mm, and power levels matching approved ultrasound devices.

The designed head frame for the snapshot measurement of ICP non-invasively was fitted onto the heads of healthy volunteers or glaucoma patients, and it was convenient for the positioning and orientation of an ultrasonic transducer (**Fig. 2.1B** and **2.1C**). Firstly, the edge of ICA (which means the depth where OA branches from the ICA) should be identified. Secondly, the edge of ICA as the reference depth, and the intracranial and extracranial segments of OA can be selected with respect to anatomical studies that previously defined the range of OA depths (Erdogmus & Govsa, 2006; Hayreh & Dass, 1962; Jimenez-Castellanos *et al.*, 1995), and then reliable snapshot measurement can be done. The depths of the located segments from the closed eyelid were noted in millimeters. When IOA was selected simultaneously with EOA, the positions of the circular ultrasonic transducer (UT), which is 14 mm in diameter, were noted. **Fig. 2.1A** shows an example of the marked positions of UT on the closed eyelid. We chose the average orientation of UT placed on the closed eyelid in the case of the identified edge of ICA, and IOA was selected simultaneously with EOA. **Fig. 2.1B** and **2.1C** show a schematic representation of the measured alpha and beta angles of UT.

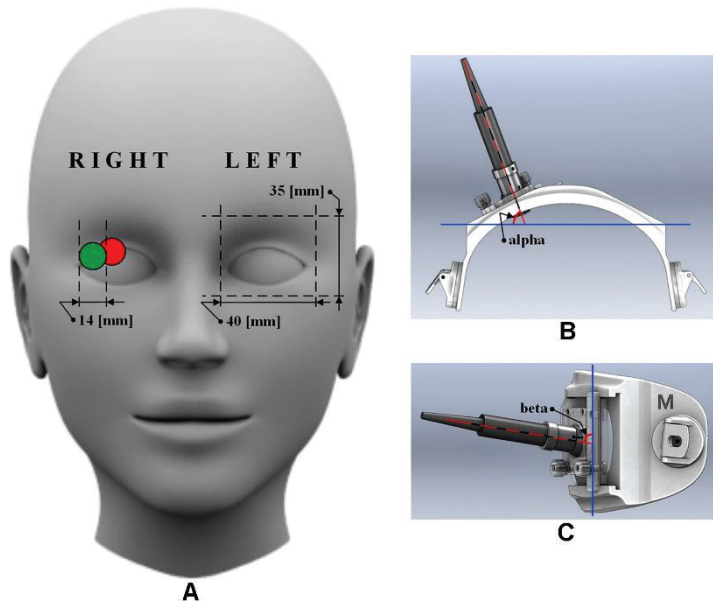


Fig. 2.1. Illustration of positions and angles of an ultrasonic transducer (UT) on the closed eyelid for the measurement. **A**, Example of the relative positions of UT, which is 14 mm in diameter, on the closed eyelid for the edge of the internal carotid artery (the red circle on the right eye) and for the selected depth of the intracranial segment of the ophthalmic artery simultaneously with the depth of the extracranial segment of the ophthalmic artery (the green circle on the right eye). The average adult human orbit geometry (the height and width) is illustrated on the left eye. **B**, the top view of the head frame, is illustrated for UT positioning and orientation. Angle alpha was measured between the frontal axis of the human head (the blue solid line), and the longitudinal axis of UT (the red dashed line) is shown. **C**, the side view of the head frame, is illustrated for UT positioning and orientation. Angle beta, which was measured between the vertical axis of the human head (the blue solid line), and the longitudinal axis of UT (the red dashed line) is shown (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication; Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

2.2.4. Statistical analysis

The *MedCalc* software (version 16.4.3; *MedCalc Software*, Ostend, Belgium) was used for the statistical analysis. We calculated the distance between the edge of ICA and the IOA segment (ICA-IOA) as well as the distance between the IOA and EOA segments (IOA-EOA) in millimeters. The calculation of the mean and standard deviation (SD) and a comparison of the means between two groups (patients with HTG and HVs) were analyzed as well. The t-test was used for analyzing the differences. The level of $p < 0.05$ was considered as significant.

The average adult human orbit geometry was used to estimate the window of the relative UT position on the closed eyelid in the case of the identified ICA edge

and the IOA depth were selected simultaneously with the EOA depth (Dobrovăț, Popescu, Nemtoi, Ladunca, & Haba, 2011; Rene, 2006).

2.3. Results

In this chapter, the results of the study are presented with reference to the aim of the study, which was to carry out a prospective and then a retrospective study of patients with high tension glaucoma and healthy volunteers: to analyze the location and the position of the internal carotid artery and the ophthalmic artery as a technical problem for the operator of a transcranial Doppler.

After applying the rejection criteria, twenty-five HTG patients and twenty-three HVs were included in this study. The data was collected on patients with HTG – by including 14 right eyes and 19 left eyes (in total, 33 eyes), and on HVs – by including 20 right eyes and 13 left eyes (in total, 33 eyes).

49 cases out of 66 showed that the probability to find an IOA segment at a distance not more than 5 mm from the identified ICA edge was 74%. At the same time, the maximum measured distance between the selected IOA segment and the identified ICA edge was 9 mm in four cases. In addition to that, it was 8 mm in one case; 7 mm in five cases; and 6 mm in seven cases. With some exceptional cases, this result supports the proposed method that the IOA segment can be found at a distance 3–5 mm away from the identified ICA edge.

61 cases out of 66 showed that the probability to find an EOA segment at 8–12 mm from the selected IOA segment was 92%. It was 7 mm in one case; 13 mm in two cases; 15 mm in one case; 16 mm in one case. With these exceptional cases, the proposed method which is that the EOA segment is 8–12 mm away from the selected IOA segment is supported by this result.

The depths of the ICA edge, the selected IOA and the selected EOA, the calculated distances between the edge of ICA and the IOA segment (ICA edge-IOA), and the calculated distances between the IOA and EOA segments (IOA-EOA) for HTG patients are shown in **Table 2.1**. HV data of the depths of the ICA edge, the selected IOA and the selected EOA, the calculated distances between the edge of ICA and the IOA segment (ICA edge-IOA), and the calculated distances between the IOA and EOA segments (IOA-EOA) for HTG patients are presented in **Table 2.2**. The mean depth of the ICA edge for patients with HTG was 64.3 ± 4.4 mm; it was 63.0 ± 4.0 mm for HVs. The difference between the groups was not statistically significant ($p = 0.21$). The mean depth of the IOA segment for patients with HTG was 59.2 ± 3.5 mm; it was 59.3 ± 3.4 mm for HVs. The difference between the groups was not statistically significant ($p = 0.91$). The difference between the mean depth of the EOA segment for patients with HTG [48.5 mm ($SD = 3.8$ mm)] and HVs [49.8 mm ($SD = 3.3$ mm)] was not statistically significant ($p = 0.14$).

Table 2.1. Data of depths and distance of ICA edge, IOA and EOA in patients with high tension glaucoma. Patients with high tension glaucoma data included 25 patients and 33 examined eyes. Means $\pm$ SD are also presented. R indicates the right eye; L, left eye; ICA edge, identified depth of edge of the internal carotid artery from the closed eyelid; IOA, chosen depth of the intracranial segment of the ophthalmic artery from the closed eyelid; EOA, chosen depth of the extracranial segments of the ophthalmic artery from the closed eyelid; ICA edge-IOA, distance between the identified internal carotid artery edge and the chosen intracranial segment of the ophthalmic artery; IOA-EOA, distance between the chosen intracranial and extracranial segments of the ophthalmic artery (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

No	Eye	ICA edge, mm	IOA, mm	EOA, mm	ICA edge-IOA, mm	IOA-EOA, mm
1	L	60	55	44	5	11
2	R	72	65	50	7	15
	L	60	57	46	3	11
3	R	61	58	46	3	12
	L	58	55	47	3	8
4	R	64	59	49	5	10
5	R	60	57	47	3	10
	L	60	57	47	3	10
6	R	60	58	47	2	11
7	L	65	58	47	7	11
8	L	64	57	47	7	10
9	L	60	54	43	6	11
10	L	68	62	46	6	16
11	R	62	56	44	6	12
12	L	64	57	45	7	12
13	R	62	59	49	3	10
	L	62	58	48	4	10
14	R	62	56	45	6	11
	L	68	59	49	9	10
15	R	73	69	58	4	11
	L	65	62	52	3	10
16	L	65	60	50	5	10
17	R	66	57	47	9	10
	L	61	56	43	5	13
18	R	70	62	53	8	9

Table 2.1. (Continued)

No	Eye	ICA edge, mm	IOA, mm	EOA, mm	ICA edge-IOA, mm	IOA-EOA, mm
19	L	60	57	44	3	13
20	L	74	65	55	9	10
21	R	68	59	51	9	8
22	L	68	64	56	4	8
23	R	59	57	47	2	10
24	R	70	64	54	6	10
	L	70	64	54	6	10
25	L	62	60	51	2	9
MEAN		64.3	59.2	48.5	5.2	10.7
SD		4.4	3.5	3.8	2.2	1.7

Table 2.2. Data of depths and distance of ICA edge, IOA and EOA in healthy volunteers. Healthy volunteers' data included 23 volunteers and 33 examined eyes. Means $\pm$ SD are also presented. R indicates the right eye; L, left eye; ICA edge, identified depth of edge of the internal carotid artery from the closed eyelid; IOA, chosen depth of the intracranial segment of the ophthalmic artery from the closed eyelid; EOA, chosen depth of the extracranial segments of the ophthalmic artery from the closed eyelid; ICA edge-IOA, distance between the identified internal carotid artery edge and the chosen intracranial segment of the ophthalmic artery; IOA-EOA, distance between the chosen intracranial and extracranial segments of the ophthalmic artery (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

No	Eye	ICA edge, mm	IOA, mm	EOA, mm	ICA edge - IOA, mm	IOA - EOA, mm
1	R	62	59	49	3	10
	L	56	53	45	3	8
2	R	60	57	48	3	9
	L	58	55	45	3	10
3	R	62	58	48	4	10
	L	64	60	50	4	10
4	R	66	61	51	5	10
	L	58	55	45	3	10
5	R	58	55	45	3	10
	L	58	54	44	4	10
6	R	69	65	55	4	10
	L	67	62	52	5	10

Table 2.2. (Continued)

No	Eye	ICA edge, mm	IOA, mm	EOA, mm	ICA edge - IOA, mm	IOA - EOA, mm
7	R	61	58	48	3	10
	L	54	51	42	3	9
8	R	70	65	55	5	10
	L	71	66	56	5	10
9	R	64	62	52	2	10
	L	64	60	50	4	10
10	R	64	61	50	3	11
	L	65	59	52	6	7
11	R	62	57	49	5	8
12	L	65	61	50	4	11
13	L	62	59	49	3	10
14	R	62	59	50	3	9
15	L	64	61	51	3	10
16	R	61	58	48	3	10
17	R	62	59	51	3	8
18	R	66	63	53	3	10
19	R	65	61	52	4	9
20	R	71	64	55	7	9
21	R	64	61	51	3	10
22	R	61	58	49	3	9
23	R	64	61	52	3	9
MEAN		63.0	59.3	49.8	3.7	9.6
SD		4.0	3.4	3.3	1.1	0.9

The distribution graphs showing the data of patients with HTG and HVs include the identified depths of the edge of ICA as well as the chosen depth of the IOA and EOA segments (**Fig. 2.2.**). The distribution graphs showing the data of patients with HTG and HVs include the calculated distances between the identified segments (**Fig. 2.3.**).

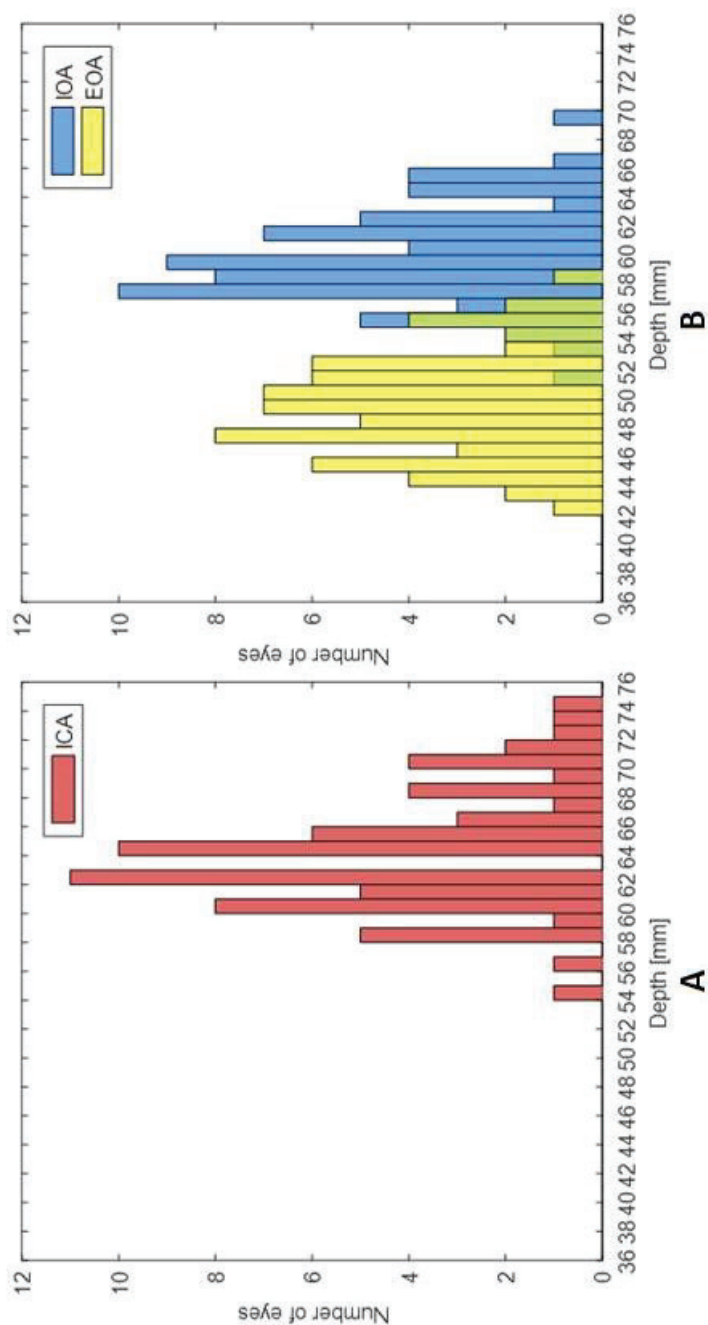


Fig. 2.2. Distribution graphs of A, identified depths of the edge of the internal carotid artery (ICA) B, depths of the chosen intracranial segment of the ophthalmic artery (IOA) simultaneously with the chosen extracranial segment of the ophthalmic artery (EOA). Data collected on 25 patients with high tension glaucoma (14 right eyes and 19 left eyes) and 23 healthy volunteers (20 right eyes and 13 left eyes) is included (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

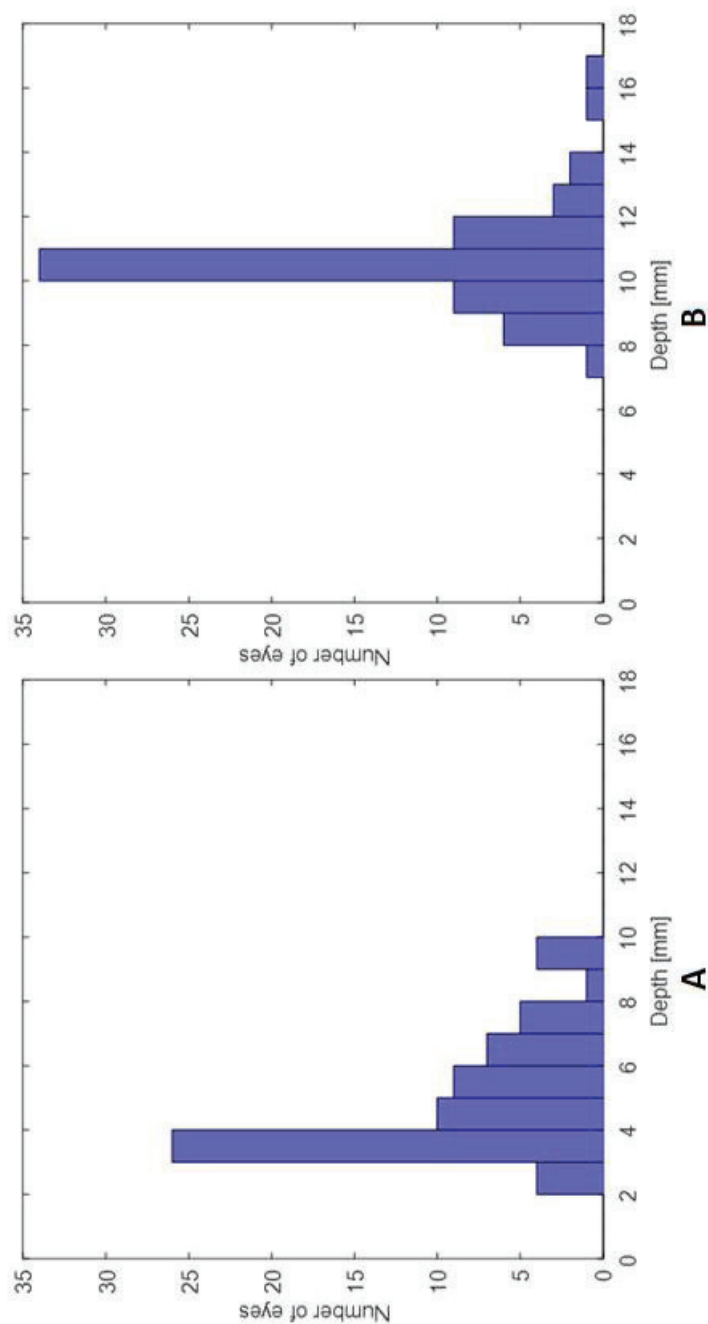


Fig. 2.3. Distribution graphs of A, distances between the identified depth of the internal carotid artery (ICA) edge and the chosen depth of the intracranial segment of the ophthalmic artery (IOA) (ICA-IOA) B, distances between the chosen depth of IOA and the extracranial segment of the ophthalmic artery (EOA) (IOA-EOA). Data collected on 25 patients with high tension glaucoma (14 right eyes and 19 left eyes) and 23 healthy volunteers (20 right eyes and 13 left eyes) is included (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

We measured the alpha and beta angles of UT on the closed eyelid on 13 healthy volunteers by including 10 right eyes and 3 left eyes. We decided not to measure the alpha and beta angles of UT on patients with HTG because of the workload at the eye clinic. The results are presented in **Table 2.3**.

The mean angle alpha in the case of the chosen IOA segment simultaneously with EOA was $62.3^{\circ} \pm 4.8^{\circ}$. The mean angle alpha in the case of the identified ICA edge was $68.7^{\circ} \pm 21.0^{\circ}$. However, the difference between the two groups was not statistically significant ($p = 0.30$). The mean angle beta in the case of the chosen IOA segment simultaneous with EOA was $90.3^{\circ} \pm 4.3^{\circ}$; it was $99.4^{\circ} \pm 6.3^{\circ}$ for the identified ICA edge. The difference was statistically significant ($p = 0.0002$).

Table 2.3. Angles of the ultrasonic transducer on the closed eyelid in the case of the identified ICA edge and IOA segment chosen simultaneously with EOA in healthy volunteers. Data of depths and distance of ICA edge, IOA and EOA in healthy volunteers. Data of 13 healthy volunteers with 13 examined eyes is presented. Means $\pm$ SD are also presented. R indicates the right eye; L, left eye; ICA edge, the identified depth of the edge of the internal carotid artery from the closed eyelid; IOA, the chosen depth of the intracranial segment of the ophthalmic artery from the closed eyelid; EOA, the chosen depth of extracranial segments of the ophthalmic artery from the closed eyelid; alpha, the angle between the longitudinal axis of the ultrasonic transducer and the frontal axis of the human head; beta, the angle between the longitudinal axis of the ultrasonic transducer and the vertical axis of the human head (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

No.	Eye	IOA and EOA		ICA edge	
		alpha, °	beta, °	alpha, °	beta, °
1	R	59.0	89.0	68.5	96.5
2	L	59.5	92.8	54.0	105,5
3	L	64.0	88.5	50.5	102.0
4	R	69.0	85.5	50.0	93.5
5	L	67.5	88.0	27.7	93.0
6	R	68.5	91.0	55.0	104.0
7	R	57.0	90.0	94.0	102.0
8	R	63.5	100	98.0	108.0
9	R	66.0	85.0	71.5	107.5
10	R	62,5	91.0	98.0	99.5
11	R	60.0	97.5	74.0	88.0
12	R	61.0	90.5	74.5	93.0
13	R	52.5	85.0	77.5	103.0
MEAN		62.3	90.3	68.7	99.4
SD		4.8	4.3	21.0	6.3

The relative UT positions on the closed eyelid in the case of the identified edge of ICA and the IOA segment chosen simultaneously with EOA were registered on 33 eyes of patients with HTG and 33 eyes of healthy volunteers. By using the average adult human orbit geometry, we estimated that the UT surface in all the cases of simultaneously chosen IOA and EOA segments fall into a window of 26 mm in width and 20 mm in height (**Fig. 2.4A**). The UT surface in all the cases of the identified edge of ICA falls into a window of 28 mm in width and 22 mm in height (**Fig. 2.4B**).

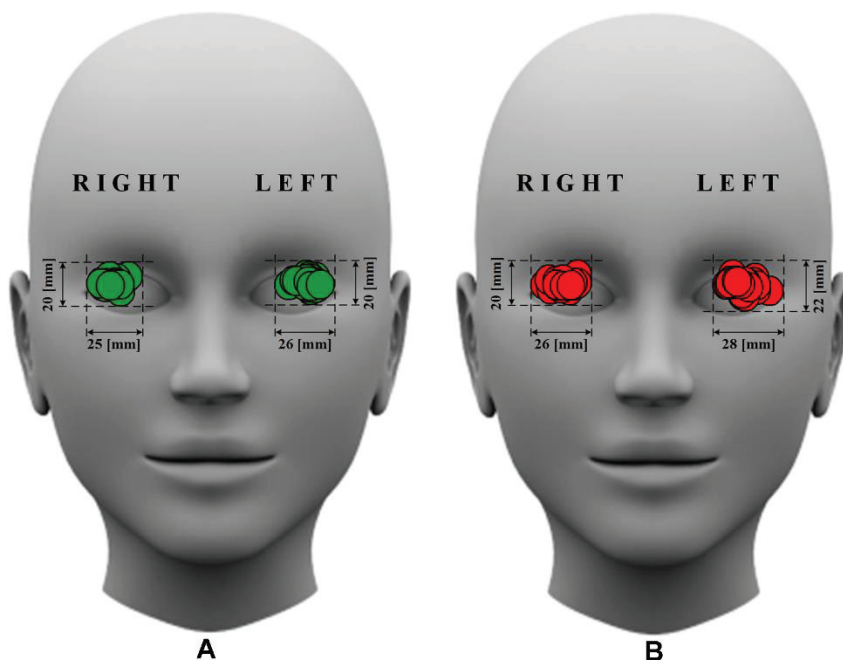


Fig. 2.4. Relative positions of the ultrasonic transducer on the closed eyelid. A, chosen intracranial segment of the ophthalmic artery simultaneously with the extracranial segment of the ophthalmic artery and B, the identified edge of the internal carotid artery. The width and height of the window within which the UT surface falls are indicated in millimeters (adapted from Hamarat *et al.*, 2017. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

2.4. Discussion

TCD methodology for the clinical practice is used to measure the distance of the identified arteries from the external surface of the closed eyelid. High tension glaucoma can cause deformation of the internal structures of the eyeball. That is why, the measured distances of the identified arteries of patients with HTG might be different from the values obtained for healthy volunteers. As a matter of fact, the

distances between the edge of ICA and the chosen IOA segment as well as the distances between the chosen IOA and the chosen EOA segments should be selected independently from the thickness of the eyelid, and patient-specific anatomical features affect the eyeball and orbit before non-invasive ICP snapshot measurement.

We prospectively tested the proposed method for the simultaneous location of the intracranial and extracranial segments of OA starting from identifying the edge of ICA. Firstly, the edge of ICA is considered where OA branching should be identified. By using the identified edge of ICA as the reference depth, the intracranial segment of OA should be selected at 3–5 mm away from the edge of ICA. Then, the extracranial segment of OA can be selected at 8–12 mm away from the chosen depth of the intracranial segment of OA.

The ICA edge as well as the IOA and EOA segments were located by using a multi-depth TCD device (*BNS ICP 3, Boston Neuroscience, Waltham, MA, USA*) dedicated to ICP snapshot measurement non-invasively. 49 cases out of 66 showed that there is 74% probability for the chosen IOA segment to be located at a distance of not more than 5 mm from the identified edge of ICA. In 17 cases out of 66, the IOA segment for non-invasive ICP measurement was chosen not according to the proposed method (3–5 mm away from the identified edge of ICA), the maximum chosen distance was 9 mm, which is in the range of the IOA distance regarding anatomical studies (0.5–9.5 mm away from the identified edge of ICA). 61 cases out of 66 showed that there is a 92% probability for the chosen EOA segment to be in the range of 8–12 mm from the chosen IOA segment. However, the EOA segment chosen at a distance of more than 12 mm from the chosen IOA is in the range of the extracranial portion of the OA, which can be confirmed by the spectral pattern viewed in TCD. IOA and EOA segments were selected on the grounds of the proposed method because it was not possible to locate the blood flow in the proposed distance range, or the TCD signal was too weak to measure ICP non-invasively.

The positions of UT on the closed eyelid for the identification of the edge of ICA and for selecting the IOA segment simultaneously with EOA are subject to individual variabilities. Thus, it is a difficult task for the operator who manually locates OA segments for the non-invasive measurement of ICP. The window of the location areas defined in this study gives a high probability to find the edge of ICA and IOA with EOA segments for non-invasive ICP snapshot measurement.

As a result, the UT angles in the case of the identified edge of ICA are significantly different from the UT angles in the case of the chosen IOA segment simultaneously with EOA. This study suggests that the operator who measures the ICP by using the proposed technique in this study should expect to use different angles for the edge of the ICA and OA segments.

This study has several limitations. The investigation included a limited number of adult subjects; thus, the investigation in children might produce different results. All the examined subjects in both groups were Caucasian; therefore, we cannot assume that same results would be obtained in other races.

Future studies should have involved medical imaging techniques, such as magnetic resonance imaging (MRI). Abnormal anatomical structures around the ICA and OA which can influence the accuracy of the location can be identified by MRI. Medical imaging techniques can improve the accuracy and precision of identifying the IOA and EOA segments.

This study can be used as guidelines to locate intracranial and extracranial segments of the ophthalmic artery to perform a reliable and non-invasive snapshot measurement of the intracranial pressure, which is important for the diagnosis and/or treatment of glaucoma.

2.5. Conclusions

We demonstrated a new methodology which suggests how to identify the edge of ICA as the reference depth to locate the intracranial and extracranial segments of the ophthalmic artery for the reliable snapshot measurement of the absolute value of the intracranial pressure.

3. GRAPHICAL AND STATISTICAL ANALYSIS OF THE OCULOCARDIAC REFLEX DURING NON-INVASIVE INTRACRANIAL PRESSURE MEASUREMENT

3.1. Introduction

The Ascher reflex, also the oculocardiac reflex (OCR), is a cardiac phenomenon which is triggered by physical stimulation of the eye (Ohashi, Kase, & Yokoi, 1986). In 1908, Ascher and Dagnini described this phenomenon. Today, OCR is a subtype of the trigeminocardiac reflex which is a well-known brainstem reflex (Sandu, Cornelius, *et al.*, 2010). OCR can cause some physical responses in the heart, including bradycardia, arrhythmia, and even cardiac arrest (Ohashi *et al.*, 1986; Paton, Boscan, Pickering, & Nalivaiko, 2005; Yi & Jee, 2008). OCR can be evoked by pressure on the ocular globe, traction on the extrinsic muscles of the eye, intraorbital injections, hematomas, acute glaucoma, and/or stretching of the eyelid muscles (Blanc, Hardy, Milot, & Jacob, 1983). The stimulus signal is primarily transmitted to the ophthalmic division of the trigeminal nerve (V1), which then connects to the ciliary ganglion and visceral motor nucleus of the vagus nerve. The longest cranial and major parasympathetic nerve, the vagus nerve, supplies parasympathetic fibers to all major organs, including the heart (Lang, Lanigan, & van der Wal, 1991). The OCR threshold is calculated by a decrease in the mean heart rate (MHR) relative to the baseline heart rate (BHR) recorded before physical stimulation of the eye. There are several thresholds for the evoked OCR (Seshubabu, 1998), such as a 10% decrease (Eustis, Eiswirth, & Smith, 1992; Vrabec, Preslan, & Kushner, 1987), and a 20% decrease in BHR (Karaman *et al.*, 2016; Karhunen, Cozanitis, & Brander, 1984; Lai, Hsu, Wang, Cheng, & Wu, 2014). Another threshold for the evoked OCR is a decrease of 10 beats per minute compared with the baseline (Yu & Wang, 1991).

A novel method of non-invasive snapshot measurement of the absolute value of ICP was developed in the Health Telematics Science Institute of Kaunas University of Technology in Lithuania (Ragauskas, Daubaris, Dziugys, Azelis, & Gedrimas, 2005). This method and the non-invasive arterial blood pressure measurement share similar principles. The novel method uses transcranial Doppler (TCD) ultrasonography to assess the pulse waves of the ophthalmic artery (OA) during gradual externally applied pressure (P_e) over a closed eyelid that is transmitted to the eye and orbital (peri-ocular) tissues. Previous studies reported the accuracy, precision, and diagnostic reliability of this non-invasive ICP measurement technique (Bershad *et al.*, 2016; Ragauskas *et al.*, 2012; Ragauskas *et al.*, 2014); however, the incidence of the evoked OCR has never been studied previously.

The aim of this study was to carry out a retrospective study of patients with neurological, traumatic brain injury and glaucoma as well as healthy volunteers: to analyze the Oculocardiac reflex as a safety problem for the patients and volunteers during continuous ICP monitoring.

3.2. Materials and methods

3.2.1. Equipment and measurement technique

TCD examination is done with a *BNS ICP 3* (Boston Neuroscience, Waltham, MA, USA) device with the following parameters in use: ultrasound probe central frequency of 2 MHz, sample volume size equal to 3 mm, and power levels matching the approved ultrasound devices.

The intracranial and extracranial parts of OA (Hayreh, 2006; Hayreh & Dass, 1962) as a scale for detecting the pressure balance between ICP and the gradual externally applied pressure [$P_e(t)$] are used in the non-invasive ICP absolute value measurement method. An illustration of these novel measurement techniques is depicted in **Fig. 3.1**. A toroidal-shaped soft plastic cuff which is filled with air is installed into the head frame together with an ultrasonic transducer to transmit pressure to orbital tissues. P_e affects the non-compressible orbital tissues with the extracranial segment of OA, but not the intracranial segment of OA due to the segmentation by the dura matter (**Fig. 3.1.A**). P_e is controlled by a pressure controller and can be selected from 0 to 48 mmHg (maximum) with pressure steps set by the operator (**Fig. 1.B.**). The two-depth TCD is used for continuously monitoring the blood flow velocity pulsation of the intracranial and extracranial parts of OA.

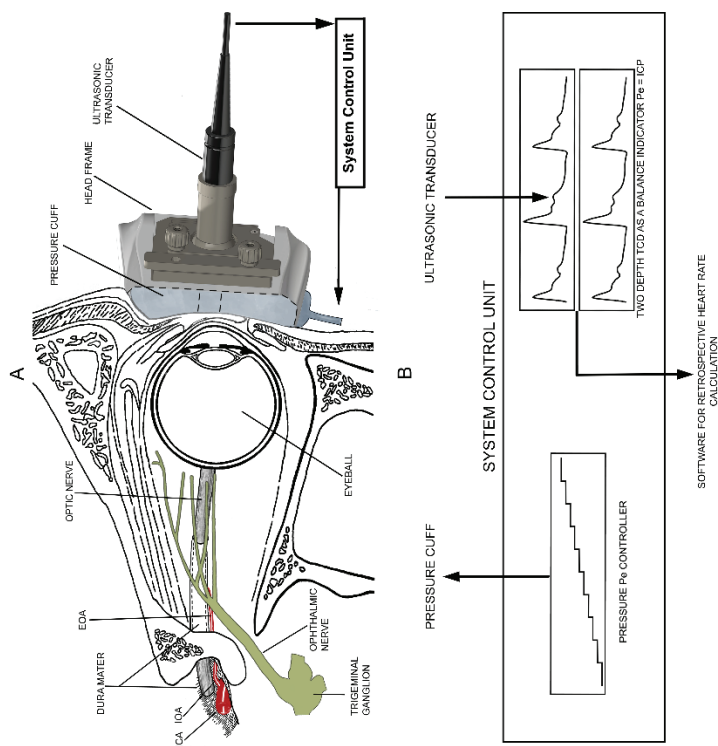


Fig 3.1.1. Illustration of non-invasive intracranial pressure (ICP) measurement equipment *BNS ICP 3*. (A) Relevant orbit and brain anatomy in contact with ICP measurement device. (B) Block diagram of the system control unit. ICA – internal carotid artery; IOA – intracranial part of the ophthalmic artery; EOA – extracranial part of the ophthalmic artery; TCD – transcranial Doppler; P_e – external pressure applied to the ocular globe (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

3.2.2. Subjects and settings

Patients with neurological and ophthalmological (glaucoma) diseases and healthy volunteers underwent a non-invasive ICP measurement in the setting of several prospective research studies from October 2009 to December 2016 at the Texas Medical Center at Baylor College of Medicine affiliate hospitals (Baylor Saint Luke's Medical Center, or Baylor Clinics), the Department of Neurosurgery at Kantonsspital Aarau, the Department of Neurology and Eye Clinic at the Hospital of Lithuanian University of Health Sciences, and the Health Telematics Science Institute of Kaunas University of Technology. The Baylor College of Medicine Institutional Review Board, Swissmedic Ethics Committee, and Kaunas Regional Biomedical Research Ethics Committee approved the protocols of the prospective studies whose data was used for this retrospective OCR analysis. The patients' written consent was obtained in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194).

Inclusion and exclusion criteria were applied in this retrospective study. The inclusion criteria were as follows: all the prospective research studies were conducted by using a non-invasive ICP measurement technology. The exclusion criteria were as follows: (1) measurements did not contain BHR, i.e., with a heart rate at $P_e = 0$ mmHg; (2) the signals of the pulse waves of the blood flow in OA collected by TCD were too weak for reliable heart rate (HR) calculation at any gradual externally applied pressure step; (3) repeated measurements from the same subject.

All patients' clinical charts were retrospectively reviewed. Patients' demographic information was collected including gender, age, and clinical condition whereas information of the gender and age was collected for healthy volunteers.

3.2.3. Data processing

The *BNS ICP 3* device does not have an integrated electrocardiogram (ECG) monitoring channel; therefore, the automatic HR calculation algorithm was developed to test HR variations by using TCD data accumulated during non-invasive ICP measurement. Examination of OCR is usually done by ECG; however, pulse waves measured in the intracranial vessels using TCD remain an accurate technique. A schematic representation of a 10-sec time period of pulse wave spectrograms recorded at different pressure steps during the non-invasive ICP measurement is shown in **Fig. 3.2**. Firstly, the maximum frequency envelope is calculated by the algorithm that is represented by the outer green line of the spectrogram. Then, the maximum frequency envelope is used for the detection of systolic blood flow velocities and systolic time moments which are shown as red dots. Finally, these detected time moments are used for the calculation of MHR at each different pressure step of non-invasive ICP measurement. The HR values and mean HR values are presented at different P_e steps in **Fig. 3.2.A** and **3.2.B**.

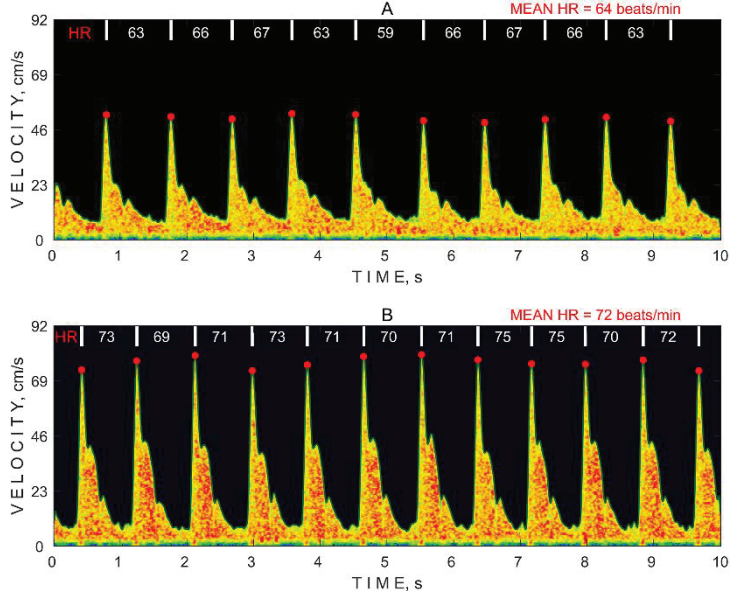


Fig. 3.2. Example spectrograms of pulse waves of blood flow in the ophthalmic artery collected with transcranial Doppler by using different external pressure steps. (A) 0 mmHg; (B) 48 mmHg. HR – heart rate (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

3.2.4. Statistical analysis

The BHR value is calculated from MHR at $P_e=0$ mmHg (minimal physical stimulation of the eye when the ultrasonic transducer is gently resting on the upper eyelid). We calculated the differences between BHR and MHR at every P_e step and used the following equation for the calculation of percentages:

$$HR_{\text{diff}} = \frac{MHR - BHR}{BHR} 100\% \quad (3)$$

here, HR_{diff} serves as a parameter for the detection of OCR.

All the subjects were enrolled in a repeated-measures analysis of variance to compare HR at different P_e steps. We used Kolmogorov-Smirnov ($n>50$) and Shapiro-Wilk ($n<50$) tests to examine the data distribution normality. We also used Mauchly's test to examine sphericity. We drew a histogram of HR_{diff} of all the subjects to summarize the HR_{diff} values calculated at all of the P_e steps applied on the ocular globe.

IBM SPSS Statistics software (version 23.0; *IBM Corporation*, Armonk, NY, USA) was used for statistical analysis. The level of significance was defined as $p<0.05$.

3.3. Results

One hundred and fifty-seven subjects were included in the retrospective study of OCR analysis. We excluded repeated measurements on the same subject to eliminate correlated data points. The mean age ($\pm$ SD) was 47.6 ($\pm$ 14.4) years (range: 20–75 years), and the male:female ratio was 57:100. The demographic data of the subjects divided into four groups is presented in **Table 3.1**.

Table 3.1. Demographic data of all subjects in this retrospective study (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

Subject group	No. of subjects	Age	Gender, female, %
		Mean $\pm$ SD (range), years	
TBI patients	8	53.3 $\pm$ 10.2 (37–69)	50.0
Neurologic patients	10	41.0 $\pm$ 12.3 (21–60)	60.0
Glaucoma patients	83	53.4 $\pm$ 12.5 (24–75)	72.3
Healthy volunteers	56	39.4 $\pm$ 13.2 (20–72)	53.6

TBI, traumatic brain injury; SD, standard deviation

A typical HR variation of a single subject recorded during non-invasive ICP measurement is shown graphically (**Fig. 3.3.**).

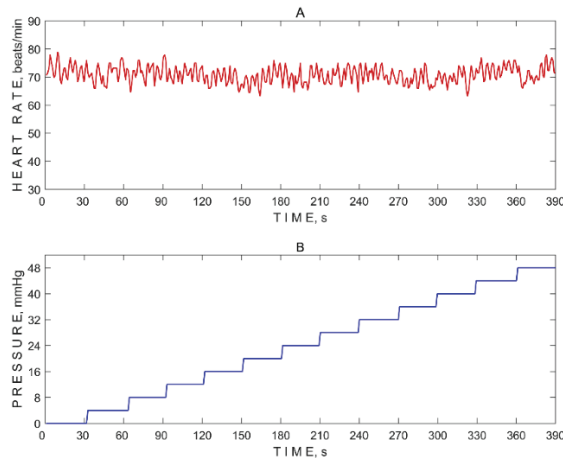


Fig. 3.3. Graphic visualization of typical heart rate variation. (A) Healthy volunteer's heart rate variation. (B) Pressure increase of 4 mmHg per pressure $P_e(t)$ step (time period of approximately 30 seconds each) was used on the ocular globe from 0 mmHg to 48 mmHg (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

There is no standard setup for the maximum applied external pressure (i.e., 48 mmHg) and the pressure increase per pressure step (i.e., 4mmHg) for non-invasive

ICP measurements; therefore, the setup can be changed according to the clinical study protocol.

We presented the number of performed measurements by using different protocol parameters according to the subject type in all groups in **Table 3.2**. The transition time between two successive pressure steps affects the time period of each pressure step. 30 sec was the average time period for non-invasive ICP measurements. However, a 6-min time period was used between the pressure steps for 10 healthy volunteers out of 157 subjects. The reliable non-invasive ICP measurement needs the number of TCD pulse waves per pressure step.

Table 3.2. Used parameters for non-invasive intracranial pressure measurement according to group (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

Subject group	Pressure steps, mmHg	Time period, sec.	Body position	No. of measurements
TBI patients	0; 4; 8; 12; 16; 20	30	HUT 20 deg	7
	0; 4; 8; 12	30	HUT 20 deg	1
Neurologic patients	0; 4; 8; 12; 16; 20; 24	30	LD	6
	0; 4; 12; 16; 20; 24	30	LD	2
	0; 4; 8; 12; 16; 20; 24; 28	30	LD	1
	0; 4; 8; 12; 16; 20; 24; 28; 32; 36	30	LD	1
Glaucoma patients	0; 4; 8; 12; 16; 20	30	Supine	83
Healthy volunteers	0; 4; 8; 12; 16; 20	30	Supine	38
	0; 4; 8; 12; 16; 20; 24; 28; 32; 36; 40; 44; 48	30	HDT 30 deg	3
	0; 4; 8; 12; 16; 20; 24; 28; 32; 36; 40; 44; 48	30	Supine	5
	0; 8; 12; 16; 24; 32; 40; 48	360	Supine	8
	0; 8; 12; 16; 24; 32	360	Supine	1
	0; 4; 8; 12; 16; 24; 32; 40; 48	360	Supine	1

TBI, traumatic brain injury; HUT, head up tilt; HDT, head down tilt; Time period, duration of one pressure step; LD, lateral decubitus

We calculated MHR separately for pressure steps of each measurement. Repeated-measures analysis of variance was performed in order to compare the MHR at different levels of pressure. MHR data matched the normality assumptions according to the Kolmogorov-Smirnov or Shapiro-Wilk test at each different Pe step (the results are presented in **Table 3.3**).

Table 3.3. Results of heart rate and tests of data normality at pressure steps from 0 mmHg to 48 mmHg (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

Pe, mmHg	Mean±SD	95% CI of the mean	Med	Min	Max	K-S test value	df	p value	Skewness (SE)	Kurtosis (SE)
0	64.8±8.9	63.4–66.2	64.3	42.4	89.4	0.047	157	0.200	0.25(0.19)	-0.17(0.38)
4	63.8±8.8	62.4–65.3	63.2	41.9	90.1	0.057	148	0.200	0.49(0.20)	0.15(0.39)
8	64.5±8.8	63.1–65.9	63.9	42.3	89.6	0.054	155	0.200	0.34(0.19)	-0.17(0.39)
12	64.5±8.8	63.1–65.8	63.6	42.6	91.0	0.066	157	0.096	0.40(0.19)	-0.07(0.39)
16	64.6±8.8	63.2–66.0	63.9	41.8	90.0	0.056	156	0.200	0.26(0.19)	0.04(0.39)
20	64.5±9.1	63.0–66.0	63.5	41.4	89.2	0.070	146	0.078	0.40(0.20)	-0.21(0.39)
24	63.6±9.6	59.8–67.3	63.4	40.9	87.8	0.973*	28	0.662	0.11(0.44)	0.56(0.86)
28	66.7±9.5	58.7–74.8	66.6	53.4	86.3	0.936*	10	0.508	0.42(0.68)	-0.96(1.30)
32	66.5±8.1	62.6–70.3	69.6	53.1	80.0	0.913*	19	0.083	-0.43(0.52)	-0.94(1.01)
36	65.3±9.3	58.2–72.4	64.6	54.1	79.8	0.920*	9	0.389	0.19(0.72)	-1.54(0.94)
40	66.0±8.2	61.8–70.2	69.3	51.7	80.5	0.917*	17	0.131	-0.37(0.55)	-0.79(0.93)
44	62.5±9.1	54.9–70.2	59.1	53.6	74.1	0.878*	8	0.051	0.45(0.75)	-2.12(1.48)
48	66.3±8.1	62.1–70.5	67.6	51.9	77.3	0.942*	17	0.340	-0.38(0.55)	-1.09(1.06)

Pe, external pressure applied to the ocular globe; SD, standard deviation; CI, confidence interval; Med, median; K-S test, Kolmogorov-Smirnov test; df, degrees of freedom; SE, standard error

*Shapiro-Wilk test

Mauchly's test showed that the assumption of sphericity was violated ($p=0.047$); therefore, the degrees of freedom were corrected by using Greenhouse Geisser estimates of sphericity ($\epsilon=0.23$). According to the obtained results, no significant effect on MHR [$F(2.71, 18.95) = 0.644$; $p=0.581$] was observed at different levels of pressure.

We calculated the differences between BHR and MHR and expressed them as percentages for OCR detection. We drew a histogram of HR_{diff} values for subjects from all the groups (**Fig. 3.4.**). HR_{diff} values with the minus sign represent a decrease in MHR compared with BHR, while the plus sign represents an increase in MHR compared with BHR.

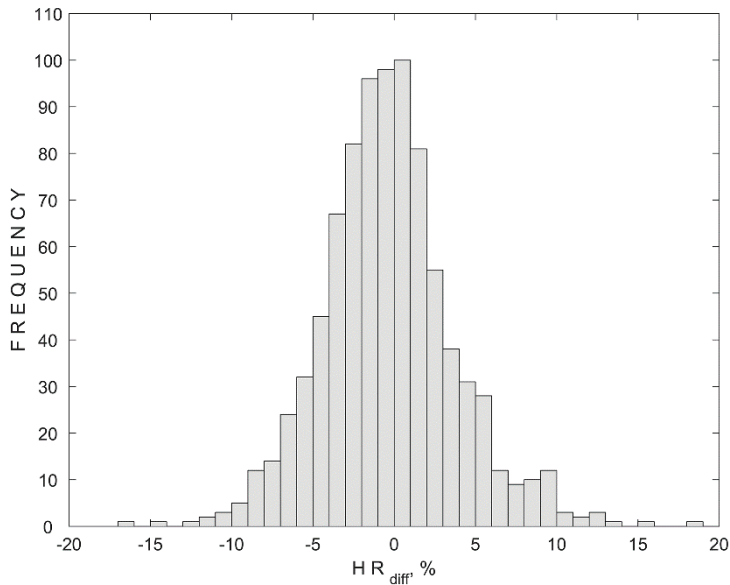


Fig. 3.4. HR_{diff} histogram for all subjects involved in this study, and, in total, 870 external pressure steps were applied during non-invasive intracranial pressure measurements (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

The 20% decrease in MHR compared to BHR is considered as a firm threshold of the evoked OCR. The histogram of HR_{diff} shows a 20% decrease which was not reached in any of the 870 pressure steps. The 10% decrease in MHR compared to BHR is also considered to be a threshold of the evoked OCR. We observed that 8 pressure steps (0.9% of the total used pressure steps) were reached and/or passed this threshold in 4 subjects. Among the 4 subjects, 3 were healthy volunteers and one was a glaucoma patient.

3.4. Discussion

The underlying mechanism of OCR has not yet been fully discovered (Schaller *et al.*, 2009). OCR studies mainly focused on understanding the physiological parameters, the molecular mechanisms, and the hemodynamic changes (Sandu, Cornelius *et al.*, 2010; Sandu, Spiriev, Lemaitre, Filis, & Schaller, 2010; Schaller, Sandu, Cornelius, Filis, & Perez-Pinzon, 2009). In this retrospective study, the prevalence of OCR was investigated by using *BNS ICP 3*. This study found out that a gradual external pressure applied to the ocular globe during the non-invasive ICP measurement did not result in OCR at the threshold of a 20% decrease in the HR criterion and rarely resulted in OCR at the threshold of a 10% decrease in the HR criterion.

The threshold of the evoked OCR remains debatable. Several studies define OCR based on the changes in HR from the baseline – a 10% decrease [8, 9], a 20% decrease (Karaman *et al.*, 2016; Karhunen *et al.*, 1984; Lai *et al.*, 2014), or a decrease of 10 beats per minute (Yu & Wang, 1991). In this study, 8 pressure steps (in 3 healthy volunteers and 1 glaucoma patient) exceeded the threshold of a 10% decrease in MHR compared to BHR. The HR variations in these 4 subjects are presented in Fig. 3.5. together with the gradual pressure steps applied on the ocular globe. It was observed that HR did not rapidly decrease when external pressure was applied on the ocular globe.

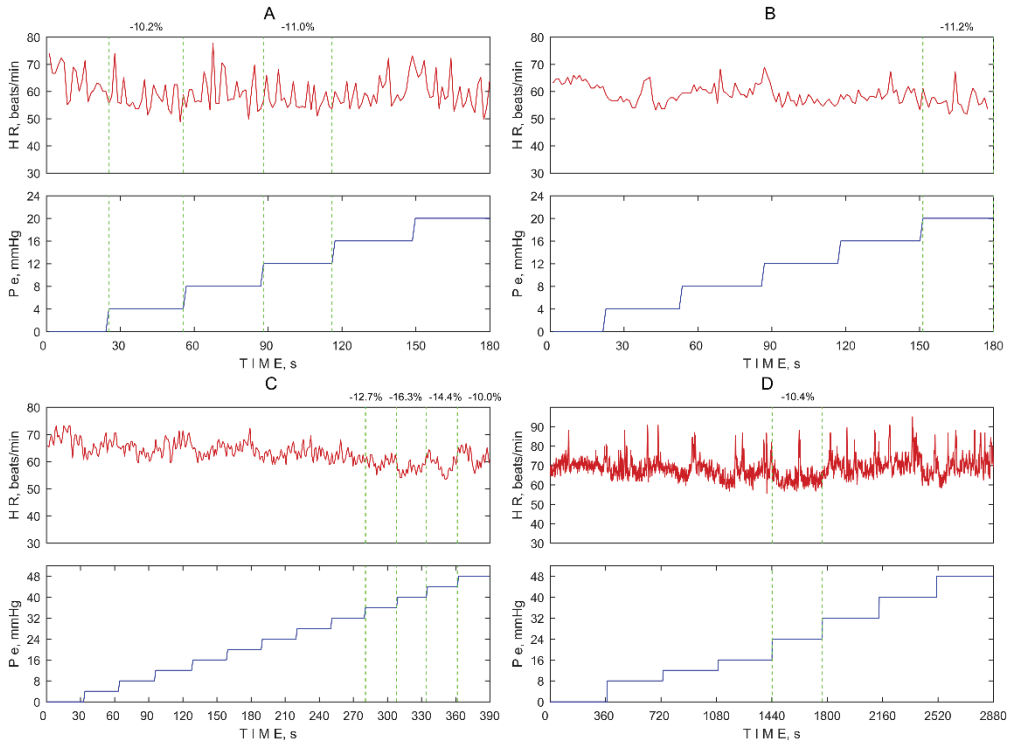


Fig. 3.5. Heart rate (HR) variation presented at every external pressure step (Pe) applied on the ocular globe. (A) Healthy subject. (B) Glaucoma patient. (C) Healthy subject. (D) Healthy subject (adapted from Hamarat *et al.*, 2018. Co-authorship of the study and joint publication: Laimonas Bartusis, PhD; Mantas Deimantavičius, MSc.)

The normal HR variability might influence MHR during non-invasive ICP measurement; therefore, changes in MHR might not necessarily be related to OCR. The HR variability is related to age, and it ranges from 8.97% to 13.70% (Umetani, Singer, McCraty, & Atkinson, 1998). Another study showed that HR variability ranges from 12.96% to 13.55% in the active population (Corrales *et al.*, 2012). A review in healthy adults found that HR variability was 10% (Nunan, Sandercock, & Brodie, 2010).

There are several limitations of this study, thus it is essential to highlight them. The evoked OCR is more common in children (Bhargava, Thomas, Chakravorty, & Dutt, 2014); therefore, the incidence of OCR is age-dependent. Thus, most clinical studies of OCR are reported during strabismus surgery in children (Blanc *et al.*, 1983; Choi *et al.*, 2007; Paton *et al.*, 2005; Zhang, Gu, & Lu, 2008). Up to date, non-invasive ICP measurements have been conducted only in adult subjects; therefore, we cannot assume that non-invasive ICP measurement could produce OCR in children. The mean was 47.6 years (range: 20–75 years) in

this retrospective analysis. The *BNS ICP 3* device is intended to be used mostly for adult glaucoma patients, but not children or anesthetized patients.

ECG monitoring was not used in this study since clinically significant changes in HR and/or arrhythmias were not expected in this population. During non-invasive ICP measurement, non-detectable cardiac arrhythmias might be produced, but that did not transmit pulse waves to the intracranial vessels which were being measured. However, this is unlikely to skip beat or arrhythmia. This would be detected as an irregularity of the pulse waves or as an interval between pulse waves in the intracranial vessels.

The reason for not observing OCR in our study is likely the low magnitude of the tractional force on the extraocular muscles or the level of the applied pressure on the ocular globe. Previous studies reported that the force of acute traction reaching a peak at not less than 150 grams (maximum=300 grams) in extraocular muscles is needed to evoke OCR, and slow gradual traction often failed to evoke OCR (Blanc *et al.*, 1983; Vrabec *et al.*, 1987). Thus, acute force of traction reaching up to 300 grams often evoked OCR (86.7%). The force of traction using a 4-0 suture silk loop can produce a pressure of hundreds of mmHg to evoke OCR (Blanc *et al.*, 1983). The slow increase in pressure (4 mmHg pressure increase per pressure step with each step taking 30 sec) on the ocular globe and the low level of the maximum applied pressure (48 mmHg) can be the explanation for the lack of an evoked OCR.

It is even speculated that the evoked OCR is a result of increased oxygen requirements due to diving or operation (Sandu, Spiriev, *et al.*, 2010). The subjects who underwent non-invasive ICP measurement were not experiencing such a stress.

3.5. Conclusions

In this retrospective study, we observed a very low incidence of evoked OCR during a non-invasive ICP measurement with the gradual external pressure (from 0 mmHg to 48 mmHg) on the ocular globe in adult patients with neurological and ophthalmological (glaucoma) diseases and healthy volunteers. Further studies are needed to investigate a clinically significant OCR in children or patients with an underlying cardiovascular disease.

4. NON-INVASIVE CEREBROVASCULAR AUTOREGULATION ASSESSMENT USING THE VOLUMETRIC REACTIVITY INDEX

4.1. Introduction

The brain needs adequate nutritional blood flow since it has high metabolic demand. The rate of the cerebral blood flow (CBF) in the adult is about 750 milliliters per minute or 15% of the cardiac output. The cerebral vascular system has to respond to any changes in ABP or ICP in order to maintain stable CBF. A constant CBF is maintained by cerebral blood vessels over a wide range of systemic ABP levels by means of myogenic, neurogenic, and metabolic mechanisms (Chillon & Braumbach, 2002; Paulson, Strandgaard, & Edvinsson, 1990). The mechanism known as cerebrovascular autoregulation (CA) stabilizes CBF despite fluctuations in the cerebral perfusion pressure (CPP).

The outcomes for traumatic brain injury (TBI) patients are affected by the impaired CA (Czosnyka *et al.*, 1997; Czosnyka, Brady, Reinhard, Smielewski, & Steiner, 2009; Svirni & Newel, 2010; Preiksaitis *et al.*, 2016; Sorrentino *et al.*, 2012). There are several studies showing that TBI patients had a favorable outcome if CPP was maintained close to the optimal CPP values (Aries *et al.*, 2012; Depreitere *et al.*, 2014; Zweifel *et al.*, 2008). Thus, CA monitoring is needed to establish the optimal, individualized treatment applying the optimal CPP treatment strategy for patients with TBI (Aries *et al.*, 2012).

Continuous bedside monitoring of CA is a part of multimodal monitoring for individualized targeted patient treatment strategies by using the optimal CPP. According to recommendations for healthcare professionals issued by the Neurocritical Care Society and the European Society of Intensive Care Medicine (Le Roux *et al.*, 2014). The treatment depends on identifying the optimum CPP at the point where cerebrovascular reactivity works best (Aries *et al.*, 2012; Petkus *et al.*, 2017; Rasulo *et al.*, 2011; Le Roux *et al.*, 2014; Steiner *et al.*, 2002).

Several approaches estimated CA status by measuring fluctuations in CPP and CBF (Czosnyka, Smielewski, Kirkpatrick, Menon, & Pickard, 1996; Eames, Blake, Dawson, Panerai, & Potter, 2002) as well as cerebral vascular resistance relative to changes in CPP (or ABP) (Czosnyka *et al.*, 1997). CA assessment methods depend on the application of the surrogate physiological parameters which allow replacing virtually impossible non-invasive CBF monitoring. The pressure reactivity index (PRx) as the moving Pearson's correlation coefficient (r) between slow waves of ABP(t) and ICP(t) over a time window of a few minutes is used to estimate invasive continuous CA clinically (Czosnyka *et al.*, 1997, 2009; Preiksaitis *et al.*, 2016; Sorrentino *et al.*, 2012).

$$PRx(t) = r(ABP_{sw}(t); ICP_{sw}(t)) \quad (4)$$

here, PRx – pressure reactivity index, ABP_{sw} – arterial blood pressure slow wave, ICP_{sw} – intracranial; pressure slow wave.

The ABP and ICP slow waves (also called ‘B-waves’) frequency is 0.5 to 3 cycles per minute, which reflects the vasogenic activity of CA; therefore, they are used to determine PRx(t) (Spiegelberg, Krause, & Kurtcuoglu, 2016). PRx(t) values are between -1 and +1, and they nonlinearly reflect the phase shift between ABP(t) and ICP(t) slow waves. During the normal CBF autoregulation (intact CA), the values of PRx(t) are negative. The dilation or constriction are the active reactions in the cerebral vessels (capillaries and arterioles) in order to maintain stable CSF in the case of slow ABP fluctuations. Changes in the vessel diameter cause the opposite changes in ICP or ABP waves; therefore, the PRx(t) value is negative (Schmidt *et al.*, 2016). During impaired CBF autoregulation, cerebral vessels cannot regulate CBF and ensure metabolic supply to brain cells. The synchronic fluctuation in ABP(t) and ICP(t) slow waves is caused by a passive response to ABP in the cerebral vessel diameter; therefore, the PRx(t) value is positive. PRx=+1 is the critical value because it represents the complete impairment of CA (Czosnyka *et al.*, 1997; Czosnyka *et al.*, 2009; Czosnyka, Czosnyka, Momjian, & Pickard, 2004; Schmidt *et al.*, 2016). Thus, the CA status can be determined between PRx highly positive (on average impaired) and PRx negative (on average intact) by PRx(t) monitoring.

The current practical method to calculate PRx with continuous CA assessment is based on invasive ICP and ABP monitoring. Thus, this method is useful for patients in intensive care units (ICUs). There is no gold standard for CA monitoring, but monitoring PRx is widely accepted in the clinical practice (Le Roux *et al.*, 2014). There are limitations in this method, including surgical procedures for implanting invasive ICP sensors into brain ventricles or the parenchyma tissue. The currently existing non-invasive methods for CA assessment are based on a physiological parameter which is trying to replace CBF monitoring.

$$\text{CA index} = r(\text{ABPsw}(t); X(t)) \quad (5)$$

here, X(t) is a non-invasively-monitored CBF surrogate (blood velocity in the brain artery, regional oxygenation or hemoglobin in the cortex, or cerebral blood volume) (Lang, Mehdorn, Dorsch, & Czosnyka, 2002; Larsen, Olsen, Hansen, Paulson, & Knudsen, 1994; Ragauskas, Daubaris, Petkus, Ragaisis, & Ursino, 2005; Rivera-Lara *et al.*, 2017; Zweifel, Castellani, Czosnyka, Carrera, *et al.*, 2010).

The method of non-invasively assessing CA is based on transcranial Doppler (TCD) (Lang *et al.*, 2002; Larsen *et al.*, 1994). Cerebral blood velocity monitored in the middle cerebral artery (MCA) is used to calculate the cerebrovascular autoregulation index (Mx) based on TCD as a moving correlation coefficient between the blood velocity in MCA and ABP.

Another non-invasive method is based on near infrared spectroscopy (NIRS) intended to monitor regional hemoglobin oxygen saturation in the external part of the prefrontal cortex and to calculate the correlation coefficient between the measured local oxygen saturation and ABP. This is called the COx (or TOx) index (Rivera-Lara *et al.*, 2017; Zweifel, Castellani, Czosnyka, Carrera, *et al.*, 2010).

However, this method is dependent on local measurements. Measurements of blood velocity measurements in the local cerebral artery and brain oxygenation in the external part of the prefrontal cortex cannot reflect the autoregulatory dynamics of the brain overall.

In this study, an innovative non-invasive ultrasonic CA monitoring method based on real time measurements of integrated blood volume reactions in the brain was investigated. The aim was to determine the clinical applicability of this non-invasive CA monitoring method and to perform a prospective comparative clinical study of simultaneous invasive and non-invasive CA monitoring of ICU patients.

4.2. Materials and methods

This study was conducted from 2013 to 2017 at National Vilnius University Hospital and Vilnius University Hospital Santaros Klinikos. It was approved by Vilnius Regional Biomedical Research Ethics Committee (protocol No. 158200-06-498-145, protocol No. 2012-06-12, 158200-15-801-323, 2015-10-06 and protocol No. 158200-16-854-364, 2016-07-12). A written informed consent was obtained from each patient or an appropriate relative.

61 patients with severe TBI who were in various pathophysiological states requiring continuous multimodal monitoring for treatment were enrolled. Multimodal monitoring included ABP measurements (a needle sensor in the radial artery) using *Datex Ohmeda* or *Draeger Infinity Delta* monitors and continuous invasive ICP measurements (a Codman ventricular or parenchymal sensor). The non-invasive ultrasonic monitoring system developed by the Health Telematics Science Institute at Kaunas University of Technology was used to monitor Fluctuations in intracranial blood volume (IBV)

ICM+ software (Cambridge, UK) was used to collect monitoring data and to calculate real time invasive and non-invasive CA indexes from ICP, ABP, and IBV. We calculate and visualize invasive CA indexes over the entire treatment period. However, we calculate non-invasive CA indexes simultaneously with invasive indexes over a 1-hour period and, if possible, we repeat it. We do not use non-invasively monitored CA indexes for treatment decision making.

4.2.1. Non-invasive cerebrovascular autoregulation assessment

The non-invasive ultrasonic monitoring system depends on the time-of-flight (TOF) measurement principle. Therefore, this system is capable to sense changes in IBV which are used as a surrogate of CBF changes for CA assessment (Petkus, Krakauskaitė, *et al.*, 2014; Vytautas Petkus, Preiksaitis, *et al.*, 2014; Petkus *et al.*, 2002; Ragauskas, Daubaris, Petkus, *et al.*, 2005). A head frame with a pair of ultrasonic transducers on either side of the patient's head was used to transmit and receive the ultrasound wave through the intracranial media including the brain parenchyma tissue and ventricles. Ultrasound speed (C) is greater in blood

comparing to other intracranial components (Petkus *et al.*, 2002); therefore, the increase of the blood volume within the acoustic path resulted in increases in the average relative ultrasound speed ($C(t)/C_0$). This value is inversely proportional to TOF; therefore, $\Delta IBV(t) \sim C(t)/C_0 \sim 1/TOF(t)$.

IBV (slow, respiratory, and pulse waves) can be affected by ICP changes. This can be explained by the ‘volume-pressure curve’ which turns into exponential behavior at high ICP values (Avezaat, van Eijndhoven, & Wyper, 1979; Czosnyka & Pickard, 2004; Schmidt *et al.*, 2016). Thus, IBV slow waves were used as surrogates for ICP waves to estimate non-invasive CA; therefore, the non-invasive CA index is defined as volumetric reactivity index $VRx(t)$ which is calculated as a moving correlation coefficient between slow waves of the $IBV(t)$ and $ABP(t)$.

$$VRx = r(ABP_{sw}(t); IBV_{sw}(t)) \quad (6)$$

here, VRx – volumetric reactivity index; ABP_{sw} – arterial blood pressure slow wave; IBV_{sw} – intracranial blood volume.

4.2.2. Data processing

The sampling frequency of raw ABP, ICP, and IBV data was 300 Hz. The recorded data was decimated to a 1-Hz sampling frequency and filtered with band-pass filters to extract the slow $ABP(t)$, $ICP(t)$, and $IBV(t)$ waves in the frequency range of 0.0083 to 0.033 Hz (corresponding to a period of 0.5–2.0 minutes). *ICM+* software was used to calculate non-invasive VRx and invasive PRx indexes within a 5-min time window, and it included 300 pairs of signal samples in each window. Example raw signals, slow waves filtered from $ABP(t)$, $ICP(t)$, and $IBV(t)$ signals, and $VRx(t)$ and $PRx(t)$ of a TBI patient are presented in **Fig. 4.1**. Positive values for $VRx(t)$ represent impaired CA (**Fig. 4.1.**), whereas negative values indicate intact CA (**Fig. 4.2.**) (Czosnyka *et al.*, 1997; Czosnyka *et al.*, 2009, 1996).

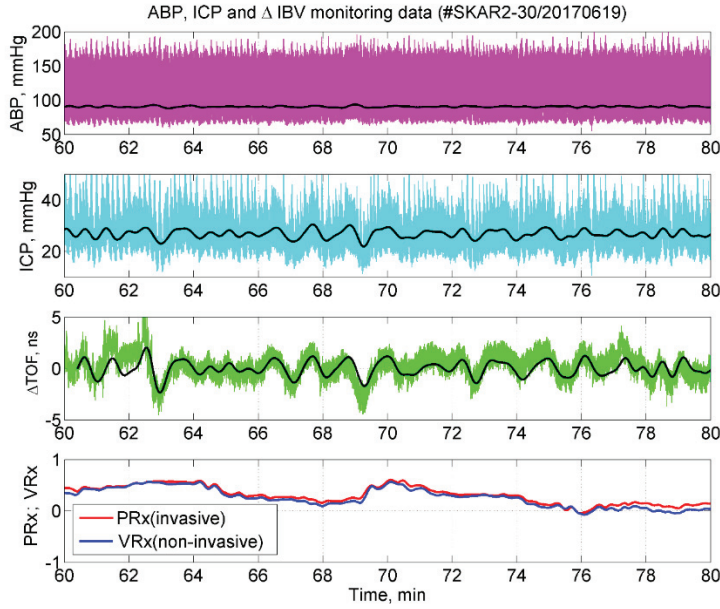


Fig. 4.1. Example of ICP(t), ABP(t), and IBV(t) raw data of monitoring, filtered slow waves (solid black curves) and cerebrovascular autoregulation indexes (PRx(t), VRx(t)) calculation over a 20-minute time interval. IBV(t) slow waves are expressed as changes in the time-of-flight signal ($\Delta\text{TOF}(t)$). Both indexes show similar information about the impairment of CA (when $\text{PRx} > 0$, $\text{VRx} > 0$). Correlation coefficient between ICP(t) and IBV(t) slow waves is 0.861, thus showing that it is possible to use IBV slow waves as ICP surrogate for calculating non-invasive VRx index (adapted from Petkus *et al.*, 2019)

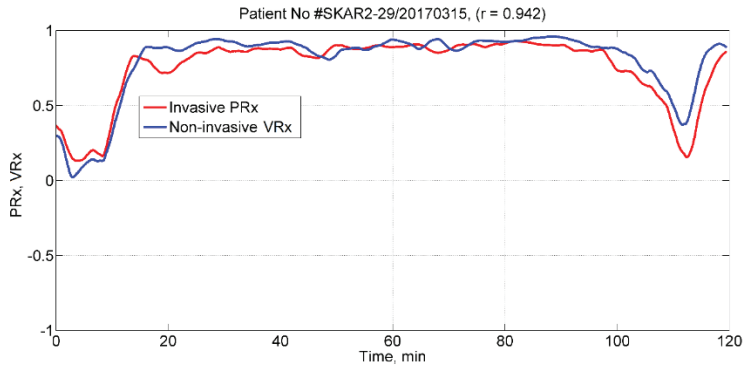


Fig. 4.2.A. Examples of 2-hour sessions comparing invasive and non-invasive cerebrovascular autoregulation (CA) monitoring for patients with impaired CA (adapted from Petkus *et al.*, 2019)

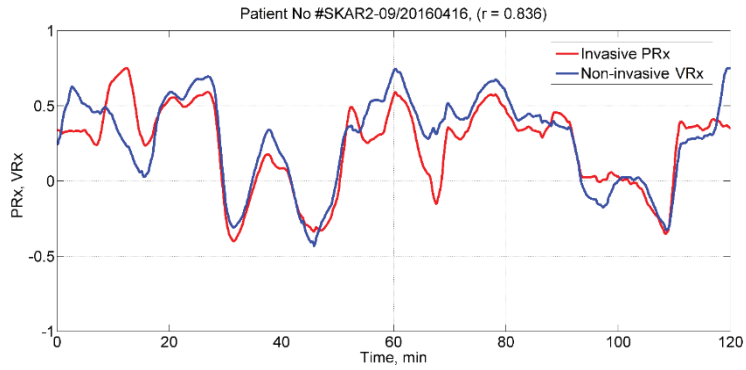


Fig. 4.2.B. Examples of 2-hour sessions comparing invasive and non-invasive cerebrovascular autoregulation (CA) monitoring for patients with intermediate CA (adapted from Petkus *et al.*, 2019)

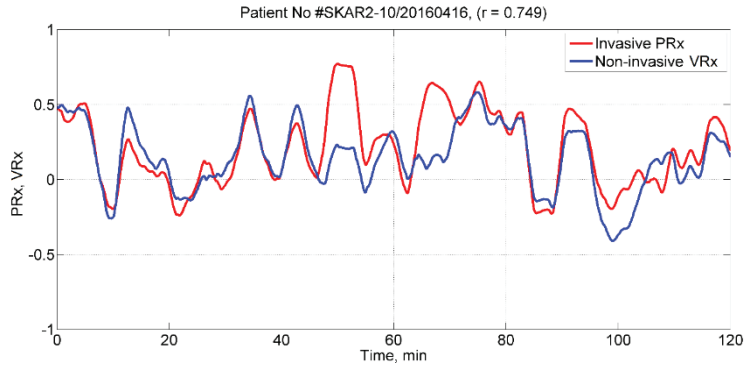


Fig. 4.2.C. Examples of 2-hour sessions comparing invasive and non-invasive cerebrovascular autoregulation (CA) monitoring for patients with intermediate CA (adapted from Petkus *et al.*, 2019)

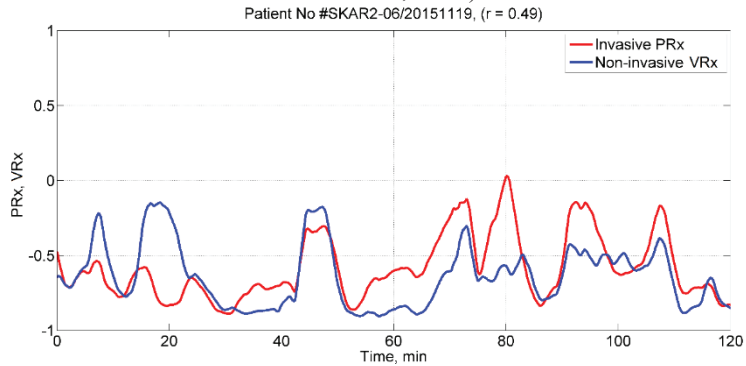


Fig. 4.2.D. Examples of 2-hour sessions comparing invasive and non-invasive cerebrovascular autoregulation (CA) monitoring for patients with intact CA (adapted from Petkus *et al.*, 2019)

Patients are divided into two groups; survivors and non-survivors. We calculated averaged values for VRx, PRx, ICP, and ICP and IBV slow wave amplitudes for each group. We used the Hilbert transform to extract envelopes and to estimate the amplitudes of ICP and IBV slow waves. The nonparametric Mann-Whitney test was used for their differences assuming that distributions were non-normal. We performed a linear regression and Bland Altman analysis for PRx and VRx. We averaged PRx and VRx data during each single invasive and non-invasive simultaneous PRx(t) and VRx(t) monitoring session in order to produce one value per patient. We calculated Pearson's correlation coefficient between PRx and VRx averaged data at a 5-min time window and over each monitoring session. We calculated the standard deviation of the difference between PRx and VRx in order to analyze the influence of the slow wave amplitude and expressed it as a function distributed over the range of amplitudes of ICP and IBV slow waves.

4.3. Results

Non-invasive VRx indexes were monitored simultaneously with invasive PRx indexes during the comparative monitoring sessions for 61 TBI patients. Monitoring sessions ranged between 1 to 4 hours per patient, totaling at 100 hours over the entire cohort. Demographic patient data is presented in **Table 4.1**. 2-hour monitoring sessions of comparisons between VRx and PRx when CA was impaired and intact are shown in **Fig. 4.2**.

The correlation coefficient between VRx(t) and PRx(t) averaged over a 5-min time interval was 0.724 ($p < 0.001$; 95% CI (0.695–0.750)) for groups. The standard deviation of the difference between VRx and PRx was 0.292; the bias between VRx and PRx was -0.063 ± 0.073 (95% CI (-0.136–0.01)). The 1201 pairs of VRx and PRx indexes which are averaged per 5-min time windows were used for the calculation of the correlation coefficient and the standard deviation.

Table 4.1. Demographic characteristics, clinical findings, and averaged values of data gathered while monitoring TBI patients (adapted from Petkus *et al.*, 2019)

	Surv ivors	Non -survivors	Tota l	<i>p</i> value
Patient's No.	41	20	61	-
Sex (male/female)	35/6	16/4	52/9	-
Age, mean (SD), yrs.	36.2 (15.6)	46.1 (15.6)	39.5 (16.1)	0.024*
GCS, median (IQR)	6 (4-7)	4 (3-5)	5 (4-7)	0.016*
Head surgery*** / without head surgery****	23/18	15/5	38/23	-
Average PRx, mean (SD)**	0.06 (0.27)	0.34 (0.37)	0.16 (0.33)	0.002*
Average VRx, mean (SD)**	0.02 (0.32)	0.21 (0.34)	0.08 (0.33)	0.019*
Average ICP, mean (SD)**	15.2 (7.0)	20.0 (18.7)	16.8 (11.9)	0.437
Amplitude of ICP slow waves, mean (SD)**, mm Hg	2.06 (1.22)	0.90 (0.43)	1.70 (1.17)	<0.001*
Amplitude of IBV slow waves, mean (SD)**, ns	4.49 (7.45)	2.51 (3.12)	3.84 (6.41)	0.012*

SD – standard deviation, IQR – interquartile range, GCS – Glasgow Coma Scale, ICP – intracranial pressure, PRx – pressure reactivity index, vPRx – non-invasive volumetric pressure reactivity index, IBV – intracranial blood volume. Patient outcome was evaluated 6 months after hospital discharge.

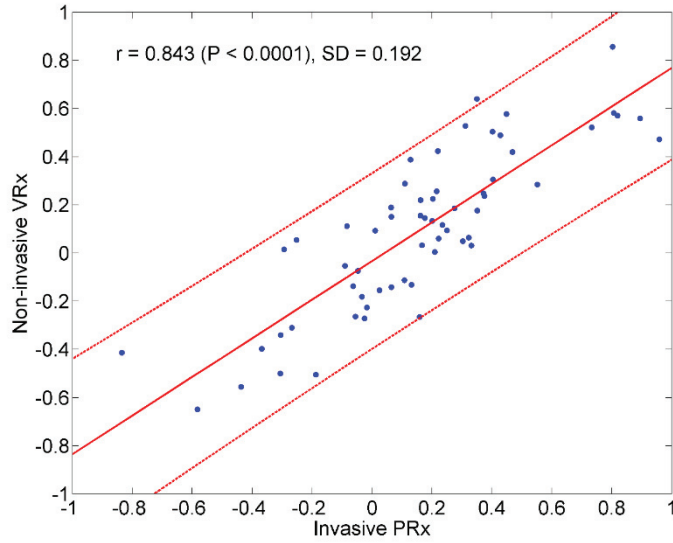
*statistically significant at $p < 0.05$.

**averaged values during limited-time simultaneous invasive and non-invasive cerebrovascular autoregulation monitoring sessions.

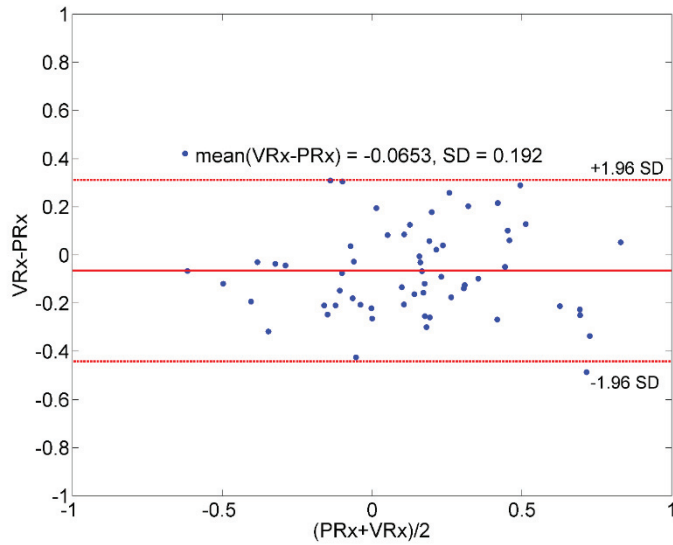
*** CA monitoring performed for patients after head surgery procedures (evacuation of hematomas, intracerebral or epidural hemorrhage after craniotomy).

**** CA monitoring performed for those patients who did not undergo head surgery

The correlation coefficient between VRx(t) and PRx(t) averaged per patient's monitoring session was 0.843 ($p < 0.001$; 95% CI (0.751–0.903)) (61 pairs of indexes). The standard deviation of the difference between VRx and PRx averaged per patient's monitoring sessions was 0.192; the bias was -0.065 ± 0.048 (95% CI ($-0.103 - -0.017$)). The linear regression and Bland Altman plots between the pairs of VRx and PRx indexes averaged per patient's monitoring sessions are shown in **Fig. 4.3**

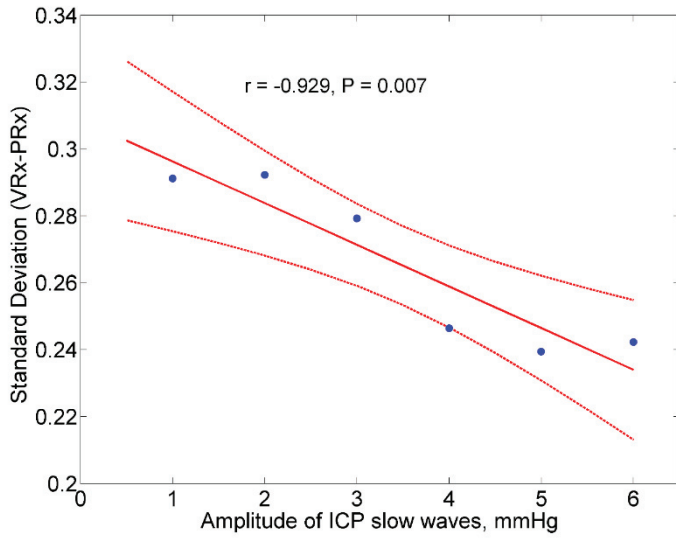


A

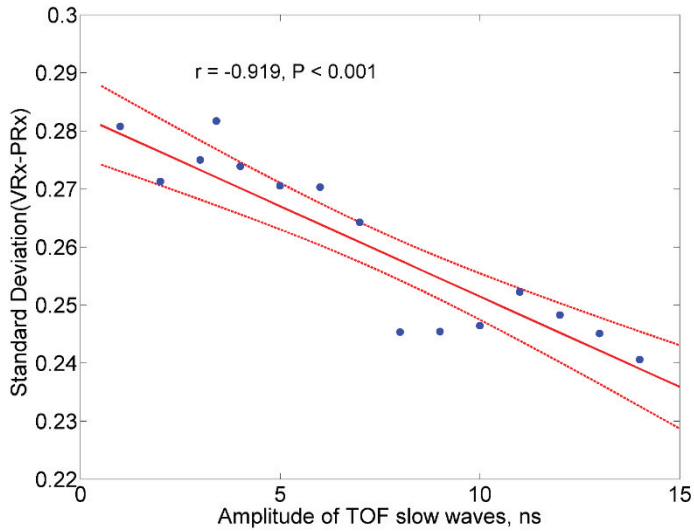


B

Fig. 4.3. Comparison of non-invasive VRx and invasive PRx indexes by regression line (A) and Bland Altman plot (B). The VRx and PRx indexes are averaged over each patient's CA monitoring session (one value per patient, 61 TBI patients' data points). The correlation coefficient between vPRx and PRx indexes is $r = 0.843$. The standard deviation of the difference between the indexes is $SD=0.192$. Bias is -0.065 (adapted from Petkus *et al.*, 2019)



A



B

Fig. 4.4. Distribution of differences between non-invasive VRx and invasive PRx indexes (expressed as standard deviation of the difference between indexes) and the amplitudes of ICP (A) and IBV slow waves (B). Amplitude of IBV slow waves is expressed as amplitude of time-of-flight (TOF) slow waves. VRx and invasive PRx indexes were averaged over a 5-min time window (adapted from Petkus *et al.*, 2019)

We calculated the distributions of difference between PRx and VRx data over the range of amplitudes of ICP and IBV slow waves (**Fig. 4.4.**). We found statistically significant differences between the survivors and non-survivors in average values of PRx, VRx, amplitudes of ICP/IBV slow waves as well as in age and Glasgow Comma scale (GCS) (**Table 4.1.**).

4.4. Discussion

Clinical testing of a non-invasive CA assessment method was performed by comparing non-invasively monitored VRx(t) index to the invasive PRx(t) index. Since there is no gold standard index of cerebral autoregulation, PRx was used as a reference index in this comparative study.

We analyze VRx and PRx over 61 patients and 100 hours of monitoring data and found out a significant correlation when indexes were averaged over a 5-min time window ($r = 0.724$, $p < 0.001$) as well as a much stronger correlation ($r = 0.843$, $p < 0.001$) when indexes were averaged per patient's monitoring sessions. Other non-invasive CA indexes including Mx, COx, TOx, and THx were compared against PRx. Some of them presented a significant correlation ($r \sim 0.6$) between Mx based on TCD and PRx (Budohoski, Czosnyka, *et al.*, 2012; Highton *et al.*, 2015; Zweifel *et al.*, 2008) and a good correlation ($r \sim 0.4\text{--}0.6$) between the indexes based on NIRS and PRx (Highton *et al.*, 2015; Zweifel, Castellani, Czosnyka, Helmy, *et al.*, 2010). Nonetheless, those methods based on TCD or NIRS have the primary limitation is related to local measurements. The method based on NIRS is able to monitor CA only in the cortex which is limited to a 2- to 3-cm depth (Fantini, Sassaroli, Tgavalekos, & Kornbluth, 2016). Thus, this method can be affected by the blood flow in the scalp and skull that can contaminate the NIRS signal (Scheeren & Saugel, 2017). CA has different dynamic characteristics in the cortex, in the white matter, and in the cerebellum, respectively (Lang *et al.*, 2005). In the case of Mx, a different hemisphere can provide different information about CA, and such CA asymmetry is common after TBI (Horsfield, Jara, Saeed, Panerai, & Robinson, 2013).

Some studies used ROC analysis on Mx to explore its diagnostic capability for the prediction of the Patient's outcome (Budohoski, Czosnyka, *et al.*, 2012; Budohoski, Reinhard, *et al.*, 2012; Zweifel *et al.*, 2008; Zweifel, Castellani, Czosnyka, Carrera, *et al.*, 2010). In this study, statistically significant associations between the average PRx and VRx values were found during that limited time interval with the patient survival rate (**Table 4.1.**). With a limited time of CA monitoring, the data that is missing over most of the patient's treatment time cannot provide reliable information for the outcome prognosis. Unfavorable outcomes for TBI patients can be significantly affected by the duration of the single longest CA impairment episodes, rather than with averaged PRx(t) values or the average time of all CA impairment episodes (Preiksaitis *et al.*, 2016).

The unfavorable outcome for TBI patients is associated with the average PRx above 0.2 or prolonged CA impairment events when PRx is above 0.5 to 0.7 [6, 12, 33, 38–40]. PRx = 0 is a mathematical threshold separating impaired CA from intact CA. PRx values are close to zero when the amplitudes of slow ICP(t) and ABP(t) waves are too low, or their signal-to-noise ratios are too low.

What regards the method of continuous CA assessment, slow fluctuation in ABP and ICP waves were used for calculating PRx (Czosnyka & Pickard, 2004; Czosnyka *et al.*, 2009; Spiegelberg *et al.*, 2016). Amplitudes of slow waves influence the reliability of CA indexes whether measured invasively or non-invasively, since Spontaneous slow waves are intermittent (Spiegelberg *et al.*, 2016). The presence of the transmission of rhythmic changes in the cerebral blood volume in response to changes in ABP is considered as the origin of slow waves (Spiegelberg *et al.*, 2016). The generation, amplitude, and frequency of slow B-waves can be affected by A brain-stem rhythm, rhythmic changes in the partial pressure of arterial CO₂, the time constant of autoregulation, the speed of ABP reduction, and the value of CPP (Spiegelberg *et al.*, 2016). The periodical or single ABP changes or slow waves can be generated by artificial breath-holding, pharmacological intervention, body tilting, leg-cuff tests (Lang *et al.*, 2005; Spiegelberg *et al.*, 2016). Under ICU conditions, this artificial test cannot be applied to a patient with TBI.

In the case of analysis of the slow wave amplitude on the difference between the indexes, the coincidence between VRx(t) and PRx(t) indexes is better when the amplitudes of slow waves increase (**Fig. 4.4.**). When the amplitude of the ICP slow waves was ~5 mmHg, the standard deviation of this difference was less by ~20% (**Fig. 4.4.A.**). When the IBV slow wave amplitude was measured as changes in the TOF signal reached ~10 ns, there was a similar decrease in the standard deviation (**Fig. 4.4.B.**). According to these results, greater amplitudes in ICP and IBV slow waves mean fewer errors when assessing PRx and VRx indexes. As a matter of fact, the greater amplitude in the intracranial slow waves (ICP and IBV) means a better outcome for the patient with TBI (**Table 4.1.**). These results comply with the findings of other studies that low amplitude B-waves were found to be associated with impaired CA, therefore, with a fatal outcome after a head injury (Balestreri *et al.*, 2005; Spiegelberg *et al.*, 2016).

Although PRx and VRx give clinically similar diagnostic information of the CA status, there are some methodological differences. ICP and IBV changes are manifested according to the pressure-volume curve that also characterizes the changing brain compliance. The slope between ICP and IBV changes is different for different brain compliance conditions, which results in different sensitivities for ABP changes. IBV fluctuations cause smaller fluctuations in the amplitude of the slow waves of ICP at higher compliance conditions. On the contrary, ICP waves appear to be higher at lower brain compliance. ICP is usually measured in the brain parenchyma, assuming that the pressure is uniformly distributed over the entire cranial cavity. When hematomas are present, pressure difference of up to 5 mmHg

can be observed between the two hemispheres (Qiu, Jiang, Xiao, Wang, & Shen, 2014; Sahuquillo, Poca, Arribas, Garnacho, & Rubio, 1999). Therefore, TBI patients with hematomas may have CA asymmetry (Horsfield *et al.*, 2013). Thus, in VRx measurements, IBV fluctuations can be measured in both hemispheres within the acoustic path that passes from the left side of the temporal bones to the right side of the temporal bones.

Even though there are differences, VRx and PRx can provide a global estimate of CA.

The average ICP of the entire cranium covering all the regions where CBF is regulated or disturbed requires calculating the invasive index (PRx). On the other hand, the average IBV measurement over the acoustic path is needed to calculate the non-invasive index (VRx).

4.5. Limitations

The limited number of patients is the main limitation of this study. The data showed similarities between the indexes, but more data is needed to assess their relationship with the patient's outcome including such additional factors as the age, gender, GCS, etc.; it would be beneficial to perform ROC analysis for predicting the patient's outcome. The non-invasive CA monitoring method has a technological limitation which is a common problem in all ultrasound-based technologies. Trained personnel is needed at the patient's bedside to supervise the use of this non-invasive CA monitoring. The movement of the patient can cause artifacts and may require readjustment of the ultrasonic probes. Those are the main limitations for long-time monitoring. However, up to 4 hours of monitoring on comatose ICU patients is successfully performed. We gained reliable coincidence between PRx and VRx.

The final limitation is the absence of a gold standard in CA monitoring.

4.6. Conclusions

In this prospective clinical study, we found that the non-invasive ultrasonic volumetric reactivity index (VRx) monitoring based on ultrasonic time-of-flight measurements of intracranial blood volume dynamics has a significant coincidence with the invasive PRx index. The non-invasive ultrasonic volumetric reactivity index (VRx) based on integral IBV measurements within the acoustic path that crosses both hemispheres can be used as a non-invasive cerebrovascular autoregulation index to reflect integral information of the CA status over the entire cranium in the same way as PRx. The coincidence between the invasive and non-invasive CA assessment methods is better when higher-amplitude IBV and ICP slow waves are present.

5. NON-INVASIVE CONTINUOUS INTRACRANIAL PRESSURE MONITORING

5.1. Introduction

The cranium has a rigid structure and contains 3 main components: brain – 80–85%, blood – 8–12%, CSF – 3–10%. A change in the volume of any component causes a change in the volume of another component so that to maintain the balance and the cerebral volume dynamics according to Monroe-Kellie doctrine. There are initial compensatory mechanisms of a total of 150ml (Wilson, 2016), either diverting CSF from the subarachnoid space to the lumbar theca, or increasing the venous outflow (**Fig. 5.1.**). Once these compensatory mechanisms have been exhausted, a rapid raise in ICP will occur (**Fig. 5.2.**).

$$VIC = V_{\text{blood}} + V_{\text{brain}} + V_{\text{CSF}} + V_{\text{mass}} \quad (7)$$

here, VIC – intracranial volume, V_{blood} – blood volume, V_{brain} – brain volume, V_{CSF} – CSF volume, V_{mass} – mass volume (e.g., tumor, hematoma, abscess).

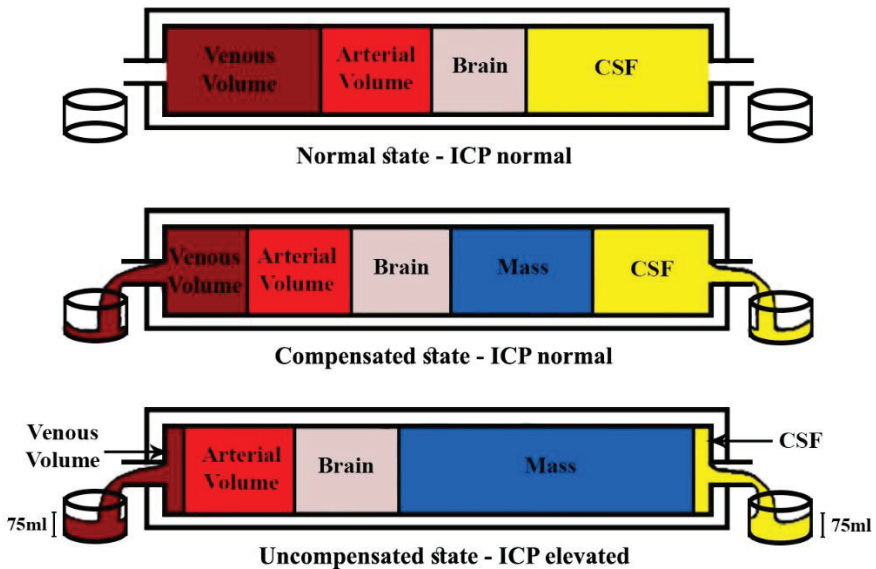


Fig. 5.1. Intracranial compensation for expanding mass. When the increase in the intracranial volume passes the critical volume – 150ml – a dangerous rise in ICP may occur

When the intracranial volume increases, blood and CSF are the main protection for the brain. There is some initial compensation in the volume of blood and/or CSF to prevent major changes in the intracranial compliance with a minimal increase in ICP.

The continuous monitoring of intracranial pressure (ICP) is clinically important when a sudden pathophysiological ICP variation may occur. Such spontaneous ICP change is common in patients with a traumatic brain injury (TBI) (Abdelsadig, Kumar Kanodia, Badran, Abdelsadig, & Ballantyne, 2017). Therefore, intracranial pressure monitoring is mostly performed in patients with a severe TBI (Carney *et al.*, 2017).

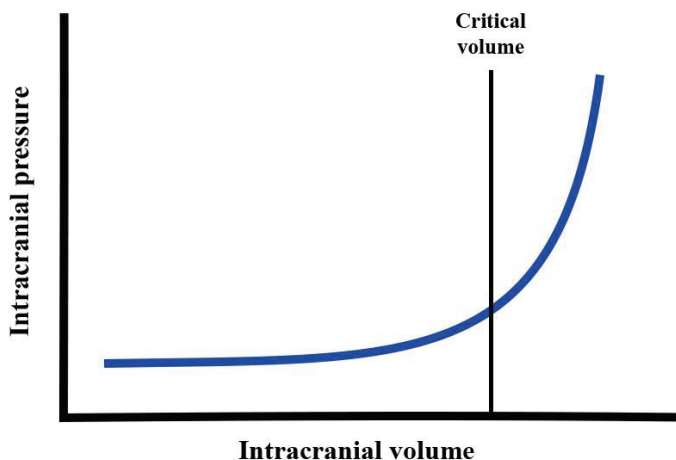


Fig. 5.2. ICP volume compliance curve. Before reaching critical volume, intracranial volume increase can be compensated with minimal ICP increase. Once the critical volume – $\approx 150\text{ml}$ – has been reached, ICP rises rapidly

The Glasgow Coma Scale (GCS) is the most common scoring system that is used to describe the level of consciousness in a patient with TBI (**Table 5.1.**).

Table 5.1. GCS measurement functions

Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4 = spontaneous	5 = orientated	6 = obeys command
3 = to sound	4 = confused	5 = localizing
2 = to pressure	3 = words, but not coherent	4 = normal flexion
1 = none	2 = sounds, but no words	3 = abnormal flexion
NT = not testable	1 = none	2 = extension
	NT = not testable	1 = none
		NT = not testable

The brain injury classified as: **Severe:** GCS 8 or less; **Moderate:** GCS 9 to 12; **Mild:** GCS 13 to 15. It is recommended to monitor ICP on a TBI patient with a GCS score lower than 8. The Glasgow Outcome Scale (GOS) has been globally accepted for describing the outcome in head injury patients (**Table 5.2.**).

Table 5.2. Glasgow Outcome Scale

Score	Rating	Definition
5	Good recovery	Resumption of normal life despite minor deficits.
4	Moderate disability	Disabled but independent. Can work in sheltered setting.
3	Severe disability	Conscious but disabled. Dependent for daily support.
2	Vegetative state	Minimal responsiveness.
1	Death	Non-survival.

The gold standard ICP monitoring method is considered to be intraventricular drain connected to an external pressure transducer, although it has its own drawbacks, such as the difficulty of catheter insertion in the cases of advanced brain swelling, a technical problem upon insertion, bleeding and an increased risk of infection (Czosnyka & Pickard, 2004). Another major method of continuous ICP monitoring includes intraparenchymal devices (Kasotakis *et al.*, 2012) which are not as accurate as intraventricular drain, and they cannot be recalibrated once inserted, which results in a problem of zero drift, which partly limits continuous ICP monitoring from 1 up to 32 days (Akbik, Carlson, & Yonas, 2016; Al-Tamimi, Helmy, Bavetta, & Price, 2009; Koskinen & Olivecrona, 2005; Zacchetti, Magnoni, Di Corte, Zanier, & Stocchetti, 2015). Intracranial pressure tracking would still be valuable after the removal of intraparenchymal sensors on TBI patients so that to follow ICP variation after days or weeks passing since the initial head trauma.

A non-invasive intracranial pressure monitoring device would be needed in this case. Unfortunately, there is no such device available in the clinical market. TCD-based methodological approaches of non-invasive ICP monitoring whose overall accuracy ranges around ± 12 mmHg are available (Cardim *et al.*, 2016). This challenges our unique TCD-based non-invasive snapshot ICP measurement technique (Ragauskas *et al.*, 2012; Ragauskas *et al.*, 2014): is it applicable for non-invasive ICP monitoring as well? We present a pilot study comparing our TCD-based non-invasive ICP monitoring results with intraparenchymal Codman microsensor readings on TBI patients thus aiming to establish their absolute and relative relationship.

5.2. Methods

5.2.1. Derivation of blood flow velocity parameter used for the ICP_{non-inv} monitoring

Power P_s of the ultrasound Doppler signal reflected from the infinitesimal volume ΔV_A of the blood flowing in the artery with artery radius R_A , can be defined as follows:

$$\Delta P_s = nA \Delta V_A . \quad (8)$$

where n is the density of particles in the blood (blood cells, contrast material, etc.) reflecting the ultrasound signal, A is a constant. The total signal power from the whole sample volume is then:

$$\begin{aligned} \Pi_s(t) &= \sum \Delta P_s = \int_V nA dV = \int_0^{R_A} \int_0^{2\pi} \int_0^{L_z} nA dz r d\varphi dr = \\ &= \int_0^{R_A} \frac{dP_s(t, r)}{dr} dr = nA \pi L_z R_A^2 = \int_0^{u_{\max}} P_s(t, u) du. \end{aligned} \quad (9)$$

where, L_z – the length of the sample volume along the artery, t – time, $P_s(t, r)$ – the signal distribution over the radial coordinate r , $P_s(t, u)$ – the signal distribution over the measured velocity u . If $L_z = \text{const}$ during the measurement, then the total signal power Π_s depends only on the cross-sectional area of the artery $S_A = \pi R_A^2$:

$$\Pi_s(t) \sim S_A(t) . \quad (10)$$

Integral of $u \cdot P_s(t, u)$ over u is proportional to the measurement angle α_s and the blood flow rate Q :

$$G_s(t) = \int u P_s(t, u) du \sim Q(t) \cdot \cos(\alpha_s) = S_A(t) \cdot V(t) \cdot \cos(\alpha_s) . \quad (11)$$

where V is the mean blood flow velocity.

This gives an idea that variations of the OA cross-sectional area in the intracranial and the extracranial segments can be compared by the integral factors

derived from the intensity of the Doppler signal. The factor is defined as an integral of the difference of the logarithms of the Doppler signal intensity P_s obtained from IOA and EOA segments of OA:

$$\begin{aligned}
 F(t) &= \int_{\tau=0}^{10} \int_u |10 \lg(P_{s,IOA}(t - \tau, u)) - 10 \lg(P_{s,EOA}(t - \tau, u))| du d\tau = \\
 &= 10 \int_{\tau=0}^{10} \int_u \left| \lg \left(\frac{P_{s,IOA}(t - \tau, u)}{P_{s,EOA}(t - \tau, u)} \right) \right| du d\tau, \quad t = [10, 20, \dots, 3590] s.
 \end{aligned} \tag{12}$$

where u is the measured velocity. In order to compare factor F with ICP monitored non-invasively, the factor was processed as follows:

1) Factor F and invasively measured ICP_{inv} were smoothed by the moving average filter of $T_{smooth} = 60$ seconds window:

$$\bar{F}(t) = \frac{1}{60} \int_{\tau=0}^{60} F(t - \tau) d\tau. \tag{13}$$

$$\overline{ICP_{inv}}(t) = \frac{1}{60} \int_{\tau=0}^{T_{smooth}} iICP(t - \tau) d\tau. \tag{14}$$

2) The smoothed factor $\bar{F}$ was rescaled according to $\overline{ICP_{inv}}$ values by

$$f(t) = a + b \cdot \bar{F}(t) \tag{15}$$

so that scale coefficients a and b would satisfy the condition of equality of the standard deviations and means of rescaled factor f and $\overline{ICP_{inv}}$:

$$\begin{cases} std(f(t)) = std(\overline{ICP_{inv}}(t)) \\ mean(f(t)) = mean(\overline{ICP_{inv}}(t)) \end{cases}, \quad t = [T_{smooth}, t_{end}]. \tag{16}$$

5.2.2.Clinical material

This pilot study was conducted at the Department of Neurosurgery, National Vilnius University Hospital. The study was based on 7 TBI patients who underwent a brain surgery with ICP monitoring implantation. The demographic data and the clinical features of the patients are presented (**Table 5.3.**).

Table 5.3. Demographic data and clinical features of the patients included in this pilot study. GCS – Glasgow coma scale, GOS – Glasgow outcome scale DAI – diffuse axonal injury, SDH – subdural hematoma, DBI – diffuse brain injury, ICP – intracranial pressure.

Patient No	Age, years	Gender	GCS on admission	Diagnosis	Surgery type	GOS
1	44	Male	3	DAI with skull open fractures	Intraparenchymal ICP	1
2	39	Male	8	DAI, SDH	Intraparenchymal ICP	5
3	26	Female	7	DAI, SDH	Intraparenchymal ICP	1
4	19	Male	7	DBI	Intraventricular ICP	4
5	29	Female	5	DAI	Intraparenchymal ICP	4
6	20	Female	4	DAI	Intraparenchymal ICP	3
7	20	Male	7	DAI	Intraparenchymal ICP	3

The study design was approved by the local research and ethics committee (No. 158200-15-801-323). Informed consent was obtained from each patient's relative. ICP monitoring data was collected between May 2016 and January 2018.

5.2.3.ICP monitoring and data sampling

The setup and execution of the simultaneous ICP and blood flow velocity parameter (BFVP) monitoring in the ophthalmic artery are shown (Fig. 5.3.). An invasive Codman ICP monitor with a catheter tip sensor (*Johnson & Johnson Professional, Inc.*, Raynham, MA, USA) measured direct ICP (ICPD). Intracranial pressure data was sampled at 300 Hz and recorded on a computer featuring *ICM+*

software (version 8.2; *ICM+ Software*, University of Cambridge, UK) via *Datex-Ohmeda* (*Datex-Ohmeda, Inc.*, Madison, WI, USA) patient vital signs monitor.

The suggested non-invasive ICP monitoring method is based on measuring the pulsatility index of the blood flow in the intracranial and extracranial segments of the ophthalmic artery simultaneously. Then, the calculated blood flow velocity parameter is used for non-invasive ICP monitoring. After the initial patient-specific calibration of blood flow velocity parameter by using invasive ICP data, we monitored ICP continuously for a 1-hour time period. During this time interval, we did not calibrate the blood flow velocity parameter.

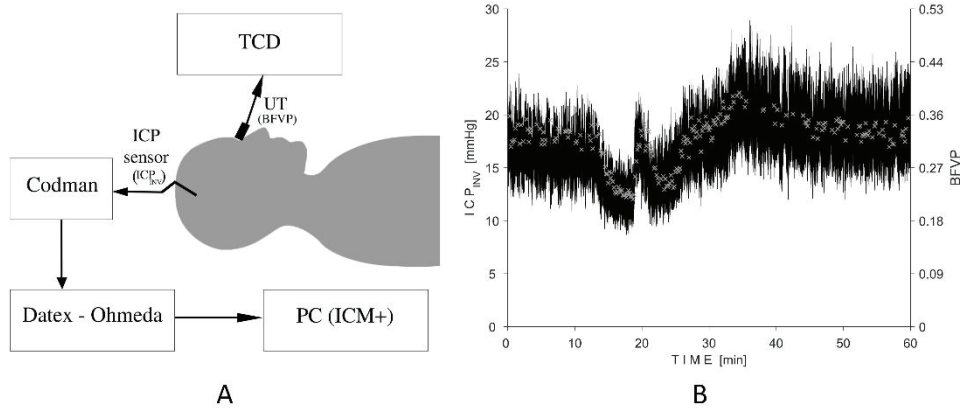


Fig. 5.3. (A) Setup of the simultaneous direct intracranial pressure (ICPD) and blood flow velocity parameter (BFVP) monitoring in the ophthalmic artery. (B) Execution of simultaneous ICP_{inv} and BFVP monitoring in Patient 1 with a spontaneous ICP change

5.2.4. Novel non-invasive cerebral autoregulation monitoring by using OA

Two 2-MHz probes were mounted on an individually fitted headframe. The blood flow velocity (BFV) was recorded by using a two-depth transcranial Doppler. A single measurement consisted of an hour's blood flow velocity recording, simultaneously with invasive ABP and ICP recording. The sampling frequency of raw ABP and ICP data was 300 Hz, and the sampling frequency of raw BFV was 1 Hz. The Bandpass-Chebyshev type I filter (specific order 10) was used to extract the slow ABP(t), ICP(t), and BFV(t) waves in the frequency range from 0.0083 to 0.02 Hz (corresponding to a period of 50 sec to 2.0 minutes). The non-invasive CA index by using OA is defined as a non-invasive pressure reactivity index $nPRx(t)$ which is calculated as a moving correlation coefficient between the slow waves of BFV(t) and ABP(t).

$$nRx = r(ABPsw(t); BFVsw(t)) \quad (17)$$

here, nRx – non-invasive pressure reactivity index; $ABPsw$ – arterial blood pressure slow wave; $BFVsw$ – blood flow velocity.

Sample raw signals of $ABP(t)$, $ICP(t)$, and $BFV(t)$ signals, and $nPRx(t)$ and $PRx(t)$ of a TBI patient are presented in **Fig. 5.4**. Positive values for $nPRx(t)$ represent impaired CA, and negative values indicate intact CA (Czosnyka *et al.*, 1997; Czosnyka *et al.*, 2009, 1996).

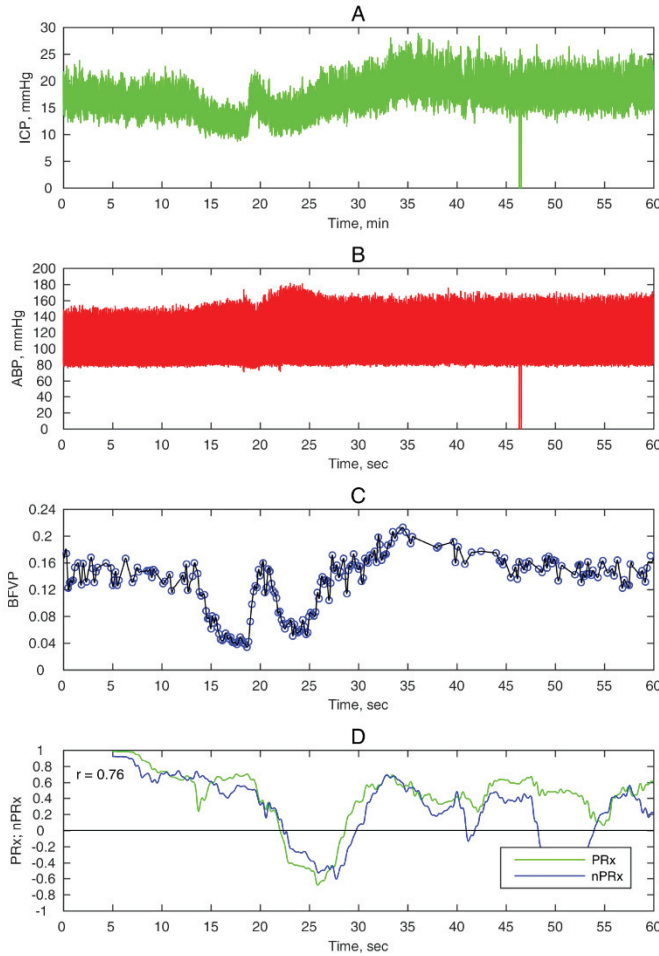


Fig. 5.4. Example of $ICP(t)$, $ABP(t)$, and $IBV(t)$ raw data of monitoring and cerebrovascular autoregulation indexes ($PRx(t)$, $VRx(t)$) calculation for one-hour time interval. Both indexes show similar information about the impairment of CA (when $PRx > 0$, $nPRx > 0$)

5.2.5.Statistical analysis

The Bland Altman plot, also known as the difference plot, is a graphical method to compare two measurement techniques (Bland and Altman, 1999, Bland and Altman, 1986). In this method, the differences between these compared techniques are plotted against the mean of these techniques. The middle horizontal line indicated the total mean of the measured differences, while the other two outer horizontal lines indicate ± 1.96 of the standard deviation (SD) of the measured differences.

Linear regression is the most basic and commonly used predictive analysis which is used to explain the relationship between one dependent variable and one or more independent variables. The maximum and the minimum points of each measurement are detected and used for the calibration of non-invasive ICP monitoring data according to the invasive timeline.

5.3.Results

5.3.1.Patient No. 1

The patient was subjected to 1-hour simultaneous invasive and non-invasive ICP(t) monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. The BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. Raw data is presented in **Fig. 5.5**. The range of invasive ICP fluctuated between 12–22 mmHg.

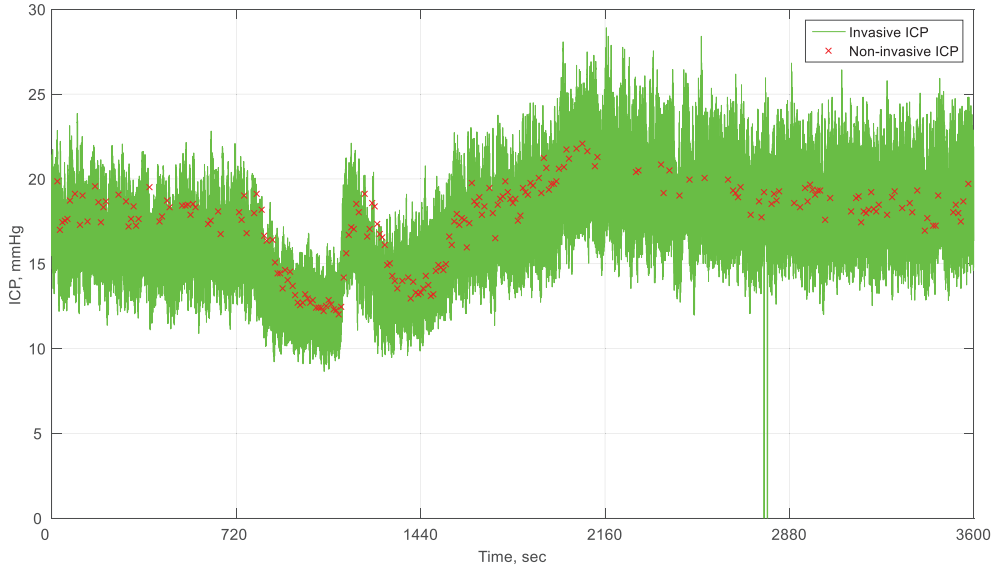


Fig. 5.5. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{non-invasive} = 56.3 \times BFVP + 10.1 \quad 18)$$

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.6**). A 60-sec. moving average filter is used for data filtration. 223 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

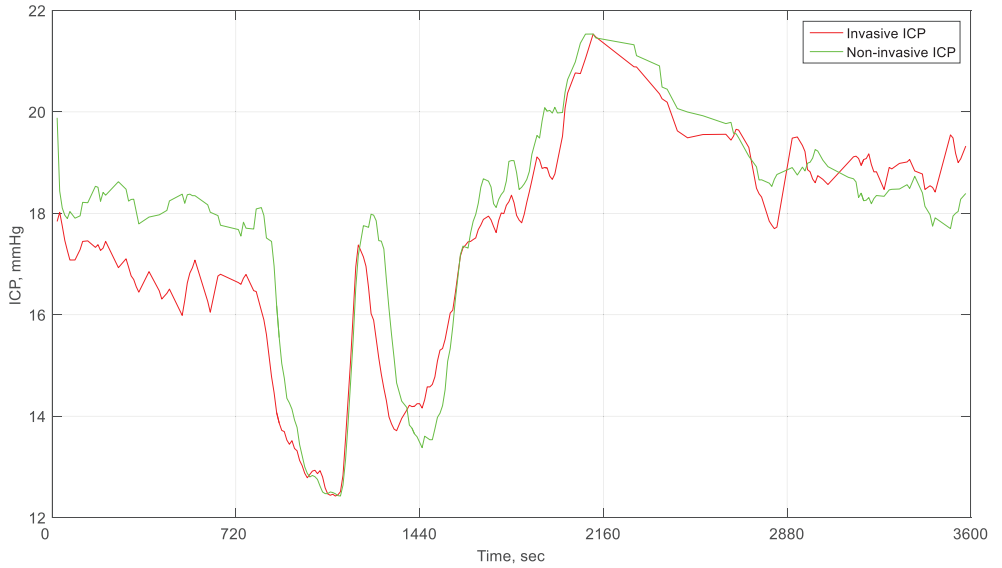


Fig. 5.6. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between the invasively collected ICP monitoring data and the non-invasively collected ICP monitoring data (**Fig. 5.7**). Mean $\pm$ SD is 0.43 ± 0.91 mmHg.

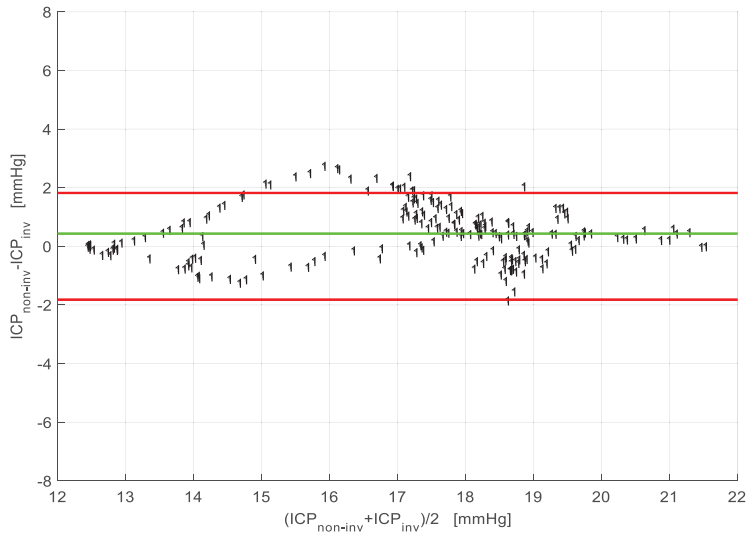


Fig. 5.7. Bland Altman plotting of Patient No. 1

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 223 data points of the first patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.8**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

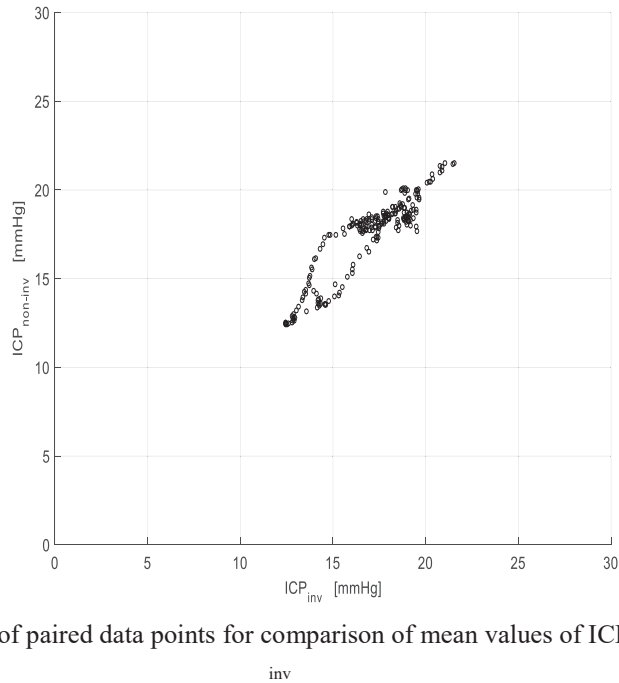


Fig. 5.8. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.2.Patient No. 2

The patient was subjected to 1-hour simultaneous invasive and non-invasive ICP(t) monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. The obtained raw data is presented in **Fig. 5.9**. The range of invasive ICP fluctuated between 16–19 mmHg.

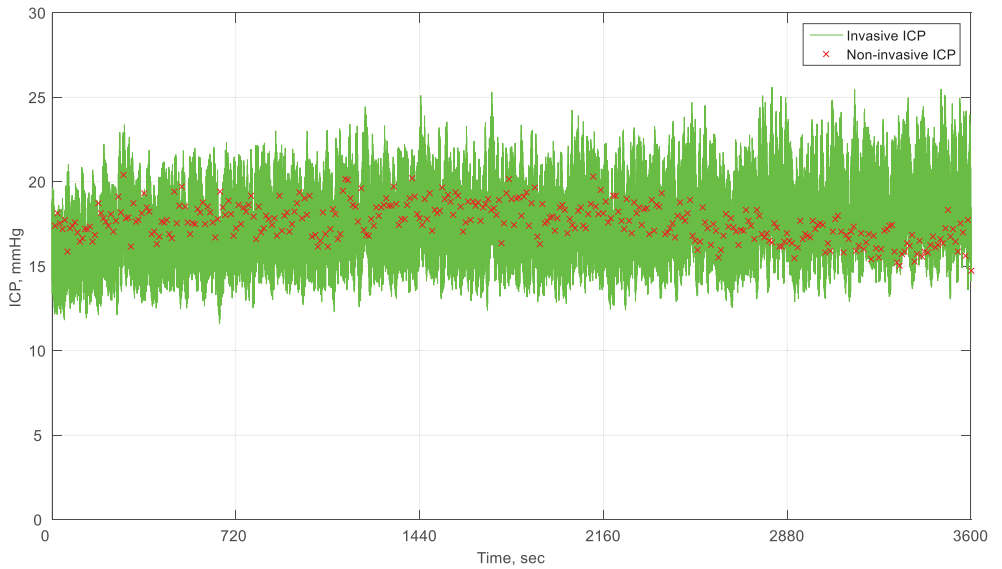


Fig. 5.9. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{invasive}=263.8 \times BFVP + 11.8$$

19)

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.10.**). A 60-sec. moving average filter is used for data filtration. 360 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

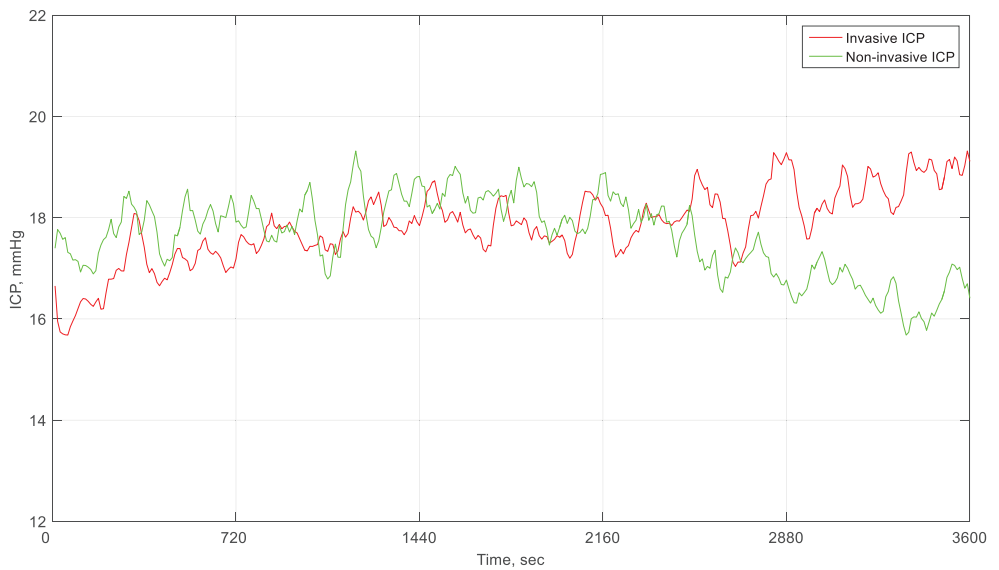


Fig. 5.10. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between the invasively collected ICP monitoring data and the non-invasively collected ICP monitoring data (**Fig. 5.11.**). Mean $\pm$ SD is -0.22 ± 1.23 mmHg.

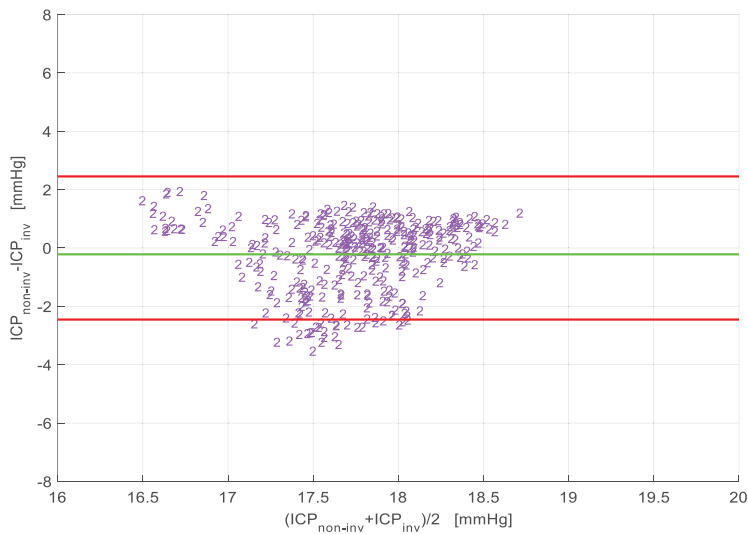


Fig. 5.11. Bland Altman plotting of Patient No. 2

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 360 data points of the second patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.12**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

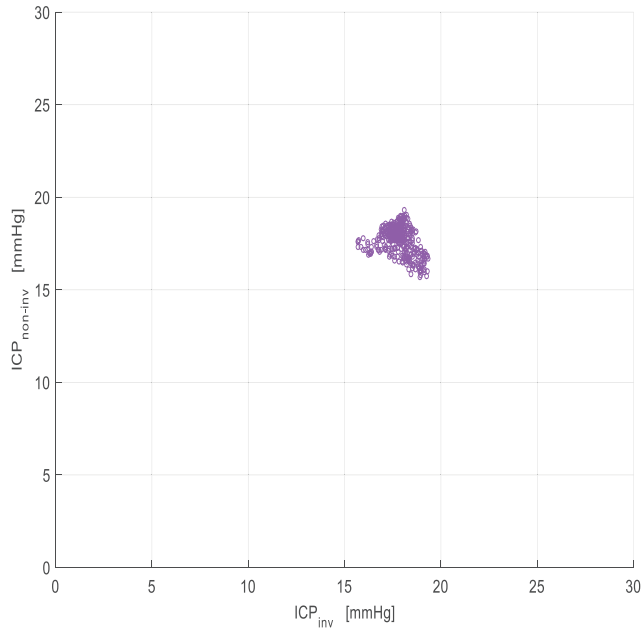


Fig. 5.12. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.3. Patient No. 3

The patient was subjected to 1-hour simultaneous invasive and non-invasive ICP(t) monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. The BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. Raw data is presented in **Fig. 5.13**. The range of invasive ICP fluctuated between 8–11 mmHg.

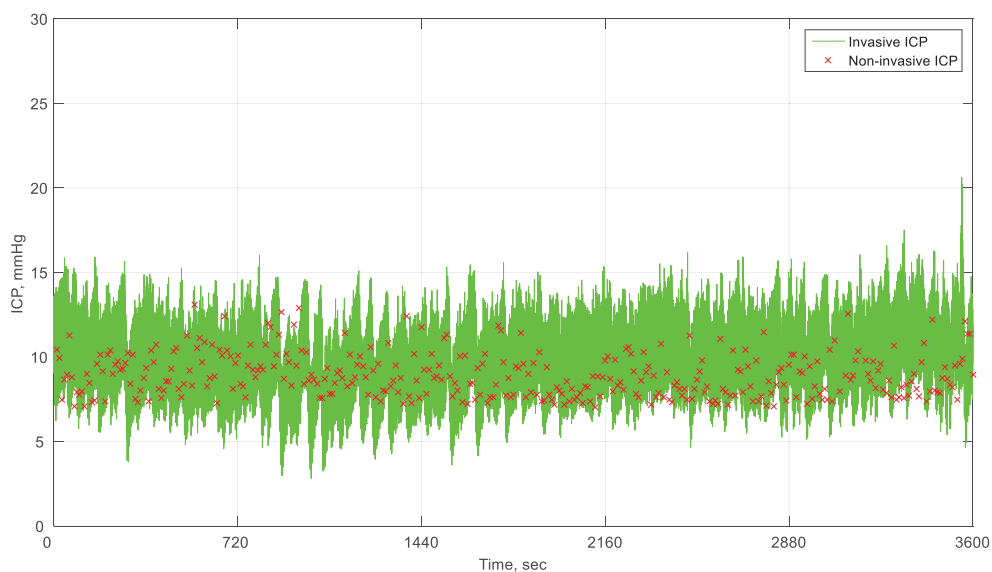


Fig. 5.13. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{invasive} = 70.4 \times BFVP + 6.2 \quad 20)$$

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.14**). A 60-sec. moving average filter was used for filtration. 356 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

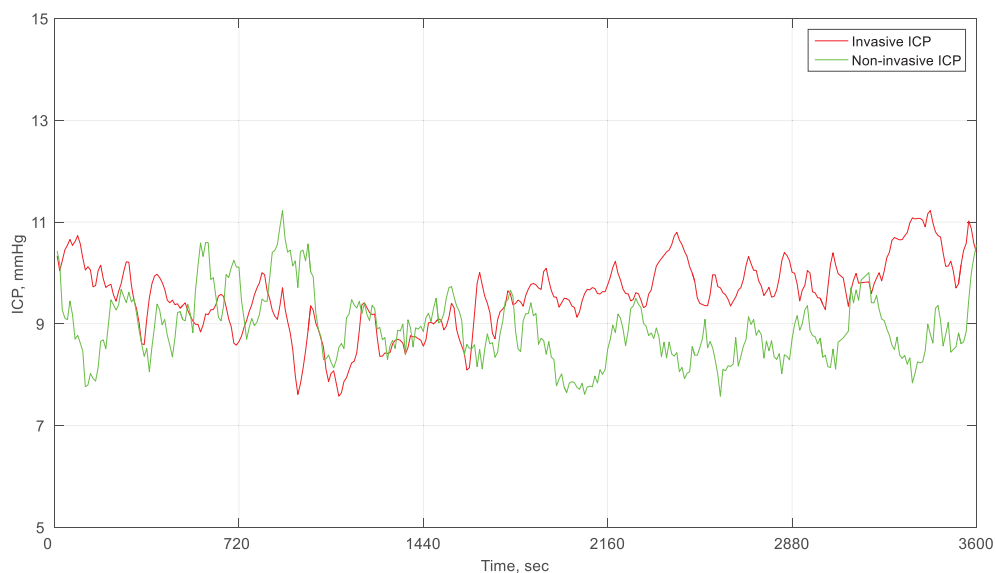


Fig. 5.14. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between invasively collected ICP monitoring data and non-invasively collected ICP monitoring data (**Fig. 5.15.**). Mean $\pm$ SD is -0.65 ± 1.07 mmHg.

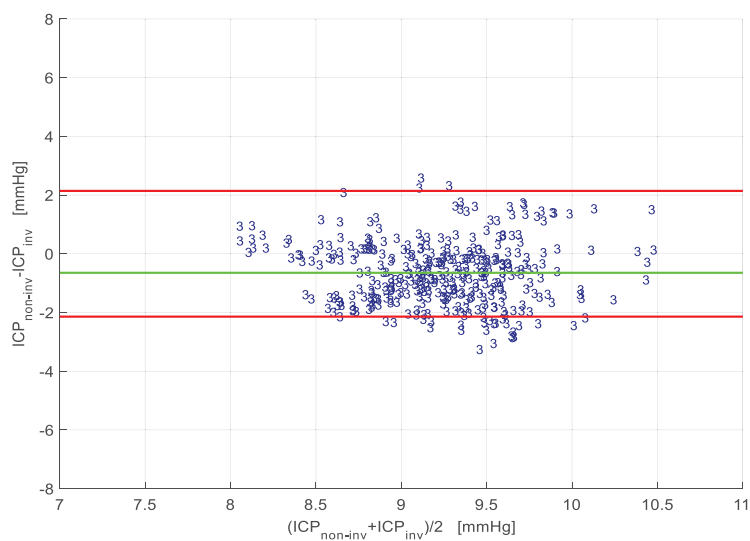


Fig. 5.15. Bland Altman plotting of Patient No. 3

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 356 data points of the third patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.16**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

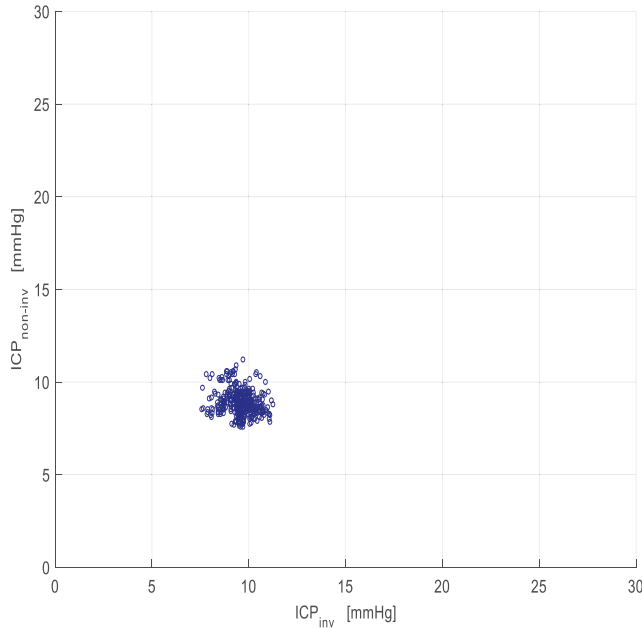


Fig. 5.16. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.4. Patient No. 4

The patient was subjected to 1-hour simultaneous invasive and non-invasive $ICP(t)$ monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. The BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. Raw data is presented in **Fig. 5.17**. The range of invasive ICP fluctuated between 17–33 mmHg.

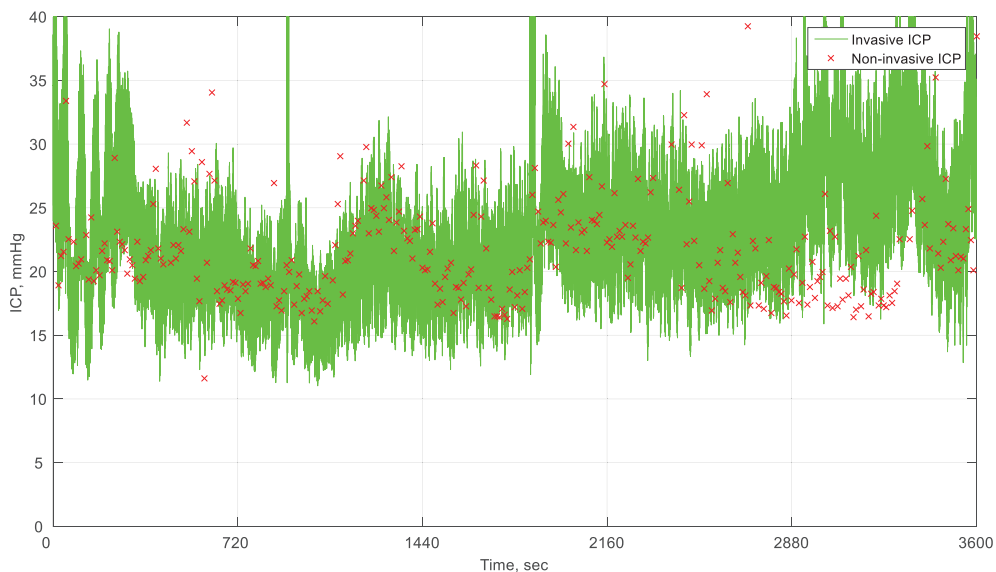


Fig. 5.17. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{invasive} = 298.9 \times BFVP + 11.6 \quad 21)$$

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.18**). A 60-sec. moving average filter is used for data filtration. 340 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

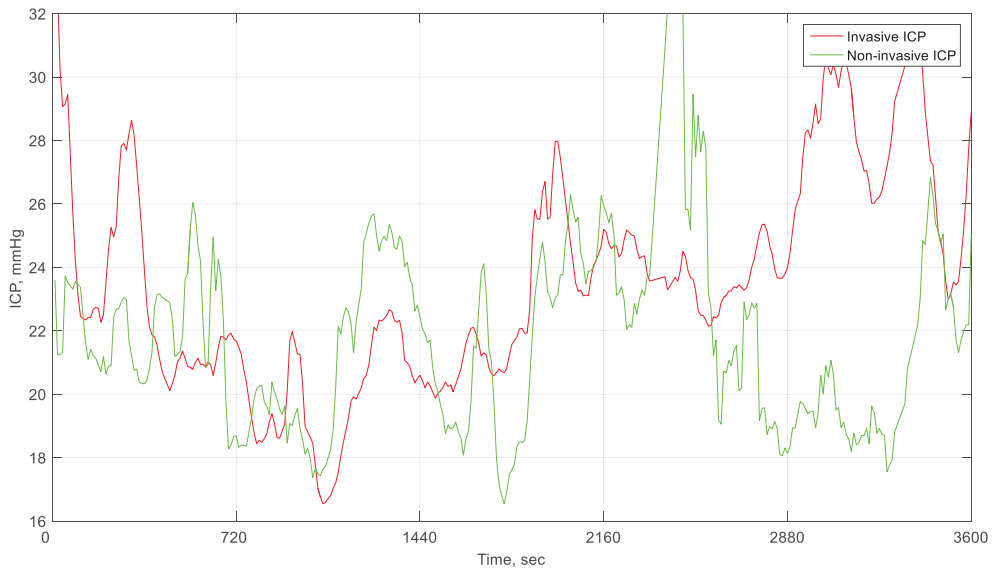


Fig. 5.18. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between invasively collected ICP monitoring data and non-invasively collected ICP monitoring data (**Fig. 5.19.**). Mean $\pm$ SD is -1.70 ± 4.21 mmHg.



Fig. 5.19. Bland Altman plotting of Patient No. 4

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 340 data points of the fourth patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.20**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

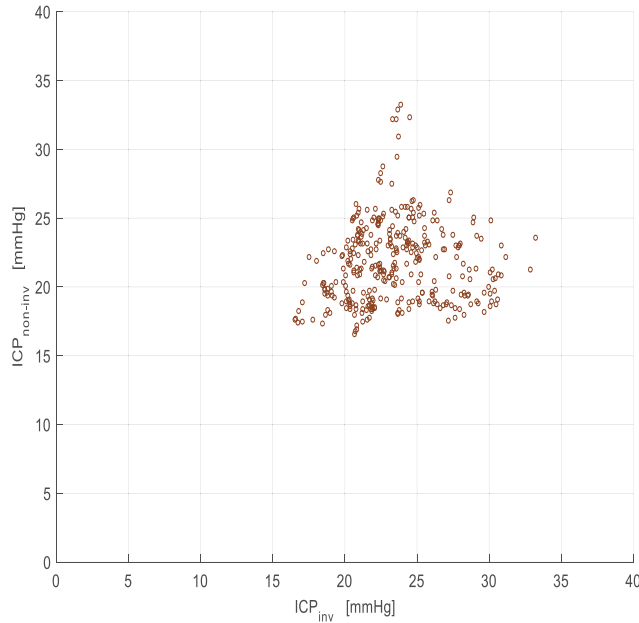


Fig. 5.20. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.5. Patient No. 5

The patient was subjected to 1-hour simultaneous invasive and non-invasive ICP(t) monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. The BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. Raw data is presented in **Fig. 5.21**. The range of invasive ICP fluctuated between 10–19 mmHg.

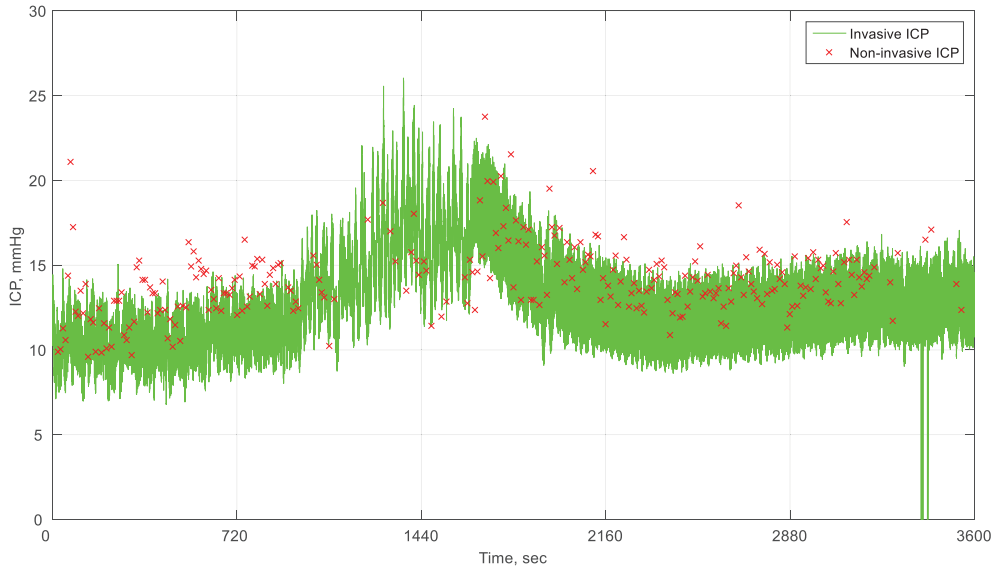


Fig. 5.21. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{invasive} = 218.9 \times BFVP + 4.5 \quad 22)$$

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.22.**). A 60-sec. moving average filter was used for filtration. 280 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

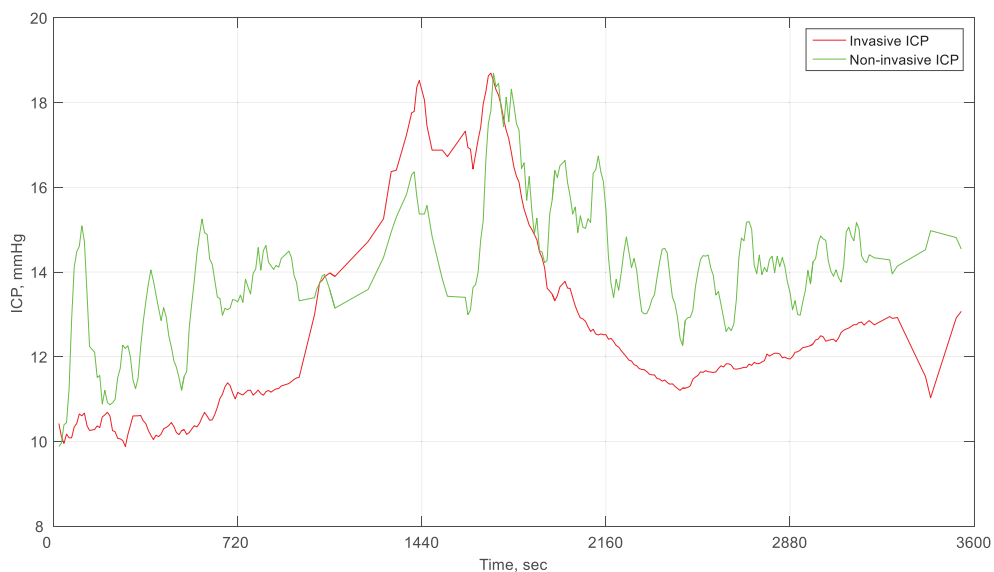


Fig. 5.22. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between invasively collected ICP monitoring data and non-invasively collected ICP monitoring data (**Fig. 5.23.**). Mean $\pm$ SD is 1.61 ± 1.61 mmHg.

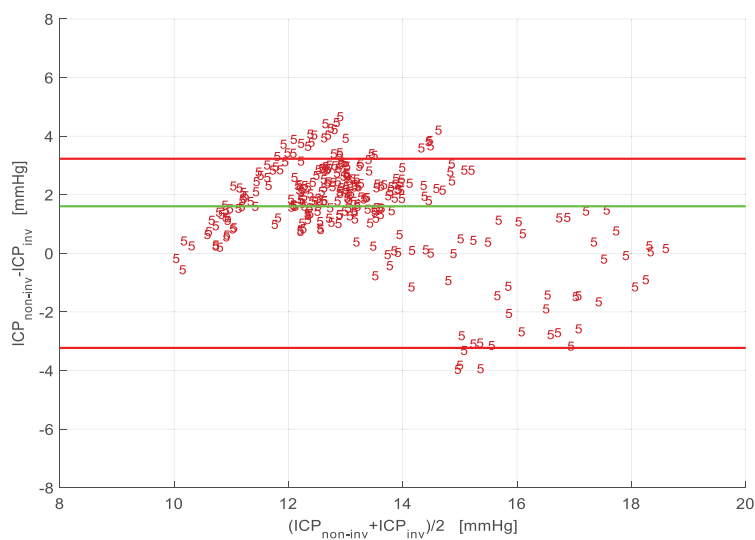


Fig. 5.23. Bland Altman plotting of Patient No. 5

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 280 data points of the fifth patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.24**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

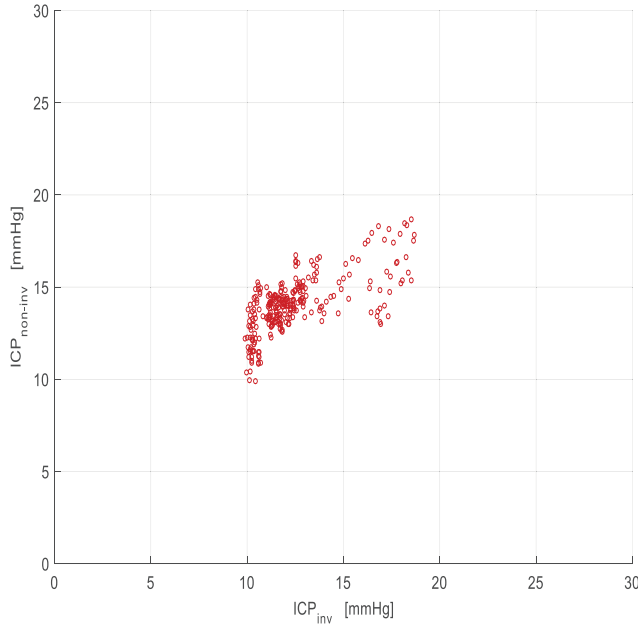


Fig. 5.24. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.6. Patient No. 6

The patient was subjected to 1-hour simultaneous invasive and non-invasive ICP(t) monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. The BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. Raw data is presented in **Fig. 5.25**. The range of invasive ICP fluctuated between 8–10 mmHg.

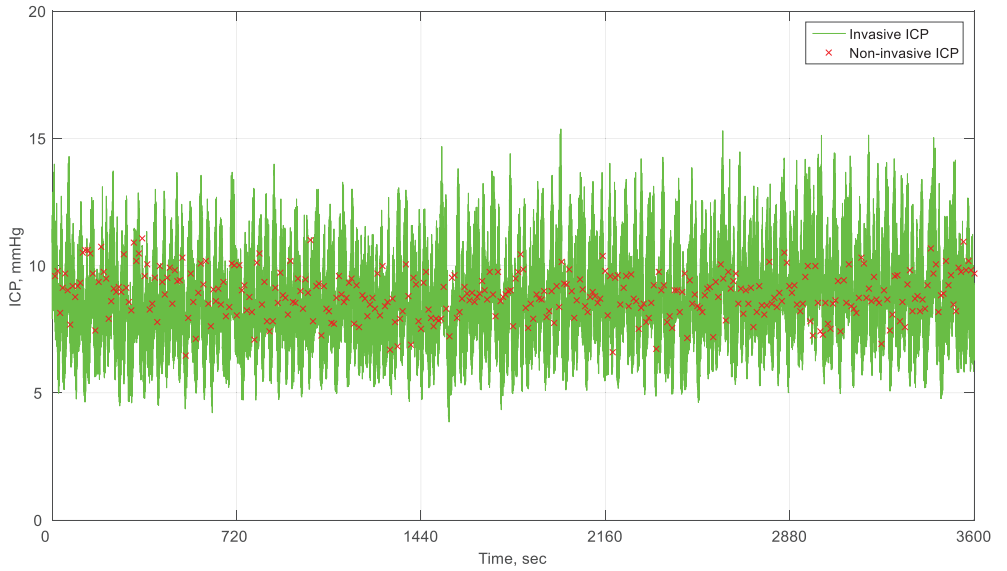


Fig. 5.25. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{invasive} = 109.8 \times BFVP + 5.8 \quad 23)$$

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.26**). A 60-sec. moving average filter was used for filtration. 360 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

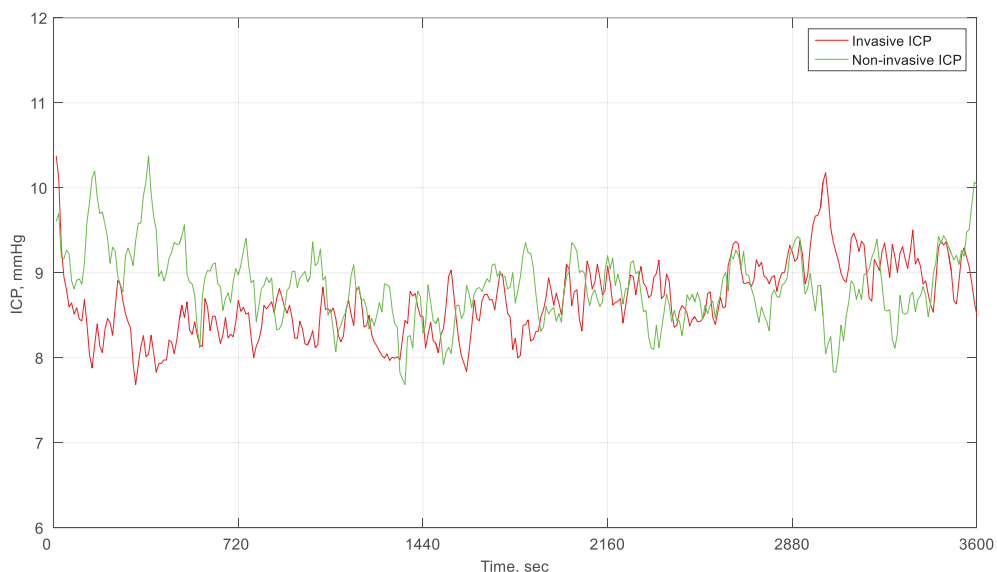


Fig. 5.26. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between invasively collected ICP monitoring data and non-invasively collected ICP monitoring data (**Fig. 5.27.**). Mean $\pm$ SD is 0.18 ± 0.64 mmHg.

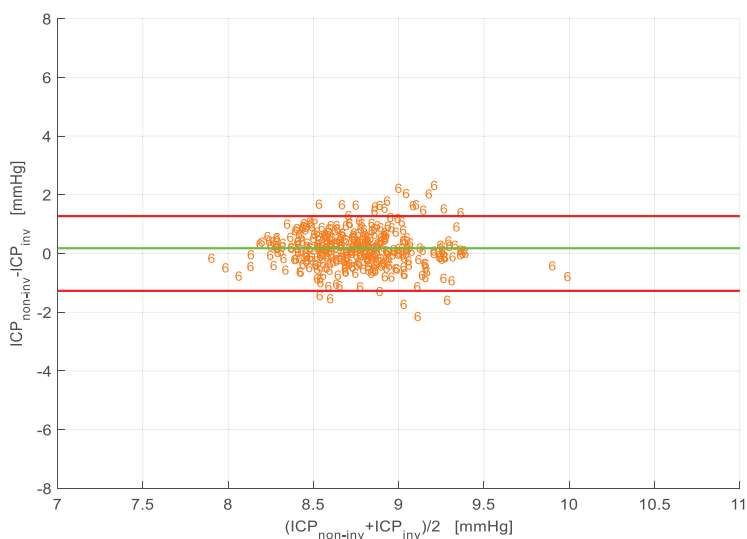


Fig. 5.27. Bland Altman plotting of Patient No. 6

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 360 data points of the sixth patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.28**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

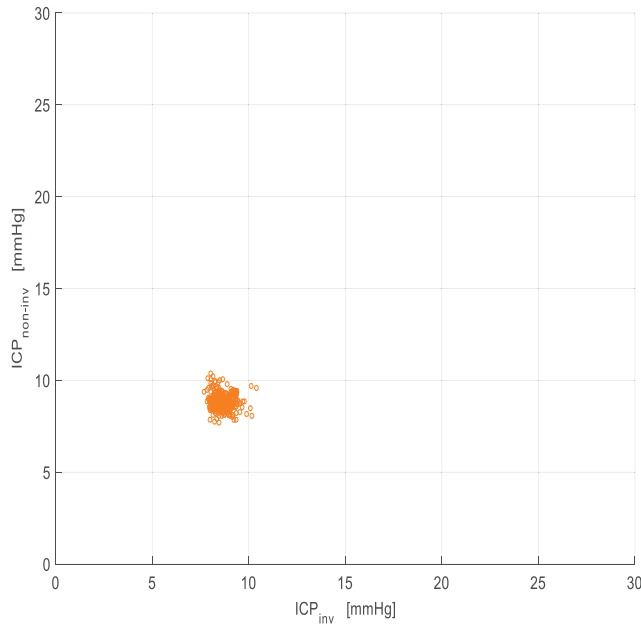


Fig. 5.28. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.7. Patient No. 7

The patients were subjected to 1-hour simultaneous invasive and non-invasive ICP(t) monitoring sessions. An invasive Codman ICP monitor with an Intraparenchymal catheter tip sensor measured direct ICP. 50 samples per second were collected with the invasive ICP monitoring setup. The BFVP monitoring by TCD was used to collect non-invasive ICP samples. A sample per 10 seconds was collected with the non-invasive ICP monitoring setup. Raw data is presented in **Fig. 5.29**. The range of invasive ICP fluctuated between 13–17 mmHg.

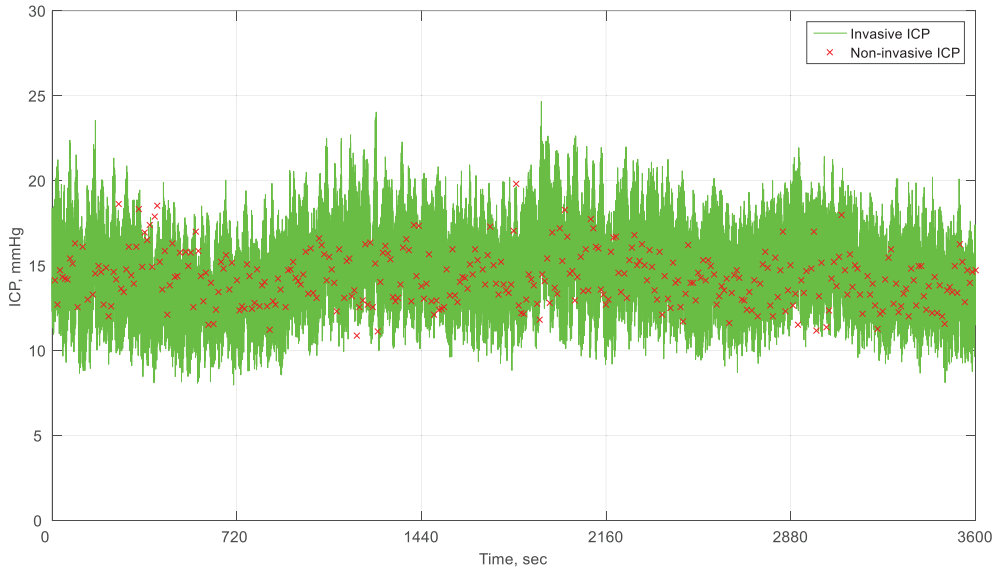


Fig. 5.29. RAW data (invasive: 50 samples per sec. Non-invasive: 1 sample per 10 sec. after calibration)

After detecting the minimum and maximum values in both the blood flow velocity parameter data collected by TCD and the invasive ICP monitoring data, the linear calibration equation is obtained. The calibration equation is used to calculate non-invasive ICP from the blood flow velocity parameter:

$$ICP_{invasive} = 586.2 \times BFVP + 6.9 \quad (24)$$

here, $ICP_{non-invasive}$ – non-invasive ICP, BFVP – blood flow velocity parameter.

Calibrated BFVP data is plotted with invasive ICP data (**Fig. 5.30.**). A 60-sec. moving average filter was used for filtration. 349 data points are paired in this comparison of invasive ICP monitoring and non-invasive ICP monitoring.

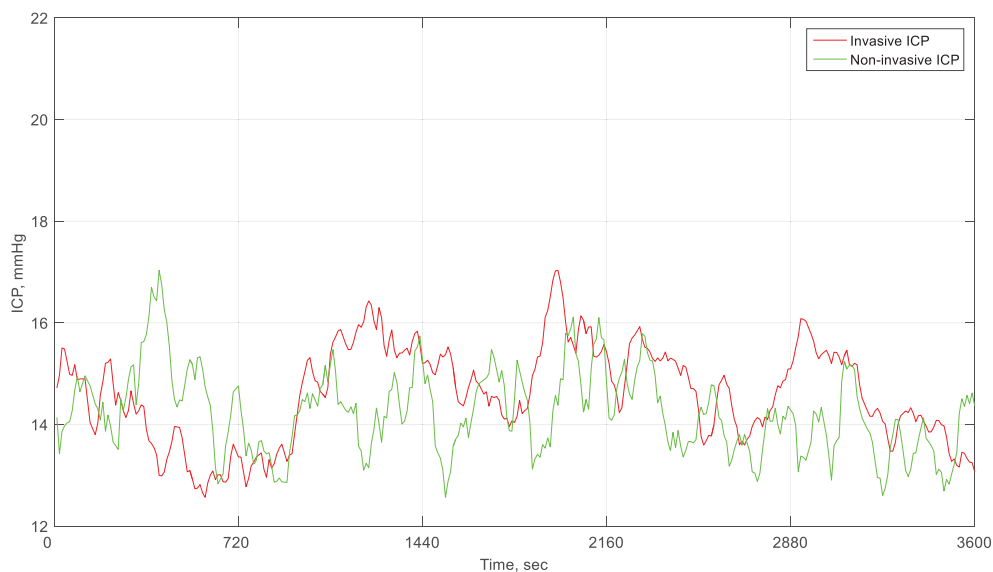


Fig. 5.30. Paired invasive and non-invasive data points after filtering (60-sec. moving average filter)

Bland Altman plotting was used between invasively collected ICP monitoring data and non-invasively collected ICP monitoring data (**Fig. 5.31.**). Mean $\pm$ SD is -0.39 ± 1.20 mmHg.

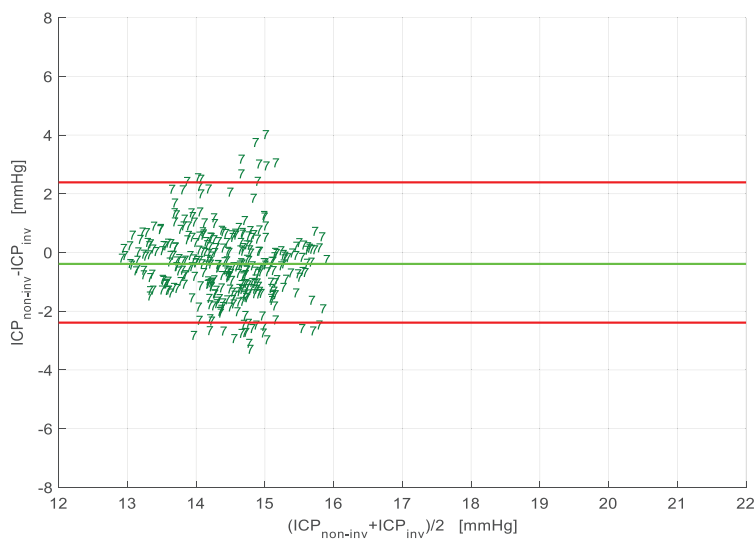


Fig. 5.31. Bland Altman plotting of Patient No. 7

Paired invasive ICP and non-invasive ICP data points were collected on an individual patient with different mean ICP values in different treatment situations. Therefore, the plot of paired 349 data points of the seventh patient for a comparison of the mean values of ICP_{inv} and $ICP_{non-inv}$ is shown in **Fig. 5.32**. The figure of the individual patient is included not for the demonstration of the correlation of invasive and non-invasive methods but actually for the demonstration of the individual mean ICP values and paired data points' distributions for stabilized patients with different TBIs and different mean ICP values.

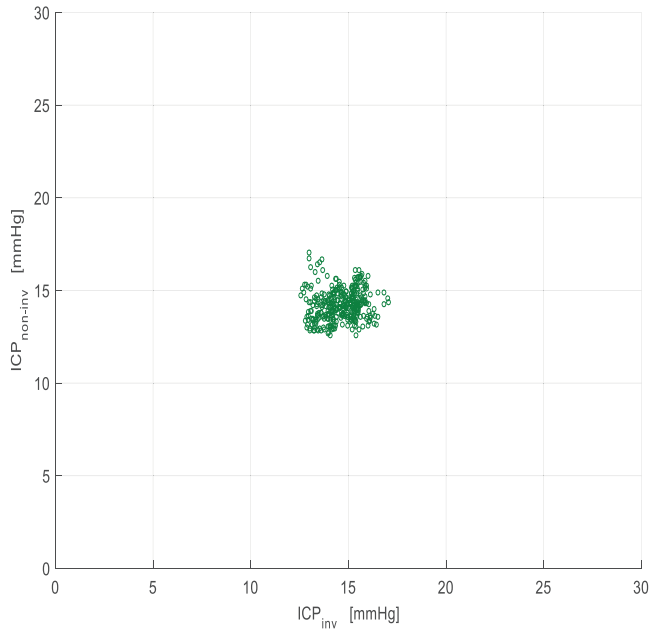


Fig. 5.32. Plot of paired data points for comparison of mean values of ICP_{inv} and $ICP_{non-inv}$

5.3.8. Novel non-invasive cerebral autoregulation monitoring using OA

Non-invasive nPRx indexes were monitored simultaneously with invasive PRx indexes during the comparative monitoring sessions for 6 TBI patients. Patient No. 4 was excluded due to lack of invasive ABP monitoring data. Preliminary results showed that the novel CA monitoring by using OA exhibited significant coincidence with the invasive PRx index. A future prospective study is suggested with a sufficient sample size in order to achieve statistical significance.

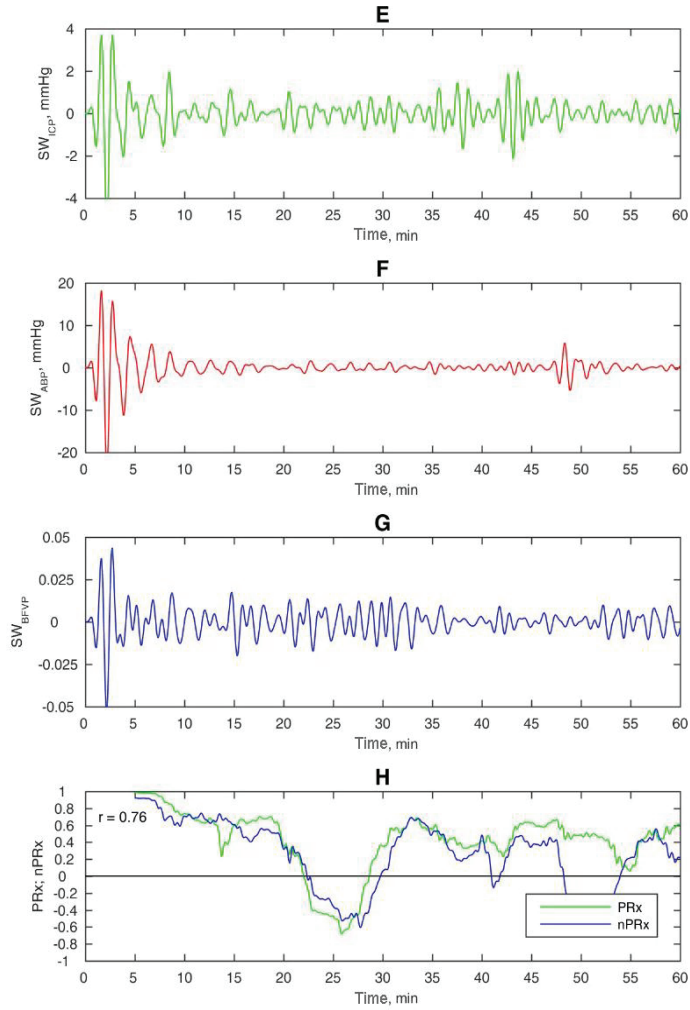


Fig. 5.33. Example of filtered slow waves of ICP(t), ABP(t), and BFVP(t) and cerebrovascular autoregulation indexes (PRx(t), VRx(t)) calculation for one-hour time interval. Both indexes show similar information about the impairment of CA (when PRx>0, nPRx>0). The correlation coefficient between ICP(t) and BFV(t) slow waves is 0.76, thus showing that it is possible to use BFVP slow waves as ICP surrogate for calculating the nPRx index.

5.4. Discussion

This study provides the first clinical data of non-invasive ICP monitoring with a two-depth transcranial Doppler in patients undergoing an invasive ICP monitoring procedure for TBI. The results demonstrate the accuracy and precision of the non-invasive ICP monitoring method compared with the invasive ICP monitoring method. We analyzed head trauma patients with spontaneous ICP variation from 8 to 33 mmHg. The data points of continuous parallel recordings of ICP values were obtained from a two-depth transcranial Doppler and an invasive Codman ICP monitor simultaneously. The total of 2,268 paired data points was obtained in the comparison of these two methods. The overall findings show a good correlation between the monitoring data collected with these two methods and show promising evidence that it is possible to monitor ICP non-invasively in patients with TBI. The total mean and SD of the measured differences between non-invasive ICP monitoring and invasive ICP monitoring are -0.18 ± 2.14 mmHg. The Bland Altman plot showed good concordance between these two monitoring methods. 95% of the observations of these compared methods fall in the interval -4.38 to 4.02 mmHg.

The ROC curve analysis shows that the non-invasive ICP monitoring device is denoted by good performance for monitoring ICP comparing to the invasive ICP monitoring device. The area under the curve (AUC) is 0.97 (95% CI = 0.96 to 0.98), the sensitivity is 0.87 (95% CI = 0.85 to 0.89), the specificity is 0.91 (95% CI = 0.90 to 0.93) when the threshold of 14.7 mmHg cutoff used. The linear regression analysis (2,268 data points, which is the total number of data points) shows a strong linear relationship between non-invasive ICP monitoring and invasive ICP monitoring, the correlation coefficient is $R^2 = 0.830$.

Up to date, invasive ICP monitoring is a fundamental tool for the decision regarding a patient's treatment in neurocritical intensive care units. In the case of invasive ICP monitoring, intraparenchymal and intraventricular monitors are the standard choice. Arguably, the intraventricular monitoring method is considered as the gold standard for ICP monitoring. The intraventricular method allows therapeutic CSF drainage and clearance of intraventricular blood (Berlin, Murray-Krezan, & Yonas, 2015; Ganslandt, Mourtzoukos, Stadlbauer, Sommer, & Rammensee, 2018; Kakarla, Kim, Chang, Theodore, & Spetzler, 2008; Rosenberg *et al.*, 2011). The intraventricular monitoring method is meant to offer continuous monitoring as well as drainage but is not meant to perform both of them simultaneously (Ganslandt *et al.*, 2018). In this method, the valve for drainage is kept closed during ICP measurement/monitoring.

The accuracy of ventricular (or EVD) ICP monitor depends on periodically opening the transducer to atmospheric pressure and returning it to the zero-reference point (Schimpf, 2012). The patient's positioning in relation to the transducer affects the accuracy of ICP readings (Zhong *et al.*, 2003). Complications in the case of ventricular catheters are 1%–10% risk of infection and 1%–2% risk of bleeding (Littlejohns & Bader, 2009). Parenchymal monitoring devices also require calibration and zeroing, even the pneumatic ICP monitor runs recalibration each 15 min during monitoring. The risk of a complication in the case of parenchymal monitoring is lower compared to ventricular catheters but still exists (Littlejohns & Bader, 2009). The suggested method based on continuous measuring of the pulsatility index of the blood flow in the intracranial and extracranial segments of the ophthalmic artery simultaneously can monitor ICP non-invasively for a 1-hour time period without recalibration. In this pilot study, we used an invasive ICP sensor for the initial calibration, however, a non-invasive ICP snapshot measurement technique which is based on TCD can be used for the initial calibration. In this case, the suggested method would be completely non-invasive to avoid any complication caused by invasive procedures.

5.5. Conclusions

The individual linear calibration equation (**Table 5.4.**) was used for each patient to transform monitored BFVP in the pressure units for a comparison with simultaneously monitored ICP_{inv}. A total of 2,268 paired data points was obtained for the final comparison from all 7 patients. The corresponding individual number of the paired data points is presented in **Table 5.4.** The total mean and SD of the measured differences between ICP_{inv} and ICP_{non-inv} is -0.18 ± 2.14 mmHg. The individual means and SDs are presented in Table 5.4.

Table 5.4. Individual parameters obtained from each patient

Pat. No.	Range of ICP _{inv} , min - max, mmHg	Calibration equation used to calculate ICP _{non-inv}	Measured differences, mean $\pm$ SD	Number of paired data points
1	12 – 22	$56.3 \times \text{BFVP} + 10.1$	0.43 ± 0.91	223
2	16 – 19	$263.8 \times \text{BFVP} + 11.8$	-0.22 ± 1.23	360
3	8 – 11	$70.4 \times \text{BFVP} + 6.2$	-0.65 ± 1.07	356
4	17 – 33	$298.9 \times \text{BFVP} + 11.6$	-1.70 ± 4.21	340
5	10 – 19	$218.9 \times \text{BFVP} + 4.5$	1.61 ± 1.61	280
6	8 – 10	$109.8 \times \text{BFVP} + 3.8$	0.18 ± 0.64	360
7	13 – 17	$586.2 \times \text{BFVP} + 6.9$	-0.39 ± 1.20	349

The measured differences are presented in **Figure 5.34.** as a Bland Altman plot for a one-minute moving average filter. The extremes are -11.74 and 9.33

mmHg, and 95% of the observations fall in the uncertainty interval of -4.38 to 4.02 mmHg.

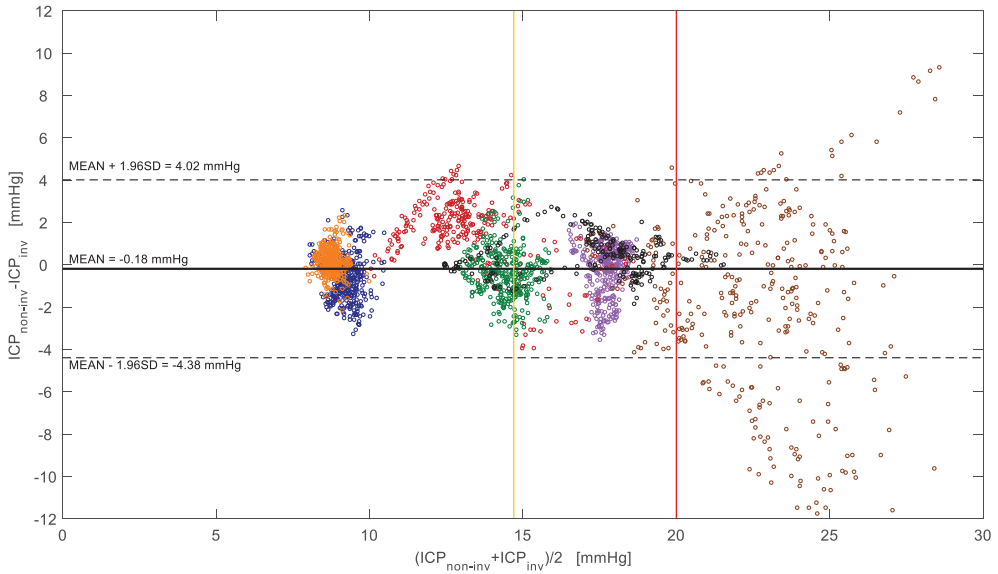


Figure 5.34. When using one-min moving average filter for ICP_{inv} and $ICP_{non-inv}$ data, Bland Altman plot shows the distribution of the measured differences between intracranial pressure monitored directly by using invasive Codman ICP monitor (ICP_{inv}) and indirectly using non-invasive two-depth transcranial Doppler ($ICP_{non-inv}$) in the entire pressure range obtained in all 7 patients. Paired data points collected from each of 7 patients are colored differently: first patient – black color, second patient – violet color, third patient – blue color, fourth patient – brown color, fifth patient – red color, sixth patient – orange color, seventh patient – green color. The thick horizontal line indicates the total mean of the measured differences while two dashed horizontal lines indicate ± 1.96 of the standard deviation (SD) of the measured differences. The yellow vertical line indicates a threshold of 14.7 mmHg which is considered as an elevated ICP in neurology, the red vertical line indicates a threshold of 20 mmHg which is usually used as an indicator to start treatment in neurosurgery

The measured differences are presented in **Figure 5.35.** as a Bland Altman plot for a two-minute moving average filter. The extremes are -11.74 and 9.33 mmHg, and 95% of the observations fall in the uncertainty interval of -4.14 to 4.05 mmHg.

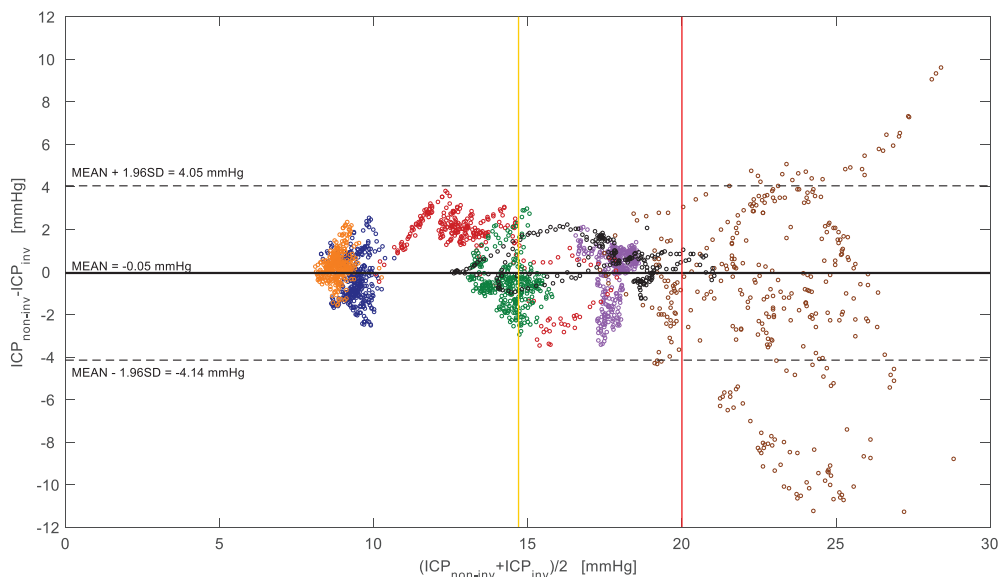


Figure 5.35. When using 2-min moving average filter for ICP_{inv} and $ICP_{non-inv}$ data, Bland Altman plot shows the distribution of the measured differences between intracranial pressure monitored directly by using invasive Codman ICP monitor (ICP_{inv}) and indirectly using non-invasive two-depth transcranial Doppler ($ICP_{non-inv}$) in the entire pressure range obtained in all 7 patients. Paired data points collected from each of 7 patients are colored differently: first patient – black color, second patient – violet color, third patient – blue color, fourth patient – brown color, fifth patient – red color, sixth patient – orange color, seventh patient – green color. The thick horizontal line indicates the total mean of the measured differences while two dashed horizontal lines indicate ± 1.96 of the standard deviation (SD) of the measured differences. The yellow vertical line indicates a threshold of 14.7 mmHg which is considered as an elevated ICP in neurology, the red vertical line indicates a threshold of 20 mmHg which is usually used as an indicator to start treatment in neurosurgery

The measured differences are presented in **Figure 5.36.** as a Bland Altman plot for a five-minute moving average filter. The extremes are -11.74 and 9.33 mmHg, and 95% of the observations fall in the uncertainty interval of -3.90 to 4.61 mmHg.

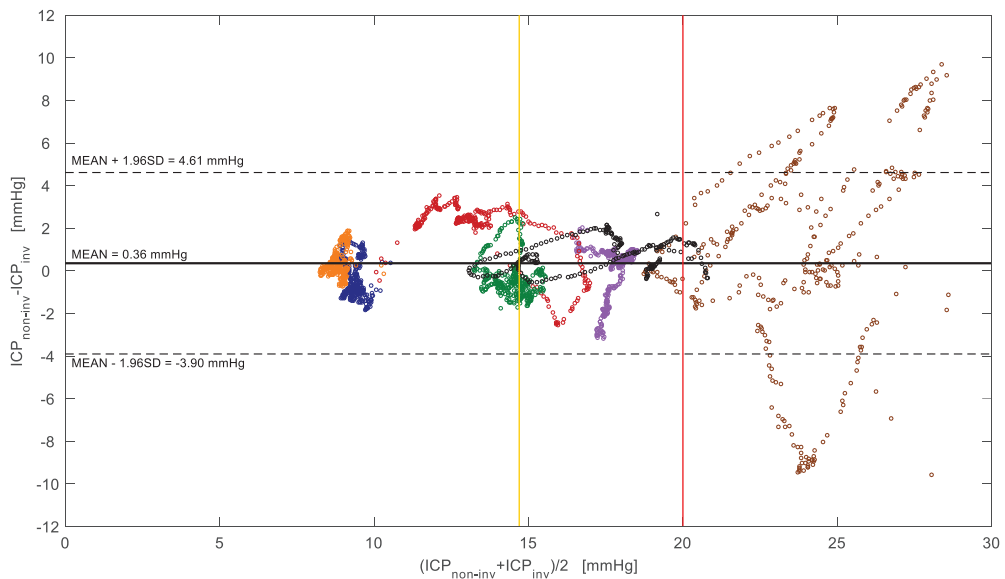


Figure 5.36. When using 5-min moving average filter for ICP_{inv} and $ICP_{non-inv}$ data, Bland Altman plot shows the distribution of the measured differences between intracranial pressure monitored directly by using invasive Codman ICP monitor (ICP_{inv}) and indirectly using non-invasive two-depth transcranial Doppler ($ICP_{non-inv}$) in the entire pressure range obtained in all 7 patients. Paired data points collected from each of 7 patients are colored differently: first patient – black color, second patient – violet color, third patient – blue color, fourth patient – brown color, fifth patient – red color, sixth patient – orange color, seventh patient – green color. The thick horizontal line indicates the total mean of the measured differences while two dashed horizontal lines indicate ± 1.96 of the standard deviation (SD) of the measured differences. The yellow vertical line indicates a threshold of 14.7 mmHg which is considered as an elevated ICP in neurology, the red vertical line indicates a threshold of 20 mmHg which is usually used as an indicator to start treatment in neurosurgery

As presented in **Fig.5.37.**, the ROC curve analysis revealed AUC of 0.97 (95% CI = 0.96 to 0.98), which corresponds to the overall performance of the noninvasive ICP monitoring and suggests that it correctly identifies ICP values with a statistically significant value $P < 0.0001$. The threshold cutoff value is 14.7 mmHg. The accuracy, precision, sensitivity and specificity for non-invasive ICP monitoring were found to be **0.99** (95% CI = 0.90 to 0.91), **0.91** (95% CI = 0.90 to 0.91), **0.87** (95% CI = 0.85 to 0.89) and **0.91** (95% CI = 0.90 to 0.93), respectively.

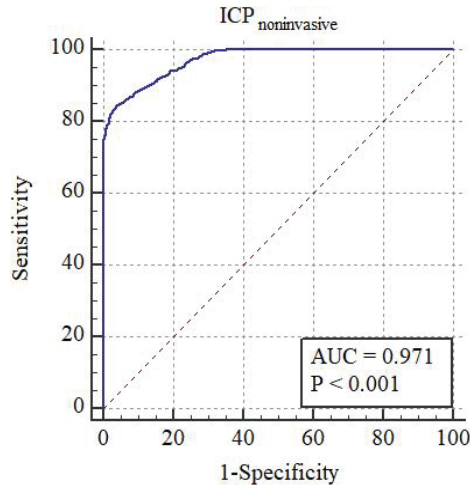


Fig. 5. 37. ROC curve for all measurements. AUC is 0.971. Threshold cutoff value is ≥ 14.7 mmHg. Significance level P is (Area=0.5) < 0.001

Equation $ICP_{non-inv} = 0.83 * ICP_{inv} + 2.27$ was found to be the best fit according to the linear regression analysis of all 2,268 data points in the case of using a one-min moving average filter (**Fig. 5.38**). The linear regression analysis shows that there is a strong positive relationship between the monitoring data obtained with a two-depth transcranial Doppler and a Codman ICP monitor. The correlation coefficient is $R = 0.91$.

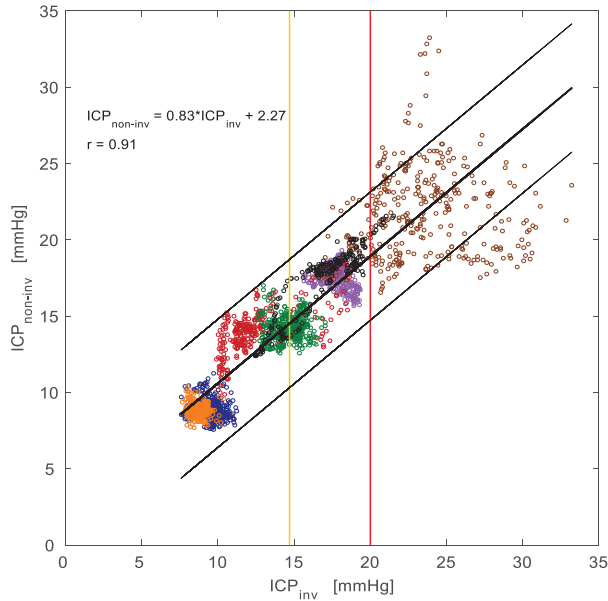


Fig. 5. 38. When using a one-min moving average filter for ICP_{inv} and $ICP_{non-inv}$ data, the Linear regression graph of all measurements shows a strong positive relationship ($r=0.91$) between the non-invasively obtained intracranial pressure values ($ICP_{non-inv}$) and the invasive ICP values (ICP_{inv}). Paired data points collected from each of 7 patients are colored differently: first patient – black color, second patient – violet color, third patient – blue color, fourth patient – brown color, fifth patient – red color, sixth patient – orange color, seventh patient – green color. The thick inclined line indicates the best linear fit between ICP_{inv} and $ICP_{non-inv}$ ($ICP_{non-inv}=0.83 \cdot ICP_{inv}+2.27$), while two dashed inclined lines indicate ± 1.96 of the standard deviation (SD) of the linear fit. The yellow vertical line indicates a threshold of 14.7 mmHg which is considered as an elevated ICP in neurology, the red vertical line indicates a threshold of 20 mmHg which is usually used as an indicator to start treatment in neurosurgery

Equation $ICP_{non-inv} = 0.85 \cdot ICP_{inv} + 2.19$ was found to be the best fit according to the linear regression analysis of all 2,268 data points in the case of using a 2-min moving average filter (**Fig. 5.39**). The linear regression analysis shows that there is a strong positive relationship between the monitoring data obtained with a two-depth transcranial Doppler and a Codman ICP monitor. The correlation coefficient is $R = 0.92$.

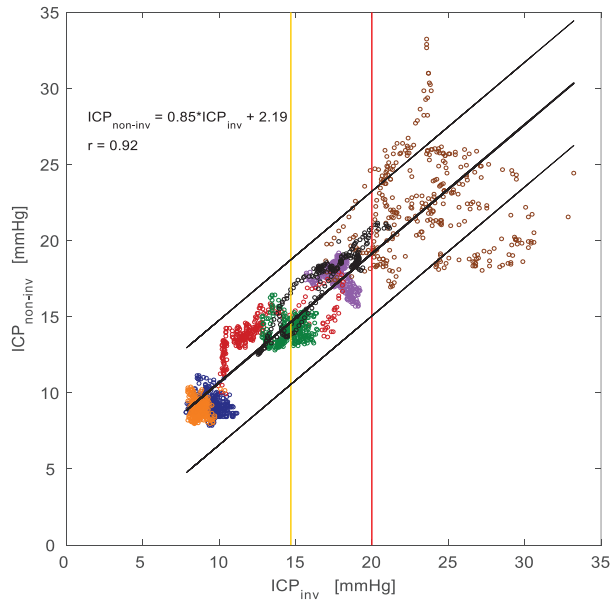


Fig. 5.39. When using a 2-min moving average filter for ICP_{inv} and ICP_{non-inv} data, the Linear regression graph of all measurements shows a strong positive relationship ($r=0.92$) between the non-invasively obtained intracranial pressure values (ICP_{non-inv}) and the invasive ICP values (ICP_{inv}). Paired data points collected from each of 7 patients are colored differently: first patient – black color, second patient – violet color, third patient – blue color, fourth patient – brown color, fifth patient – red color, sixth patient – orange color, seventh patient – green color. The thick inclined line indicates the best linear fit between ICP_{inv} and ICP_{non-inv} ($ICP_{non-inv} = 0.85 \cdot ICP_{inv} + 2.19$), while two dashed inclined lines indicate ± 1.96 of the standard deviation (SD) of the linear fit. The yellow vertical line indicates a threshold of 14.7 mmHg which is considered as an elevated ICP in neurology, the red vertical line indicates a threshold of 20 mmHg which is usually used as an indicator to start treatment in neurosurgery

Equation $ICP_{non-inv} = 0.95 \cdot ICP_{inv} + 1.03$ was found to be the best fit according to the linear regression analysis of all 2,268 data points in the case of using a 5-min moving average filter (**Fig. 5.40**). The linear regression analysis shows that there is a strong positive relationship between the monitoring data obtained with a two-depth transcranial Doppler and a Codman ICP monitor. The correlation coefficient is $R = 0.92$.

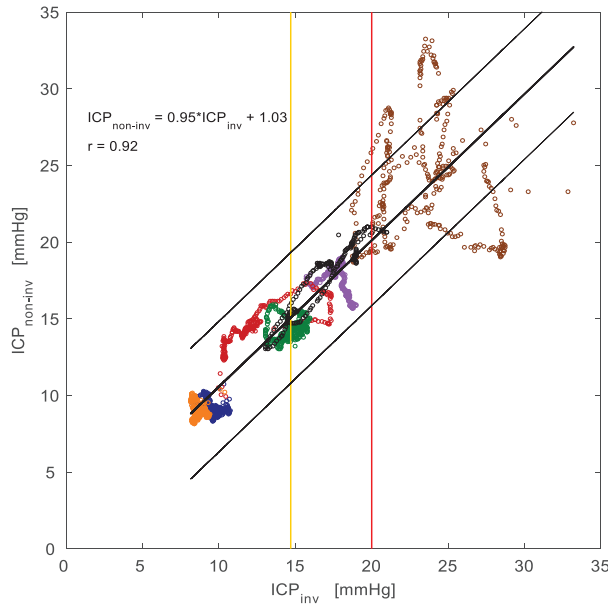


Fig. 5. 40. When using a 5-min moving average filter for ICP_{inv} and $ICP_{non-inv}$ data, the Linear regression graph of all measurements shows a strong positive relationship ($r=0.92$) between the non-invasively obtained intracranial pressure values ($ICP_{non-inv}$) and the invasive ICP values (ICP_{inv}). Paired data points collected from each of 7 patients are colored differently: first patient – black color, second patient – violet color, third patient – blue color, fourth patient – brown color, fifth patient – red color, sixth patient – orange color, seventh patient – green color. The thick inclined line indicates the best linear fit between ICP_{inv} and $ICP_{non-inv}$ ($ICP_{non-inv}=0.95 \cdot ICP_{inv} + 1.03$) while two dashed inclined lines indicate ± 1.96 of the standard deviation (SD) of the linear fit. The yellow vertical line indicates a threshold of 14.7 mmHg which is considered as an elevated ICP in neurology, the red vertical line indicates a threshold of 20 mmHg which is usually used as an indicator to start treatment in neurosurgery

5.6. Source of errors

There are several sources of errors in the non-invasive ICP monitoring method based on transcranial Doppler ultrasonography.

TCD ultrasonography is a blind method, which means that the operator is not able to control the angle between the visualized vessel and the ultrasound beam, which can be a source of an error in the velocity measurement (Aaslid *et al.*, 1982; Mariak, Krejza, Swiercz, Kordecki, & Lewko, 2002). As the angle approaches 90° and $\cos \theta$ approaches zero, the signal would be lost, and the greatest error in measurement would occur. It is recommended that the most accurate measurements can be obtained when $\theta < 60^\circ$ in the flow velocity measurement (Kirsch, 2016). In the clinical practice, this angle is accepted to be relatively small, therefore, it may introduce a small and acceptable error in the flow velocity measurements.

When the elasticity of the vessel increases, a decrease in the flow resistance can be expected, which is represented by the decreased pulsatility index and which influences the waveform of the transcranial Doppler signal (Holzschuh, Woertgen, & Brawanski, 1996). The lower regional CSF and higher cerebrovascular reactivity can occur in the case of greater aortic stiffening (Jefferson *et al.*, 2018).

Aging modifies the structures of the blood vessels, which then leads to stiffness in vessels, impaired endothelial function, and the ratio of the diastolic to systolic diameter as well as the peak expansion velocity drop significantly (Schmidt-Trucksass *et al.*, 1999). By the age of 40, the blood flow velocity decreases, which can lead to an increase in pulsatility in the middle, anterior and posterior cerebral arteries (Ackerstaff, Keunen, van Pelt, Montauban, van Swijndregt, & Stijnen, 1990). By the age of 60, CBF reduction reaches the greatest level instead of being a linear process (Chen, Rosas, & Salat, 2011).

The previous studies showed that transcranial Doppler ultrasonography suffers from insufficient accuracy with the margin of error of ± 10 – 15 mmHg in the case of ICP measurement non-invasively (Popovic *et al.*, 2009; Zhang *et al.*, 2017). The snapshot ICP measurement based on the scaling of the intracranial segment of OA and the extracranial segment of OA shows promising accuracy in the range of 4.4 – 24.3 mmHg, and 98% of the patients' measurements were within ± 4 mmHg of the lumbar-puncture-determined ICP (Ragauskas *et al.*, 2012; Zhang *et al.*, 2017). The suggested method is thus suitable for continuous non-invasive ICP monitoring.

The suggested non-invasive ICP monitoring method based on measuring the pulsatility index of the blood flow in the intracranial and extracranial segments of the ophthalmic artery simultaneously has been used in a pilot study with 7 patients.

The extremes are -11.74 and 9.33 mmHg, and 95% of the observations fall in the uncertainty interval of -4.38 to 4.02 mmHg. The accuracy, precision, sensitivity and specificity for non-invasive ICP monitoring were found to be 0.99 (95% CI = 0.90 to 0.91), 0.91 (95% CI = 0.90 to 0.91), 0.87 (95% CI = 0.85 to 0.89) and 0.91 (95% CI = 0.90 to 0.93), respectively. The total mean and SD of the measured differences between non-invasive ICP monitoring and invasive ICP monitoring are 0.086 ± 1.34 mmHg, and the correlation was 0.94 in the studied population. This is the first clinical study which showed promising results, however, the main limitation of our preliminary study is a small sample size of patients with TBI. This determines a need for a prospective study with a larger sample size in order to achieve statistical validity. Therefore, future studies are needed in order to validate the proposed method.

GENERAL CONCLUSIONS

1. Literature analysis of ICP monitoring methods showed that invasive ICP monitoring methods have several limitations, including brain hemorrhage, infection, technical failure, and they can be used in neuro-intensive care units under supervision of expert physicians. On the other hand, non-invasive ICP monitoring methods are denoted by a low infection rate, generally low cost, and can be used everywhere outside ICU, even in emergency rooms. The non-invasive ICP monitoring method based on a two-depth transcranial Doppler shows promising clinical evidence for non-invasive ICP snapshot measurement and long-term monitoring.
2. A prospective and retrospective study was performed on patients with high tension glaucoma and healthy volunteers in order to overcome one of the technical problems (the location and position of the ultrasound transducer) of the non-invasive ICP snapshot measurement device. As a result of this study, a value adding methodology was suggested. According to that, the edge of ICA will be used as the reference depth to locate the intracranial and extracranial segments of the ophthalmic artery for a reliable snapshot measurement of the absolute value of ICP. When using the suggested window on the eyelid in this study, there is a high probability to locate the edge of ICA and IOA simultaneously with EOA for the measurement. As a result of this study, the ultrasonic transducer angles beta for the edge of ICA and IOA simultaneously with EOA are statistically significantly different ($p = 0.0002$). The operator measuring the ICP based on newer suggested methodology should be aware of this difference.
3. A retrospective study was performed on patients with a neurological, traumatic brain injury and glaucoma as well as on healthy volunteers in order to analyze the incidence of the evoked OCR during the non-invasive ICP measurement with the gradual external pressure (up to 48 mmHg) on the ocular globe. OCR can be considered as a safety problem for patients and volunteers. There are several thresholds for the evoked OCR including a 10% decrease and a 20% decrease in the baseline heart rate, and the threshold of the evoked OCR remains debatable. This study found out that a gradual external pressure applied to the ocular globe during the non-invasive ICP measurement did not result in OCR at the threshold of a 20% decrease in the HR criterion and rarely reached the threshold of a 10% decrease in the HR criterion. In 3 healthy volunteers and 1 glaucoma patient, the threshold of a 10% decrease was exceeded. Yet, the heart rate did not rapidly decrease when external pressure was applied for the measurement. The heart rate variability in these cases can be caused by age instead of the oculocardiac reflex, the normal heart rate variability ranges from 8.97% to 13.70%.

4. A prospective comparative clinical study was performed on patients with a traumatic brain injury to compare real time invasive and non-invasive cerebrovascular autoregulation indexes calculated from the intracranial pressure, arterial blood pressure and intracranial blood volume. As a result, significant coincidence between the non-invasive ultrasonic volumetric reactivity index (VRx) monitoring based on ultrasonic time-of-flight measurements of the intracranial blood volume dynamics and the invasive pressure reactivity index (PRx) were found ($r=0.724$, $p < 0.001$). VRx can be used as a non-invasive cerebrovascular autoregulation index to reflect the integral information of the status of cerebrovascular autoregulation over the entire cranium in the same way as PRx. The higher amplitude of the intracranial blood volume and intracranial pressure slow waves results in better coincidence between VRx and PRx.
5. A prospective clinical study was performed on patients with a traumatic brain injury to compare the non-invasive ICP monitoring method with the invasive ICP monitoring method by means of accuracy, precision, sensitivity, and specificity. A total of 2,268 paired data points were obtained from 7 patients. The total mean and SD of the measured differences between the non-invasive ICP method and the invasive ICP method are -0.18 ± 2.14 mmHg. In Bland Altman analysis with one-minute moving average filtering, 95% of the observations fall in the interval of -4.38 to 4.02 mmHg, the extremes are -11.74 and 9.33 mmHg. ROC curve analysis revealed the area under curve (AUC) **0.971** (95% CI = 0.964 to 0.978), $P < 0.0001$, which means that strong correspondence between the non-invasive ICP method and the invasive ICP method is observed. The accuracy, precision, sensitivity and specificity for non-invasive ICP monitoring were found to be **0.99** (95% CI = 0.90 to 0.91), **0.91** (95% CI = 0.90 to 0.91), **0.87** (95% CI = 0.85 to 0.89) and **0.91** (95% CI = 0.90 to 0.93), respectively. Linear regression analysis showed strong positive relationship between the non-invasive ICP method and the invasive ICP method, with the correlation coefficient being **R = 0.83**, $P < 0.0001$.

REFERENCES

1. Aaslid, R., Markwalder, T. M., & Nornes, H. (1982). Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *Journal of neurosurgery*, 57(6), 769–774. United States.
2. Abdelsadg, M., Kumar Kanodia, A., Badran, K., Abdelsadig, K., & Ballantyne, E. (2017). Intra Cranial Pressure (ICP) Monitoring in Traumatic Brain Injury; What is the Evidence? *Open access Journal of Neurology & Neurosurgery*, 5.
3. Ackerstaff, R. G., Keunen, R. W., van Pelt, W., Montauban van Swijndregt, A. D., & Stijnen, T. (1990). Influence of biological factors on changes in mean cerebral blood flow velocity in normal ageing: a transcranial Doppler study. *Neurological research*, 12(3), 187–191. England.
4. Akbik, O. S., Carlson, A. P., & Yonas, H. (2016). The Roles of Ventricular and Parenchymal Intracranial Pressure Monitoring. *Current Neurobiology*, 07(1), 1–6.
5. Akman-Demir, G., Serdaroglu, P., & Tasci, B. (1999). Clinical patterns of neurological involvement in Behcet's disease: evaluation of 200 patients. The Neuro-Behcet Study Group. *Brain : a journal of neurology*, 122 (Pt 1, 2171–2182. England.
6. Al-Tamimi, Y. Z., Helmy, A., Bavetta, S., & Price, S. J. (2009). Assessment of zero drift in the Codman intracranial pressure monitor: a study from 2 neurointensive care units. *Neurosurgery*, 64(1), 94–99. United States.
7. Alali, A. S., Fowler, R. A., Mainprize, T. G., Scales, D. C., Kiss, A., de Mestral, C., Ray, J. G., et al. (2013). Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *Journal of neurotrauma*, 30(20), 1737–1746. United States.
8. Alexandrov, A. V, Sloan, M. A., Wong, L. K. S., Douville, C., Razumovsky, A. Y., Koroshetz, W. J., Kaps, M., et al. (2007). Practice standards for transcranial Doppler ultrasound: part I-test performance. *Journal of neuroimaging: official journal of the American Society of Neuroimaging*, 17(1), 11–18. United States.
9. Alperin, N. J., Lee, S. H., Loth, F., Raksin, P. B., & Lichtor, T. (2000). MR- Intracranial pressure (ICP): a method to measure intracranial elastance and pressure noninvasively by means of MR imaging: baboon and human study. *Radiology*, 217(3), 877–885. United States.
10. Andrews, P. J. D., Citerio, G., Longhi, L., Polderman, K., Sahuquillo, J., & Vajkoczy, P. (2008). NICEM consensus on neurological monitoring in acute neurological disease. *Intensive care medicine*, 34(8), 1362–1370. United States.
11. Aries, M. J. H., Czosnyka, M., Budohoski, K. P., Steiner, L. A., Lavinio, A., Kolias, A. G., Hutchinson, P. J., et al. (2012). Continuous determination of

- optimal cerebral perfusion pressure in traumatic brain injury. *Critical care medicine*, 40(8), 2456–2463. United States.
12. Avezaat, C. J., van Eijndhoven, J. H., & Wyper, D. J. (1979). Cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. *Journal of neurology, neurosurgery, and psychiatry*, 42(8), 687–700. England.
 13. Balestreri, M., Czosnyka, M., Steiner, L. A., Hiler, M., Schmidt, E. A., Matta, B., Menon, D., *et al.* (2005). Association between outcome, cerebral pressure reactivity and slow ICP waves following head injury. *Acta neurochirurgica. Supplement*, 95, 25–28. Austria.
 14. Ballantyne, S. A., O'Neill, G., Hamilton, R., & Hollman, A. S. (2002). Observer variation in the sonographic measurement of optic nerve sheath diameter in normal adults. *European journal of ultrasound: official journal of the European Federation of Societies for Ultrasound in Medicine and Biology*, 15(3), 145–149. Ireland.
 15. Barlow, P., Mendelow, A. D., Lawrence, A. E., Barlow, M., & Rowan, J. O. (1985). Clinical evaluation of two methods of subdural pressure monitoring. *Journal of neurosurgery*, 63(4), 578–582. United States.
 16. Bartusis, L. (2015). *Kompleksinės elektroninės sistemos, skirtos žmogaus absoliutinio intrakranijinio slėgio neinvaziniam matavimui, tyrimai*. Kaunas University of Technology.
 17. Bartusis, L., Zakelis, R., Daubaris, G., Ragauskas, A., Rutkauskas, S., Matijosaitis, V., & Preiksaitis, A. (2012). Ophthalmic Artery as a Sensor for Non-invasive Intracranial Pressure Measurement Electronic System. *Elektronika ir Elektrotechnika*, 122.
 18. Bathala, L., Mehndiratta, M. M., & Sharma, V. K. (2013). Transcranial doppler: Technique and common findings (Part 1). *Annals of Indian Academy of Neurology*, 16(2), 174–179. India.
 19. Baurmann, M. (1925). Über die Entstehung und klinische Bedeutung des Netzhautvenenpulses. *Dtsch Ophthalmol Ges*, 45, 53–59.
 20. Bellner, J., Romner, B., Reinstrup, P., Kristiansson, K.-A., Ryding, E., & Brandt, L. (2004). Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). *Surgical neurology*, 62(1), 45–51; discussion 51. United States.
 21. Berdahl, J. P., Allingham, R. R., & Johnson, D. H. (2008). Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. *Ophthalmology*, 115(5), 763–768. United States.
 22. Berdahl, J. P., Fautsch, M. P., Stinnett, S. S., & Allingham, R. R. (2008). Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. *Investigative ophthalmology & visual science*, 49(12), 5412–5418. United States.
 23. Berlin, T., Murray-Krezan, C., & Yonas, H. (2015). Comparison of parenchymal and ventricular intracranial pressure readings utilizing a novel multi-parameter intracranial access system. *SpringerPlus*, 4, 10. Switzerland.

24. Bershad, E. M., Anand, A., DeSantis, S. M., Yang, M., Tang, R. A., Calvillo, E., Malkin-Gosdin, L., *et al.* (2016). Clinical Validation of a Transcranial Doppler-Based Noninvasive Intracranial Pressure Meter: A Prospective Cross-Sectional Study. *World neurosurgery*, 89, 647-653.e1. United States.
25. Bershad, E. M., Urfy, M. Z., Pechacek, A., McGrath, M., Calvillo, E., Horton, N. J., & Voss, S. E. (2014). Intracranial pressure modulates distortion product otoacoustic emissions: a proof-of-principle study. *Neurosurgery*, 75(4), 445. United States.
26. Bhargava, D., Thomas, S., Chakravorty, N., & Dutt, A. (2014). Trigemino-cardiac Reflex: A Reappraisal with Relevance to Maxillofacial Surgery. *Journal of maxillofacial and oral surgery*, 13(4), 373–377. India.
27. Blanc, V. F., Hardy, J. F., Milot, J., & Jacob, J. L. (1983). The oculocardiac reflex: a graphic and statistical analysis in infants and children. *Canadian Anaesthetists' Society journal*, 30(4), 360–369. Canada.
28. Bradley, W. G. (2000). Normal Pressure Hydrocephalus: New Concepts on Etiology and Diagnosis. *American Journal of Neuroradiology*, 21(9), 1586 LP – 1590. Retrieved from <http://www.ajnr.org/content/21/9/1586.abstract>
29. Brain Trauma Foundation. (2007). Guidelines for the management of severe traumatic brain injury. *Journal of neurotrauma*, 24 Suppl 1, S1-106. United States.
30. BrainFacts. (2018). *Brain Facts* (8th ed.). BrainFacts.org.
31. Bruce, B. B. (2014). Noninvasive assessment of cerebrospinal fluid pressure. *Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society*, 34(3), 288–294. United States.
32. Bruder, N., N'Zoghe, P., Graziani, N., Pelissier, D., Grisoli, F., & François, G. (1995). A comparison of extradural and intraparenchymatous intracranial pressures in head injured patients. *Intensive Care Medicine*, 21(10), 850–852. Retrieved from <https://doi.org/10.1007/BF01700971>
33. Budohoski, K. P., Czosnyka, M., de Riva, N., Smielewski, P., Pickard, J. D., Menon, D. K., Kirkpatrick, P. J., *et al.* (2012). The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. *Neurosurgery*, 71(3), 651–652. United States.
34. Budohoski, K. P., Reinhard, M., Aries, M. J. H., Czosnyka, Z., Smielewski, P., Pickard, J. D., Kirkpatrick, P. J., *et al.* (2012). Monitoring cerebral autoregulation after head injury. Which component of transcranial Doppler flow velocity is optimal? *Neurocritical care*, 17(2), 211–218. United States.
35. Cardim, D., Robba, C., Bohdanowicz, M., Donnelly, J., Cabella, B., Liu, X., Cabelreira, M., *et al.* (2016). Non-invasive Monitoring of Intracranial Pressure Using Transcranial Doppler Ultrasonography: Is It Possible? *Neurocritical care*, 25(3), 473–491. United States.
36. Carney, N., Totten, A. M., O'Reilly, C., Ullman, J. S., Hawryluk, G. W. J., Bell, M. J., Bratton, S. L., *et al.* (2017). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery*, 80(1), 6–15.

- United States.
37. Chambers, I. R., Treadwell, L., & Mendelow, A. D. (2001). Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver-operating characteristic curves: an observational study in 291 patients. *Journal of neurosurgery*, 94(3), 412–416. United States.
 38. Chen, J. J., Rosas, H. D., & Salat, D. H. (2011). Age-associated reductions in cerebral blood flow are independent from regional atrophy. *NeuroImage*, 55(2), 468–478. United States.
 39. Chillon, J. M., & Braumbach, G. L. (2002). Autoregulation: arterial and intracranial pressure. In L. Edvinsson & D. Krause (eds.), *Cerebral blood flow and metabolism* (2nd ed., pp. 395–100). Philadelphia: Lippincott Williams & Wilkins.
 40. Choi, S. H., Lee, S. J., Kim, S. H., Kim, J. H., Kwon, H. H., Shin, Y. S., & Lee, K. Y. (2007). Single bolus of intravenous ketamine for anesthetic induction decreases oculocardiac reflex in children undergoing strabismus surgery. *Acta anaesthesiologica Scandinavica*, 51(6), 759–762. England.
 41. Citerio, G., Piper, I., Cormio, M., Galli, D., Cazzaniga, S., Enblad, P., Nilsson, P., *et al.* (2004). Bench test assessment of the new Raumedic Neurovent-P ICP sensor: a technical report by the BrainIT group. *Acta neurochirurgica*, 146(11), 1221–1226. Austria.
 42. Coroneos, N. J., McDowall, D. G., Gibson, R. M., Pickerodt, V. W., & Keaney, N. P. (1973). Measurement of extradural pressure and its relationship to other intracranial pressures. An experimental and clinical study. *Journal of neurology, neurosurgery, and psychiatry*, 36(4), 514–522. England.
 43. Czosnyka, M., & Pickard, J. D. (2004). Monitoring and interpretation of intracranial pressure. *Journal of neurology, neurosurgery, and psychiatry*, 75(6), 813–821. England.
 44. Czosnyka, Marek, Brady, K., Reinhard, M., Smielewski, P., & Steiner, L. A. (2009). Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocritical care*, 10(3), 373–386. United States.
 45. Czosnyka, Marek, Czosnyka, Z., Momjian, S., & Pickard, J. D. (2004). Cerebrospinal fluid dynamics. *Physiological measurement*, 25(5), R51-76. England.
 46. Czosnyka, Marek, Smielewski, P., Kirkpatrick, P., Laing, R. J., Menon, D., & Pickard, J. D. (1997). Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery*, 41(1), 11–19. United States.
 47. Czosnyka, Marek, Smielewski, P., Kirkpatrick, P., Menon, D., & Pickard, J. (1996). Monitoring of Cerebral Autoregulation in Head-Injured Patients. *Stroke; a journal of cerebral circulation*, 27, 1829–1834.
 48. Depreitere, B., Guiza, F., Van den Berghe, G., Schuhmann, M. U., Maier, G., Piper, I., & Meyfroidt, G. (2014). Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe

- traumatic brain injury based on minute-by-minute monitoring data. *Journal of neurosurgery*, 120(6), 1451–1457. United States.
49. Dobrovăț, B., Popescu, R., Nemtoi, A., Ladunca, O., & Haba, D. (2011). Orbital trauma: from anatomy to imaging patterns – a pictorial review. *Romanian Neurosurgery*.
 50. Doherty, C. M., & Forbes, R. B. (2014). Diagnostic Lumbar Puncture. *The Ulster medical journal*, 83(2), 93–102. Northern Ireland.
 51. E. Sviri, G., & W. Newel, D. (2010). Cerebral Autoregulation Following Traumatic Brain Injury. *The Open Neurosurgery Journal*, 3, 6–9.
 52. Eames, P. J., Blake, M. J., Dawson, S. L., Panerai, R. B., & Potter, J. F. (2002). Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *Journal of neurology, neurosurgery, and psychiatry*, 72(4), 467–472. England.
 53. Eide, P. K. (2008). Comparison of simultaneous continuous intracranial pressure (ICP) signals from ICP sensors placed within the brain parenchyma and the epidural space. *Medical Engineering & Physics*, 30(1), 34–40. Retrieved from <http://www.sciencedirect.com/science/article/pii/S1350453307000306>
 54. Erdogmus, S., & Govsa, F. (2006). Anatomic features of the intracranial and intracanalicular portions of ophthalmic artery: for the surgical procedures. *Neurosurgical review*, 29(3), 213–218. Germany.
 55. Eustis, H. S., Eiswirth, C. C., & Smith, D. R. (1992). Vagal responses to adjustable sutures in strabismus correction. *American journal of ophthalmology*, 114(3), 307–310. United States.
 56. Evensen, K. B., Paulat, K., Prieur, F., Holm, S., & Eide, P. K. (2018). Utility of the Tympanic Membrane Pressure Waveform for Non-invasive Estimation of The Intracranial Pressure Waveform. *Scientific Reports*, 8(1), 15776. Retrieved from <https://doi.org/10.1038/s41598-018-34083-6>
 57. Fantini, S., Sassaroli, A., Tgavalekos, K., & Kornbluth, J. (2016). Cerebral blood flow and autoregulation: Current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics*, 3, 31411.
 58. Farahvar, A., Gerber, L. M., Chiu, Y.-L., Carney, N., Hartl, R., & Ghajar, J. (2012). Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *Journal of neurosurgery*, 117(4), 729–734. United States.
 59. Fountas, K. N., Kapsalaki, E. Z., Machinis, T. G., Boev, A. N., Robinson, J. S., & Troup, E. C. (2006). Clinical implications of quantitative infrared pupillometry in neurosurgical patients. *Neurocritical care*, 5(1), 55–60. United States.
 60. Gaihede, M., Felding, J. U., & Elbrond, O. (1995). Biomechanical characteristics of the middle ear system measured by a new method. III: Comparisons with tympanometric measurements. *Acta oto-laryngologica*, 115(4), 522–527. England.

61. Ganslandt, O., Mourtzoukos, S., Stadlbauer, A., Sommer, B., & Rammensee, R. (2018). Evaluation of a novel noninvasive ICP monitoring device in patients undergoing invasive ICP monitoring: preliminary results. *Journal of neurosurgery*, 128(6), 1653–1660. United States.
62. Geeraerts, T., Launey, Y., Martin, L., Pottecher, J., Vigue, B., Duranteau, J., & Benhamou, D. (2007). Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. *Intensive care medicine*, 33(10), 1704–1711. United States.
63. Geeraerts, T., Merceron, S., Benhamou, D., Vigue, B., & Duranteau, J. (2008). Non-invasive assessment of intracranial pressure using ocular sonography in neurocritical care patients. *Intensive care medicine*, 34(11), 2062–2067. United States.
64. Gerber, L. M., Chiu, Y.-L., Carney, N., Hartl, R., & Ghajar, J. (2013). Marked reduction in mortality in patients with severe traumatic brain injury. *Journal of neurosurgery*, 119(6), 1583–1590. United States.
65. Gupta, R., & Bhatia, M. S. (2007). A report of cranial autonomic symptoms in migraineurs. *Cephalalgia : an international journal of headache*, 27(1), 22–28. England.
66. Gwer, S., Sheward, V., Birch, A., Marchbanks, R., Idro, R., Newton, C. R., Kirkham, F. J., *et al.* (2013). The tympanic membrane displacement analyser for monitoring intracranial pressure in children. *Child's nervous system : ChNS: official journal of the International Society for Pediatric Neurosurgery*, 29(6), 927–933. Germany.
67. Hamarat, Y., Bartusis, L., Deimantavicius, M., Siaudvytyte, L., Januleviciene, I., Ragauskas, A., Bershad, E. M., *et al.* (2018). Graphical and statistical analyses of the oculocardiac reflex during a non-invasive intracranial pressure measurement. *PLoS ONE*, 13(4).
68. Hamarat, Y., Deimantavicius, M., Kalvaitis, E., Siaudvytyte, L., Januleviciene, I., Zakelis, R., & Bartusis, L. (2017). Location of the internal carotid artery and ophthalmic artery segments for non-invasive intracranial pressure measurement by multi-depth TCD. *Libyan Journal of Medicine*, 12(1).
69. Hayreh, S. S. (2006). Orbital vascular anatomy. *Eye (London, England)*, 20(10), 1130–1144. England.
70. Hayreh, S. S., & Dass, R. (1962). The ophthalmic artery: i. Origin and intracranial and intra-canalicular course. *The British journal of ophthalmology*, 46(2), 65–98. England.
71. Highton, D., Ghosh, A., Tachtsidis, I., Panovska-Griffiths, J., Elwell, C. E., & Smith, M. (2015). Monitoring cerebral autoregulation after brain injury: multimodal assessment of cerebral slow-wave oscillations using near-infrared spectroscopy. *Anesthesia and analgesia*, 121(1), 198–205. United States.
72. Holzschuh, M., Woertgen, C., & Brawanski, A. (1996). Transcranial Doppler sonography in a patient with Ehlers-Danlos syndrome: case report.

- Neurosurgery*, 39(1), 170–173. United States.
73. Horsfield, M. A., Jara, J. L., Saeed, N. P., Panerai, R. B., & Robinson, T. G. (2013). Regional differences in dynamic cerebral autoregulation in the healthy brain assessed by magnetic resonance imaging. *PloS one*, 8(4), e62588. United States.
 74. Hu, H. H., Luo, C. L., Sheng, W. Y., Teng, M. M., Wong, W. J., & Luk, Y. O. (1995). Transorbital color Doppler flow imaging of the carotid siphon and major arteries at the base of the brain. *AJNR. American journal of neuroradiology*, 16(3), 591–598. United States.
 75. Hutchinson, P. J., Kolias, A. G., Tajsic, T., Adeleye, A., Aklilu, A. T., Apriawan, T., Bajamal, A. H., et al. (2019). Consensus statement from the International Consensus Meeting on the Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury: Consensus statement. *Acta neurochirurgica*, 161(7), 1261–1274. Austria.
 76. Jacks, A. S., & Miller, N. R. (2003). Spontaneous retinal venous pulsation: aetiology and significance. *Journal of neurology, neurosurgery, and psychiatry*, 74(1), 7–9. England.
 77. Jefferson, A. L., Cambroner, F. E., Liu, D., Moore, E. E., Neal, J. E., Terry, J. G., Nair, S., et al. (2018). Higher Aortic Stiffness Is Related to Lower Cerebral Blood Flow and Preserved Cerebrovascular Reactivity in Older Adults. *Circulation*, 138(18), 1951–1962.
 78. Jimenez-Castellanos, J., Carmona, A., Castellanos, L., & Catalina-Herrera, C. J. (1995). Microsurgical anatomy of the human ophthalmic artery: a mesoscopic study of its origin, course and collateral branches. *Surgical and radiologic anatomy: SRA*, 17(2), 14–16, 139–143. Germany.
 79. Johnston, I. H., & Rowan, J. O. (1974). Raised intracranial pressure and cerebral blood flow. 4. Intracranial pressure gradients and regional cerebral blood flow. *J Neurol Neurosurg Psychiatry*, 37, 585–592.
 80. Kakarla, U. K., Kim, L. J., Chang, S. W., Theodore, N., & Spetzler, R. F. (2008). Safety and accuracy of bedside external ventricular drain placement. *Neurosurgery*, 63(1 Suppl 1), ONS162-6; discussion ONS166-7. United States.
 81. Karaman, T., Demir, S., Dogru, S., Sahin, A., Tapar, H., Karaman, S., Kaya, Z., et al. (2016). The effect of anesthesia depth on the oculocardiac reflex in strabismus surgery. *Journal of clinical monitoring and computing*, 30(6), 889–893. Netherlands.
 82. Karhunen, U., Cozanitis, D. A., & Brander, P. (1984). The oculocardiac reflex in adults. A dose response study of glycopyrrolate and atropine. *Anaesthesia*, 39(6), 524–528. England.
 83. Kashif, F. M. (2011). *Modeling and Estimation for Non-invasive Monitoring of Intracranial Pressure and Cerebrovascular Autoregulation*. Massachusetts Institute of Technology.
 84. Kashif, F. M., Verghese, G. C., Novak, V., Czosnyka, M., & Heldt, T. (2012).

- Model-Based Noninvasive Estimation of Intracranial Pressure from Cerebral Blood Flow Velocity and Arterial Pressure. *Science Translational Medicine*, 4(129), 129ra44 LP-129ra44. Retrieved from <http://stm.sciencemag.org/content/4/129/129ra44.abstract>
85. Kasotakis, G., Michailidou, M., Bramos, A., Chang, Y., Velmahos, G., Alam, H., King, D., *et al.* (2012). Intraparenchymal vs extracranial ventricular drain intracranial pressure monitors in traumatic brain injury: less is more? *Journal of the American College of Surgeons*, 214(6), 950–957. United States.
 86. Kassab, M. Y., Majid, A., Farooq, M. U., Azhary, H., Hershey, L. A., Bednarczyk, E. M., Graybeal, D. F., *et al.* (2007). Transcranial Doppler: an introduction for primary care physicians. *Journal of the American Board of Family Medicine : JABFM*, 20(1), 65–71. United States.
 87. Khan, M. N., Shallwani, H., Khan, M. U., & Shamim, M. S. (2017). Noninvasive monitoring intracranial pressure – A review of available modalities. *Surgical neurology international*, 8, 51. India.
 88. Kimberly, H. H., & Noble, V. E. (2008). Using MRI of the optic nerve sheath to detect elevated intracranial pressure. *Critical Care*, 12(5), 181. Retrieved from <https://doi.org/10.1186/cc7008>
 89. Kirsch, J. D. (2016). Essentials of Transcranial Doppler Ultrasound. In L. Saba & E. Raz (eds.), *Neurovascular Imaging: From Basics to Advanced Concepts* (pp. 47–66). New York, NY: Springer New York. Retrieved from https://doi.org/10.1007/978-1-4614-9029-6_36
 90. Koskinen, L.-O. D., & Olivecrona, M. (2005). Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor system. *Neurosurgery*, 56(4), 693–698. United States.
 91. Krakauskaitė, S., Ragauskas, A., Zakelis, R., Petkus, V., Chomskis, R., Preiksaitis, A., Matijosaitis, V., *et al.* (2016). Accuracy, precision, sensitivity, and specificity of noninvasive ICP absolute value measurements. *Acta Neurochirurgica Supplement*, 122, 317–21.
 92. Kristiansson, H., Nissborg, E., Bartek, J. J., Andresen, M., Reinstrup, P., & Romner, B. (2013). Measuring elevated intracranial pressure through noninvasive methods: a review of the literature. *Journal of neurosurgical anesthesiology*, 25(4), 372–385. United States.
 93. Lai, Y.-H., Hsu, H.-T., Wang, H.-Z., Cheng, K.-I., & Wu, K.-Y. (2014). The oculocardiac reflex during strabismus surgery: its relationship to preoperative clinical eye findings and subsequent postoperative emesis. *Journal of AAPOS: the official publication of the American Association for Pediatric Ophthalmology and Strabismus*, 18(2), 151–155. United States.
 94. Lang, E. W., Mehdorn, H. M., Dorsch, N. W. C., & Czosnyka, M. (2002). Continuous monitoring of cerebrovascular autoregulation: a validation study. *Journal of neurology, neurosurgery, and psychiatry*, 72(5), 583–586. England.
 95. Lang, Erhard W., Mudaliar, Y., Lagopoulos, J., Dorsch, N., Yam, A., Griffith,

- J., & Mulvey, J. (2005). A Review of Cerebral Autoregulation: Assessment and Measurements. In J. Keneally (ed.), *Australasian Anaesthesia* (pp. 161–172). SOS Print and Media Group Sydney.
96. Lang, J.-M., Beck, J., Zimmermann, M., Seifert, V., & Raabe, A. (2003). Clinical evaluation of intraparenchymal Spiegelberg pressure sensor. *Neurosurgery*, 52(6), 1455–9; discussion 1459. United States.
97. Lang, S., Lanigan, D. T., & van der Wal, M. (1991). Trigemino-cardiac reflexes: maxillary and mandibular variants of the oculocardiac reflex. *Canadian journal of anaesthesia = Journal canadien d'anesthésie*, 38(6), 757–760. United States.
98. Larsen, F. S., Olsen, K. S., Hansen, B. A., Paulson, O. B., & Knudsen, G. M. (1994). Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke*, 25(10), 1985–1988. United States.
99. Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiological reviews*, 39(2), 183–238. United States.
100. Lenfeldt, N., Koskinen, L.-O. D., Bergenheim, A. T., Malm, J., & Eklund, A. (2007). CSF pressure assessed by lumbar puncture agrees with intracranial pressure. *Neurology*, 68(2), 155 LP – 158. Retrieved from <http://n.neurology.org/content/68/2/155.abstract>
101. Lescot, T., Reina, V., Le Manach, Y., Boroli, F., Chauvet, D., Boch, A.-L., & Puybasset, L. (2011). In vivo accuracy of two intraparenchymal intracranial pressure monitors. *Intensive care medicine*, 37(5), 875–879. United States.
102. Levin, B. E. (1978). The clinical significance of spontaneous pulsations of the retinal vein. *Archives of neurology*, 35(1), 37–40. United States.
103. Levinsky, A., Papyan, S., Weinberg, G., Stadheim, T., & Eide, P. K. (2016). Non-invasive estimation of static and pulsatile intracranial pressure from transcranial acoustic signals. *Medical engineering & physics*, 38(5), 477–484. England.
104. Lin, C. M., Lin, J. W., Tsai, J. T., Ko, C. P., Hung, K. S., Hung, C. C., Su, Y. K., et al. (2008). Intracranial pressure fluctuation during hemodialysis in renal failure patients with intracranial hemorrhage. *Acta neurochirurgica. Supplement*, 101, 141–144. Austria.
105. Littlejohns, L. R., & Bader, M. K. (eds.). (2009). *AACN-AACN protocols for practice: monitoring technologies in critically ill neuroscience patients*. Sudbury, MA: Jones and Bartlett Publishers.
106. Luerssen, T. G. (1997). Intracranial pressure: Current status in monitoring and management. *Seminars in Pediatric Neurology*, 4(3), 146–155. W.B. Saunders. Retrieved August 14, 2019, from <https://www.sciencedirect.com/science/article/abs/pii/S1071909197800332?via%3Dihub>
107. Mariak, Z., Krejza, J., Swiercz, M., Kordecki, K., & Lewko, J. (2002). Accuracy of transcranial color Doppler ultrasonography in the diagnosis of middle cerebral artery spasm determined by receiver operating characteristic

- analysis. *Journal of Neurosurgery*, 96(2), 323–330. Journal of Neurosurgery Publishing Group. Retrieved from <https://thejns.org/view/journals/j-neurosurg/96/2/article-p323.xml>
108. Marmarou, A., Saad, A., Aygok, G., & Rigsbee, M. (2005). Contribution of raised ICP and hypotension to CPP reduction in severe brain injury: correlation to outcome. *Acta neurochirurgica. Supplement*, 95, 277–280. Austria.
 109. Marshall, L. F., Smith, R. W., & Shapiro, H. M. (1979). The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. *Journal of neurosurgery*, 50(1), 20–25. United States.
 110. Mayo foundation for medical, education and research. (n.d.). Lumbar puncture (spinal tap). Retrieved July 10, 2019, from <https://www.mayoclinic.org/tests-procedures/lumbar>
 111. Medgadget. (n.d.). Intracranial Pressure Monitoring. Retrieved July 10, 2019, from <https://www.medgadget.com/2018/10/global-intracranial-pressure-monitoring-market-can-substantially-grow-by-7-11-cagr-mrfr.html>
 112. Medina Corrales, M., Torres, B., Garrido Esquivel, A., Antonio, M., Salazar, G., & Naranjo Orellana, J. (2012). Normal values of heart rate variability at rest in a young, healthy and active Mexican population. *Health*, 04.
 113. Meyerson, S. C., Avan, P. A., & Buki, B. (2003). Non-invasive method and apparatus for monitoring intracranial pressure. USA: USPTO. Retrieved from <https://patents.google.com/patent/US6589189B2/en>
 114. Michaeli, D., & Rappaport, Z. H. (2002). Tissue resonance analysis; a novel method for noninvasive monitoring of intracranial pressure. Technical note. *Journal of neurosurgery*, 96(6), 1132–1137. United States.
 115. Michalinos, A., Zogana, S., Kotsiomitris, E., Mazarakis, A., & Troupis, T. (2015). Anatomy of the Ophthalmic Artery: A Review concerning Its Modern Surgical and Clinical Applications. *Anatomy research international*, 2015, 591961. Egypt.
 116. Mick, E. C. (1991). Method and apparatus for the measurement of intracranial pressure. USA: USPTO.
 117. Mick, E. C. (1992). Method and apparatus for the measurement of intracranial pressure. USA: USPTO.
 118. Miller, J. D., Becker, D. P., Ward, J. D., Sullivan, H. G., Adams, W. E., & Rosner, M. J. (1977). Significance of intracranial hypertension in severe head injury. *Journal of neurosurgery*, 47(4), 503–516. United States.
 119. Mokri, B. (2001). The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology*, 56(12), 1746–1748. United States.
 120. Mourad, P., Mohr, B., Kliot, M., Frederickson, R. C. A., Thompson, L. R., & Seawall, J. (2005). Systems and methods for determining intracranial pressure non-invasively and acoustic transducer assemblies for use in such systems. USA: European Patent Office. Retrieved from

- <https://patents.google.com/patent/EP1633234A4>
121. Naqvi, J., Yap, K. H., Ahmad, G., & Ghosh, J. (2013). Transcranial Doppler ultrasound: a review of the physical principles and major applications in critical care. *International journal of vascular medicine*, 2013, 629378. United States.
 122. Narayan, V., Mohammed, N., Savardekar, A. R., Patra, D. P., Notarianni, C., & Nanda, A. (2018). Noninvasive Intracranial Pressure Monitoring for Severe Traumatic Brain Injury in Children: A Concise Update on Current Methods. *World neurosurgery*, 114, 293–300. United States: Elsevier. Retrieved February 19, 2019, from <https://www.sciencedirect.com/science/article/pii/S1878875018304327>
 123. Nelson, E. S., Mulugeta, L., & Myers, J. G. (2014). Microgravity-induced fluid shift and ophthalmic changes. *Life (Basel, Switzerland)*, 4(4), 621–665. Switzerland.
 124. Nourallah, B., Zeiler, F. A., Calviello, L., Smielewski, P., Czosnyka, M., & Menon, D. K. (2018). Critical thresholds for intracranial pressure vary over time in non-craniectomised traumatic brain injury patients. *Acta neurochirurgica*, 160(7), 1315–1324. Austria.
 125. Nunan, D., Sandercock, G. R. H., & Brodie, D. A. (2010). A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing and clinical electrophysiology: PACE*, 33(11), 1407–1417. United States.
 126. Ohashi, T., Kase, M., & Yokoi, M. (1986). Quantitative analysis of the oculocardiac reflex by traction on human extraocular muscle. *Investigative ophthalmology & visual science*, 27(7), 1160–1164. United States.
 127. Ozturk, T. (2011). Risks Associated with Laparoscopic Surgery.
 128. Padayachy, L., Figaji, A., & R Bullock, M. (2009). Intracranial pressure monitoring for traumatic brain injury in the modern era. *Child's nervous system: ChNS: official journal of the International Society for Pediatric Neurosurgery*, 26, 441–452.
 129. Paton, J. F. R., Boscan, P., Pickering, A. E., & Nalivaiko, E. (2005). The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited. *Brain research. Brain research reviews*, 49(3), 555–565. Netherlands.
 130. Paulson, O., Strandgaard, S., & Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovascular and brain metabolism reviews*, 2, 161–192.
 131. Petkus, V., Preiksaitis, A., Krakauskaitė, S., Bartusis, L., Chomskis, R., Hamarat, Y., Zubavičiūtė, E., et al. (2019). Non-invasive Cerebrovascular Autoregulation Assessment Using the Volumetric Reactivity Index: Prospective Study. *Neurocritical Care*, 30(1).
 132. Petkus, Vytautas, Krakauskaitė, S., Chomskis, R., Bartusis, L., Ragauskas, A., Preiksaitis, A., & Rocka, S. (2014). *Novel Technology of Non-invasive Cerebrovascular Autoregulation Monitoring. Proceedings – IEEE Symposium*

on Computer-Based Medical Systems.

133. Petkus, Vytautas, Preiksaitis, A., Krakauskaite, S., Chomskis, R., Rocka, S., Kalasauskiene, A., Kalvaitis, E., *et al.* (2014). Novel Method and Device for Fully Non- Invasive Cerebrovascular Autoregulation Monitoring. *Elektronika ir Elektrotechnika*, 20, 24–29.
134. Petkus, Vytautas, Preiksaitis, A., Krakauskaite, S., Zubaviciute, E., Rocka, S., Rastenyte, D., Vosylius, S., *et al.* (2017). Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients. *Journal of critical care*, 41, 49–55. United States.
135. Petkus, Vytautas, Ragauskas, A., & Jurkonis, R. (2002). Investigation of intracranial media ultrasonic monitoring model. *Ultrasonics*, 40(1–8), 829–833. Netherlands.
136. Popovic, D., Khoo, M., & Lee, S. (2009). Noninvasive Monitoring of Intracranial Pressure. *Recent Patents on Biomedical Engineering*, 200.
137. Preiksaitis, A., Krakauskaite, S., Petkus, V., Rocka, S., Chomskis, R., Dagi, T. F., & Ragauskas, A. (2016). Association of Severe Traumatic Brain Injury Patient Outcomes with Duration of Cerebrovascular Autoregulation Impairment Events. *Neurosurgery*, 79(1), 75–82. United States.
138. Qiu, W., Jiang, Q., Xiao, G., Wang, W., & Shen, H. (2014). Changes in intracranial pressure gradients between the cerebral hemispheres in patients with intracerebral hematomas in one cerebral hemisphere. *BMC anesthesiology*, 14, 112. England.
139. Quincke, H. (1891). *Berliner klinische Wochenschrift: Die Lumbalpunktion des Hydrocephalus*. August Hirschwald.
140. Raboel, P. H., Bartek, J. J., Andresen, M., Bellander, B. M., & Romner, B. (2012). Intracranial Pressure Monitoring: Invasive versus Non-Invasive Methods-A Review. *Critical care research and practice*, 2012, 950393. Egypt.
141. Ragauskas, A., Daubaris, G., Dziugys, A., Azelis, V., & Gedrimas, V. (2005). Innovative non-invasive method for absolute intracranial pressure measurement without calibration. *Acta neurochirurgica. Supplement*, 95, 357–361. Austria.
142. Ragauskas, A., Daubaris, G., Petkus, V., Ragaisis, V., & Ursino, M. (2005). Clinical study of continuous non-invasive cerebrovascular autoregulation monitoring in neurosurgical ICU. *Acta neurochirurgica. Supplement*, 95, 367–370. Austria.
143. Ragauskas, A., Matijosaitis, V., Zakelis, R., Petrikonis, K., Rastenyte, D., Piper, I., & Daubaris, G. (2012). Clinical assessment of noninvasive intracranial pressure absolute value measurement method. *Neurology*, 78(21), 1684–1691. United States.
144. Ragauskas, Arminas, Bartusis, L., Piper, I., Zakelis, R., Matijosaitis, V., Petrikonis, K., & Rastenyte, D. (2014). Improved diagnostic value of a TCD-based non-invasive ICP measurement method compared with the sonographic

- ONSD method for detecting elevated intracranial pressure. *Neurological research*, 36(7), 607–614. England.
145. Ragauskas, Arminas, & Daubaris, G. (1995). Method and apparatus for non-invasively deriving and indicating of dynamic characteristics of the human and animal intracranial media. USA: USPTO. Retrieved from <https://patents.google.com/patent/US5388583A/en>
 146. Ragauskas, Arminas, Daubaris, G., & Dziugys, A. (1999). Method and apparatus for determining the pressure inside the brain. USA: USPTO.
 147. Rajajee, V., Vanaman, M., Fletcher, J. J., & Jacobs, T. L. (2011). Optic nerve ultrasound for the detection of raised intracranial pressure. *Neurocritical care*, 15(3), 506–515. United States.
 148. Rasulo, F., Girardini, A., Lavinio, A., De Peri, E., Stefani, R., Cenzato, M., Nodari, I., et al. (2011). Are Optimal Cerebral Perfusion Pressure and Cerebrovascular Autoregulation Related to Long-term Outcome in Patients With Aneurysmal Subarachnoid Hemorrhage? *Journal of neurosurgical anesthesiology*, 24, 3–8.
 149. Ratanalert, S., Phuenpathom, N., Saeheng, S., Oearsakul, T., Sripairojkul, B., & Hirunpat, S. (2004). ICP threshold in CPP management of severe head injury patients. *Surgical neurology*, 61(5), 425–429. United States.
 150. Rene, C. (2006). Update on orbital anatomy. *Eye (London, England)*, 20(10), 1119–1129. England.
 151. Rivera-Lara, L., Geocadin, R., Zorrilla-Vaca, A., Healy, R., Radzik, B. R., Palmisano, C., Mirski, M., et al. (2017). Validation of Near-Infrared Spectroscopy for Monitoring Cerebral Autoregulation in Comatose Patients. *Neurocritical care*, 27(3), 362–369. United States.
 152. Rosenberg, J. B., Shiloh, A. L., Savel, R. H., & Eisen, L. A. (2011). Non-invasive methods of estimating intracranial pressure. *Neurocritical care*, 15(3), 599–608. United States.
 153. Rosenfeld, J. G., Watts, C., & York, D. H. (1986). Method and apparatus for intracranial pressure estimation. USA: USPTO. Retrieved from <https://patents.google.com/patent/US4564022>
 154. Le Roux, P. (2016). Intracranial Pressure Monitoring and Management. In D. Laskowitz & G. Grant (eds.). Boca Raton (FL).
 155. Le Roux, P., Menon, D. K., Citerio, G., Vespa, P., Bader, M. K., Brophy, G. M., Diringer, M. N., et al. (2014). Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive . *Intensive care medicine*, 40(9), 1189–1209. United States.
 156. Sahuquillo, J., Poca, M. A., Arribas, M., Garnacho, A., & Rubio, E. (1999). Interhemispheric supratentorial intracranial pressure gradients in head-injured patients: are they clinically important? *Journal of neurosurgery*, 90(1), 16–26. United States.

157. Sandu, N., Cornelius, J., Filis, A., Nothen, C., Rasper, J., Kulinsky, V. I., & Schaller, B. J. (2010). Cerebral hemodynamic changes during the trigeminocardiac reflex: description of a new animal model protocol. *The Scientific World Journal*, 10, 1416–1423. United States.
158. Sandu, N., Spiriev, T., Lemaitre, F., Filis, A., & Schaller, B. (2010). New molecular knowledge towards the trigemino-cardiac reflex as a cerebral oxygen-conserving reflex. *The Scientific World Journal*, 10, 811–817. United States.
159. Saul, T. G., & Ducker, T. B. (1982). Intracranial pressure monitoring in patients with severe head injury. *The American surgeon*, 48(9), 477–480. United States.
160. Schaller, B., Cornelius, J. F., Prabhakar, H., Koerbel, A., Gnanalingham, K., Sandu, N., Ottaviani, G., *et al.* (2009). The trigemino-cardiac reflex: an update of the current knowledge. *Journal of neurosurgical anesthesiology*, 21(3), 187–195. United States.
161. Schaller, B. J., Sandu, N., Cornelius, J. F., Filis, A., & Perez-Pinzon, M. A. (2009). Oxygen-conserving implications of the trigemino-cardiac reflex in the brain: the molecular basis of neuroprotection? *Molecular medicine (Cambridge, Mass.)*, 15(5–6), 125–126. England.
162. Scheeren, T. W. L., & Saugel, B. (2017). Journal of clinical monitoring and computing 2016 end of year summary: monitoring cerebral oxygenation and autoregulation. *Journal of clinical monitoring and computing*, 31(2), 241–246. Netherlands.
163. Schimpf, M. M. (2012). Diagnosing increased intracranial pressure. *Journal of trauma nursing: the official journal of the Society of Trauma Nurses*, 19(3), 160–167. United States.
164. Schmidt-Trucksass, A., Grathwohl, D., Schmid, A., Boragk, R., Upmeyer, C., Keul, J., & Huonker, M. (1999). Structural, functional, and hemodynamic changes of the common carotid artery with age in male subjects. *Arteriosclerosis, thrombosis, and vascular biology*, 19(4), 1091–1097. United States.
165. Schmidt, B., Czosnyka, M., Raabe, A., Yahya, H., Schwarze, J. J., Sackerer, D., Sander, D., *et al.* (2003). Adaptive noninvasive assessment of intracranial pressure and cerebral autoregulation. *Stroke*, 34(1), 84–89. United States.
166. Schmidt, B., Reinhard, M., Lezaic, V., McLeod, D. D., Weinhold, M., Mattes, H., & Klingelhofer, J. (2016). Autoregulation monitoring and outcome prediction in neurocritical care patients: Does one index fit all? *Journal of clinical monitoring and computing*, 30(3), 367–375. Netherlands.
167. Schmutzhard, J., Aregger, F. C., Otieno, A., Bunk, S., Zorowka, P., & Schmutzhard, E. (2013). Release of intracranial pressure leads to improvement of otoacoustic emissions – a case report of a Kenyan child with complicated tuberculous meningitis. *Journal of tropical pediatrics*, 59(4), 326–329. England.

168. Seshubabu, G. (1998). The oculocardiac reflex in cataract surgery in the elderly. *The British journal of ophthalmology*, 82(5), 589. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/9713075>
169. Shellock, F. (2002). Biomedical implants and devices: Assessment of magnetic field interactions with a 3.0-Tesla MR system. *Journal of magnetic resonance imaging: JMRI*, 16, 721–732.
170. Siaudvytyte, L., Januleviciene, I., Ragauskas, A., Bartusis, L., Meiliuniene, I., Siesky, B., & Harris, A. (2014). The difference in translaminar pressure gradient and neuroretinal rim area in glaucoma and healthy subjects. *Journal of ophthalmology*, 2014, 937360. United States.
171. Smith, M. (2008). Monitoring intracranial pressure in traumatic brain injury. *Anesthesia and analgesia*, 106(1), 240–248. United States.
172. Sorrentino, E., Diedler, J., Kasprowicz, M., Budohoski, K. P., Haubrich, C., Smielewski, P., Outtrim, J. G., *et al.* (2012). Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocritical care*, 16(2), 258–266. United States.
173. Spiegelberg, A., Krause, M., & Kurtcuoglu, V. (2016). B-Waves Revisited. *Interdisciplinary Neurosurgery*, 6.
174. Stein, S. C., Georgoff, P., Meghan, S., Mirza, K. L., & El Falaky, O. M. (2010). Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. *Journal of neurosurgery*, 112(5), 1105–1112. United States.
175. Steiner, L. A., Czosnyka, M., Piechnik, S. K., Smielewski, P., Chatfield, D., Menon, D. K., & Pickard, J. D. (2002). Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Critical care medicine*, 30(4), 733–738. United States.
176. Stendel, R., Heidenreich, J., Schilling, A., Akhavan-Sigari, R., Kurth, R., Picht, T., Pietilä, T., *et al.* (2003). Clinical evaluation of a new intracranial pressure monitoring device. *Acta neurochirurgica*, 145, 185–93; discussion 193.
177. Talving, P., Karamanos, E., Teixeira, P. G., Skiada, D., Lam, L., Belzberg, H., Inaba, K., *et al.* (2013). Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. *Journal of neurosurgery*, 119(5), 1248–1254. United States.
178. Taylor, W. R., Chen, J. W., Meltzer, H., Gennarelli, T. A., Kelbch, C., Knowlton, S., Richardson, J., *et al.* (2003). Quantitative pupillometry, a new technology: normative data and preliminary observations in patients with acute head injury. Technical note. *Journal of neurosurgery*, 98(1), 205–213. United States.
179. Umetani, K., Singer, D. H., McCraty, R., & Atkinson, M. (1998). Twenty-four hour time domain heart rate variability and heart rate: relations to age

- and gender over nine decades. *Journal of the American College of Cardiology*, 31(3), 593–601. United States.
180. Voulgaris, S. G., Partheni, M., Kaliora, H., Haftouras, N., Pessach, I. S., & Polyzoidis, K. S. (2005). Early cerebral monitoring using the transcranial Doppler pulsatility index in patients with severe brain trauma. *Medical science monitor: international medical journal of experimental and clinical research*, 11(2), CR49–52. United States.
 181. Vrabec, M. P., Preslan, M. W., & Kushner, B. J. (1987). Oculocardiac reflex during manipulation of adjustable sutures after strabismus surgery. *American journal of ophthalmology*, 104(1), 61–63. United States.
 182. Whitmore, R. G., Thawani, J. P., Grady, M. S., Levine, J. M., Sanborn, M. R., & Stein, S. C. (2012). Is aggressive treatment of traumatic brain injury cost-effective? *Journal of neurosurgery*, 116(5), 1106–1113. United States.
 183. Wiegand, C., & Richards, P. (2007). Measurement of intracranial pressure in children: a critical review of current methods. *Developmental Medicine & Child Neurology*, 49(12), 935–941. John Wiley & Sons, Ltd (10.1111). Retrieved from <https://doi.org/10.1111/j.1469-8749.2007.00935.x>
 184. Wilson, M. H. (2016). Monro-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure. *Journal of Cerebral Blood Flow & Metabolism*, 36(8), 1338–1350. SAGE Publications Ltd STM. Retrieved from <https://doi.org/10.1177/0271678X16648711>
 185. Xu, P., Kasproicz, M., Bergsneider, M., & Hu, X. (2010). Improved noninvasive intracranial pressure assessment with nonlinear kernel regression. *IEEE transactions on information technology in biomedicine: a publication of the IEEE Engineering in Medicine and Biology Society*, 14(4), 971–978. United States.
 186. Yang, S. H., & Liu, R. (2017). Cerebral Autoregulation. *Primer on Cerebrovascular Diseases: Second Edition*.
 187. Yi, C., & Jee, D. (2008). Influence of the anaesthetic depth on the inhibition of the oculocardiac reflex during sevoflurane anaesthesia for paediatric strabismus surgery. *British journal of anaesthesia*, 101(2), 234–238. England.
 188. York, D. H., Pulliam, M. W., Rosenfeld, J. G., & Watts, C. (1981). Relationship between visual evoked potentials and intracranial pressure. *Journal of neurosurgery*, 55(6), 909–916. United States.
 189. York, D., Legan, M., Benner, S., & Watts, C. (1984). Further studies with a noninvasive method of intracranial pressure estimation. *Neurosurgery*, 14(4), 456–461. United States.
 190. Yu, X. M., & Wang, L. H. (1991). [The oculocardiac reflex during ocular operation under various anesthesia]. [*Zhonghua yan ke za zhi*] *Chinese journal of ophthalmology*, 27(1), 34–36. China.
 191. Zacchetti, L., Magnoni, S., Di Corte, F., Zanier, E. R., & Stocchetti, N. (2015). Accuracy of intracranial pressure monitoring: systematic review and meta-analysis. *Critical care (London, England)*, 19, 420. England.

192. Zhang, K., Gu, E., & Lu, J. (2008). Setting up a heart rate alarm limit to decrease oculocardiac reflex during strabismus surgery in children. *Frontiers of Medicine in China*, 2, 295–297.
193. Zhang, X., Medow, J. E., Iskandar, B. J., Wang, F., Shokouejinejad, M., Koueik, J., & Webster, J. G. (2017). Invasive and noninvasive means of measuring intracranial pressure: a review. *Physiological measurement*, 38(8), R143–R182. England.
194. Zhao, Y. L., Zhou, J. Y., & Zhu, G. H. (2005). Clinical experience with the noninvasive ICP monitoring system BT – Intracranial Pressure and Brain Monitoring XII. In W. S. Poon, M. T. V Chan, K. Y. C. Goh, J. M. K. Lam, S. C. P. Ng, A. Marmarou, C. J. J. Avezaat, et al. (Eds.), (pp. 351–355). Vienna: Springer Vienna.
195. Zhong, J., Dujovny, M., Park, H. K., Perez, E., Perlin, A. R., & Diaz, F. G. (2003). Advances in ICP monitoring techniques. *Neurological research*, 25(4), 339–350. England.
196. Zweifel, C., Castellani, G., Czosnyka, M., Carrera, E., Brady, K. M., Kirkpatrick, P. J., Pickard, J. D., *et al.* (2010). Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. *Stroke*, 41(9), 1963–1968. United States.
197. Zweifel, C., Castellani, G., Czosnyka, M., Helmy, A., Manktelow, A., Carrera, E., Brady, K. M., *et al.* (2010). Noninvasive monitoring of cerebrovascular reactivity with near infrared spectroscopy in head-injured patients. *Journal of neurotrauma*, 27(11), 1951–1958. United States.
198. Zweifel, C., Lavinio, A., Steiner, L. A., Radolovich, D., Smielewski, P., Timofeev, I., Hiler, M., *et al.* (2008). Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. *Neurosurgical focus*, 25(4), E2. United States.

LIST OF PUBLICATIONS

Publications indexed in the Web of Science with impact factor

1. Petkus, Vytautas; Preiksaitis, Aidanas; Krakauskaitė, Solventa; Bartusis, Laimonas; Chomskis, Romanas; **Hamarat, Yasin**; Zubaviciute, Erika; Vosylius, Saulius; Rocka, Saulius; Ragauskas, Arminas. Non-invasive cerebrovascular autoregulation assessment using the volumetric reactivity index: prospective study // *Neurocritical care*. ISSN 1541-6933. eISSN 1556-0961. 2019, vol. 30, iss. 1, p. 42–50. [IF: 2.857 (2018); Q1]
2. **Hamarat, Yasin**; Bartusis, Laimonas; Deimantavicius, Mantas; Siaudvytyte, Lina; Januleviciene, Ingrida; Ragauskas, Arminas; Bershad, Eric M.; Fandino, Javier; Kienzler, Jenny; Remonda, Elke; Matijosaitis, Vaidas; Rastenyte, Daiva; Petrikonis, Kestutis; Berskiene, Kristina; Zakelis, Rolandas. Graphical and statistical analyses of the oculocardiac reflex during a non-invasive intracranial pressure measurement // *PLoS One*. eISSN 1932-6203. 2018, vol. 13, iss. 4, art. no. e0196155, p. 1–11. [IF: 2.776 (2018); Q1]
3. **Hamarat, Yasin**; Deimantavičius, Mantas; Kalvaitis, Evaldas; Šiaudvytytė, Lina; Janulevičienė, Ingrida; Žakelis, Rolandas; Bartušis, Laimonas. Location of the internal carotid artery and ophthalmic artery segments for non-invasive intracranial pressure measurement by multi-depth TCD: original article // *Libyan journal of medicine*. ISSN 1993-2820. eISSN 1819-6357. 2017, vol. 12, iss. 1, art. no. 1384290, p. 1–8. [IF: 1.656 (2017); Q2]

Publications in the Conference proceeding journals indexed in the Web of Science (without impact factor)

1. **Hamarat, Yasin**; Petkus, Vytautas; Zakelis, Rolandas; Kumpaitiene, Birute; Svagzdiene, Milda; Sirvinskas, Edmundas; Krakauskaitė, Solventa; Ragauskas, Arminas; Benetis, Rimantas. Cerebrovascular autoregulation impairments and postoperative cognitive deterioration after cardiac surgery // *Journal of the neurological sciences: abstracts from the World Congress of Neurology (WCN 2019)*, 15 October 2019, Dubai. ISSN 0022-510X. eISSN 1878-5883. 2019, vol. 405, suppl., p. 71–72.
2. **Hamarat, Yasin**; Petkus, Vytautas; Deimantavicius, Mantas; Bartusis, Laimonas; Putnynaite, Vilma; Lucinskas, Paulius; Daveckaite, Aakvile; Siaudvytyte, Lina; Maciulaityte, Eevelina; Januleviciene, Ingrida; Harris, Alon; Ragauskas, Arminas. Glaucoma and cerebral blood flow autoregulation: pilot study // *Journal of the neurological sciences: abstracts from the World Congress of Neurology (WCN 2019)*, 15 October 2019, Dubai. ISSN 0022-510X. eISSN 1878-5883. 2019, vol. 405, suppl., p. 99-100.

3. **Hamarat, Yasin**; Preiksaitis, Aidanas; Kalvaitis, Evaldas; Petkus, Vytautas; Lucinskas, Paulius; Putnynaite, Vilma; Krakauskaite, Solventa; Zubaviciute, Erika; Vosylius, Saulius; Rocka, Saulius; Rastenyte, Daiva; Marcel, J. Aries; Neumann, Jan-Oliver; Ragauskas, Arminas Patient specific TBI patients' treatment: single center study // Journal of the neurological sciences: abstracts from the World Congress of Neurology (WCN 2019), 15 October 2019, Dubai. ISSN 0022-510X. eISSN 1878-5883. 2019, vol. 405, suppl., p. 25.
4. **Hamarat, Yasin**; Deimantavicius, Mantas; Zakelis, Rolandas; Bartusis, Laimonas; Preiksaitis, Aidanas; Ragauskas, Arminas. Comparison of invasive and non-invasive intracranial pressure monitoring // European journal of neurology: 23rd meeting of the ESNCH, Prague, Czech Republic, April 13–16, 2018: book of abstracts. ISSN 1351-5101. eISSN 1468-1331. 2018, vol. 25, iss. S1, P54, p. 60.
5. Preikšaitis, Aidanas; **Hamarat, Yasin**; Deimantavičius, Mantas; Žakelis, Rolandas; Bartušis, Laimonas; Ragauskas, Arminas. Is non-invasive continuous monitoring of intracranial pressure absolute value possible? // International Journal of Stroke: Abstracts for the 22nd Meeting of the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH), 19–21 May 2017, Berlin. ISSN 1747-4930. eISSN 1747-4949. 2017, Vol. 12, iss. 1S, p. 29.

Abstracts in international conferences

1. **Hamarat, Yasin**; Deimantavicius, Mantas; Žakelis, Rolandas; Bartusis, Laimonas; Preikšaitis, Aidanas; Arminas Ragauskas (2018) “A pilot study of non-invasive intracranial pressure monitoring” Bioelectrics 2018: 15th International Bioelectrics Symposium, September 23–26, 2018, Prague, Czech Republic.
2. Petkus, Vytautas; Kumpaitienė, Birute; Krakauskaitė, Solventa; Žakelis, Rolandas; Švagždienė, Milda; Širvinskas, Edmundas; **Hamarat, Yasin**; Chomskis Romanas; Benetis, Rimantas; Ragauskas, Arminas (2017). “Continuous non-invasive monitoring of cerebrovascular autoregulation during cardiac surgery with cardiopulmonary bypass in order to protect brain from post-operative cognitive deterioration” E-poster Presentation at XXIII World Congress of Neurology, 16–21 September 2017, Kyoto, Japan.
3. **Hamarat, Yasin**; Žakelis, Rolandas; Petkus, Vytautas; Chomskis Romanas; Kumpaitienė, Birute; Švagždienė, Milda; Širvinskas, Edmundas; Benetis, Rimantas; Ragauskas, Arminas (2017). “Non-invasive Cerebral Autoregulation monitoring during Cardiac Surgery” Oral Presentation at BrainIT meeting, 11–12 September, Heidelberg, Germany.

4. **Hamarat, Yasin**; Petkus, Vytautas; Žakelis, Rolandas; Kumpaitienė, Birute; Švagždienė, Milda; Krakauskaitė, Solventa; Chomskis Romanas; Širvinskas, Edmundas; Benetis, Rimantas; Ragauskas, Arminas (2017). “System of real-time non-invasive diagnosis of cerebrovascular autoregulation impairments during cardiac surgery with cardiopulmonary bypass and assessment of postoperative deterioration of cognitive functions” Poster Presentation at BrainIT meeting, 11–12 September, Heidelberg, Germany.
5. Preikšaitis, Aidanas; **Hamarat, Yasin**; Deimantavicius, Mantas; Žakelis, Rolandas; Bartusis, Laimonas; Ragauskas, Arminas (2017). “Is non-invasive continuous monitoring of intracranial pressure absolute value possible?” Poster Presentation at BrainIT meeting, 11–12 September, Heidelberg, Germany.
6. **Hamarat, Yasin**; Petkus, Vytautas; Žakelis, Rolandas; Bartusis, Laimonas; Krakauskaitė, Solventa; Preikšaitis, Aidanas; Chomskis Romanas; Ročka, Saulius; Ragauskas, Arminas (2017). “Prospective Comparative Clinical Study of Non-Invasive Cerebrovascular Autoregulation Monitor” Poster Presentation at BrainIT meeting, 11–12 September, Heidelberg, Germany.
7. **Hamarat, Yasin**; Preikšaitis, Aidanas; Petkus, Vytautas; Zubavičiūtė, Erika; Krakauskaitė, Solventa; Ročka, Saulius; Rastenytė, Daiva; Vosylius, Saulius; Ragauskas, Arminas (2017). “Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients” Poster Presentation at BrainIT meeting, 11–12 September, Heidelberg, Germany.

SL344. 2020-07-29, 17 leidyb. apsk. l. Tiražas 12 egz. Užsakymas 155.

Išleido Kauno technologijos universitetas, K. Donelaičio g. 73, 44249 Kaunas

Spausdino leidyklos „Technologija“ spaustuvė, Studentų g. 54, 51424 Kaunas