KAUNAS UNIVERSITY OF TECHNOLOGY

MANTAS DEIMANTAVIČIUS

# THE PROBLEMS OF NON-INVASIVE MEASUREMENTS OF HUMAN BRAIN BLOOD FLOW PARAMETERS

Summary of Doctoral Dissertation
Technological Sciences, Measurements Engineering (T 010)

2022, Kaunas

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KAUNO TECHNOLOGIJOS UNIVERSITETAS

MANTAS DEIMANTAVIČIUS

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# INTRODUCTION

## The importance of the problem

Intracranial pressure is defined as the pressure of cerebral fluid inside the skull and backbone channel. The neurons of the human head brain are the most rapidly dying cells in the organism when they are not provided with oxygen and nutrient-saturated blood. Intracranial pressure (ICP) directly influences the cerebral perfusion pressure (CPP), the decrease of which below the physiological limit, typical to the individual, hinders the metabolism of brain cells and can lead to their rapid death. It is to be stressed that the disruption of provision of neurons lasting a few minutes irrevocably damages the brain tissue. The limits of physiological intracranial pressure for a healthy human depending on different factors, such as body position, physical activeness, etc., are from 7 to 15mmHg. 22 mmHg threshold of crisis intracranial pressure is the limit, by increasing of which practically defined scenarios must be taken, and ICP value of 40 mmHg and over is treated as critical and should be related to minor probability of survival, or death. The increase of intracranial pressure over the critical limit for an individual patient is evaluated as secondary damage to the brain.

In the world of clinical practice intracranial pressure is measured solely by invasive methods. These are very expensive, complicated, and risky procedures requiring a high level of expertise. Therefore, intracranial pressure is usually measured only for patients who have sustained a traumatic head injury, although this measurement can also be useful for the cases of other illnesses. Hydrocephalia, meningitis and other infections, glaucoma, haemorrhage, strokes, etc., cause ICP changes which should be measured and monitored to individualize and optimize treatment solutions. For that, non-invasive ICP measurement and monitoring procedures are necessary.

Cerebral autoregulation is an automatic process in a human organism as an ability to regulate blood flow which is stabilized seeking to ensure optimal metabolism of brain cells, i.e., neurons. The increase of intracranial pressure above the critical limit for an individual patient as well as the increase or decrease of blood pressure can be the reason of impaired cerebral autoregulation (CA). When cerebral autoregulation is impaired, the neurons are damaged or die.

Over the past 20 years, different techniques and equipment for monitoring and evaluating cerebral autoregulation (CA) have been used, such as transcranial Doppler (TCD), near infrared spectroscopy (NIRS), oxygen saturation of brain tissue, parenchymal ICP monitors, etc. Alongside with each of these monitoring methods, the indexes for CA evaluation, such as mean blood flow index (Mx), brain volumetric reactivity index (VRx), oxygen reactivity index (Orx) and intracranial pressure reactivity index (PRx) were developed. Currently, clinical practice by employing PRx to measure CA state is most widely used. However, the proof of the highest level that PRx can become the evaluation index of invasive autoregulation state recognized as a clinical standard is still missing.

Note that the most frequent reason of cerebral autoregulation impairment and sincreased intracranial pressure is traumatic brain injury, which statistically is very frequent worldwide. In 2010 alone, as many as 3 million brain injury cases were identified in the EU, and 2 million in the US, the treatment of which cost over 160 billion US dollars. According to the data of the CDC (Centers for Disease Control), brain injuries are the main reason of death and disability for patients under 45 years of age.

Worldwide clinical practice seeks to provide ICP and CA measurements for more differing groups of patients and apply the concept of precise medicine requiring the cognition of the patient's body (genetic analysis and modern diagnostic procedures) to make the most efficient and optimal treatment solutions.

The research objects of this work are non-invasive ICP absolute value and CA measurement systems as well as their applicability to implement the concept of precise medicine.

**Innovative problematic questions are raised:**

- How to develop a natural phantom of ophthalmic artery blood flow with the possibility to operate the pressure applied to the segments of the imitated ophthalmic artery?
- How to perform an error study of the ICP meter by means of ophthalmic artery segments compression natural phantom for ideal conditions when the angles of radiation by ultrasound of the imitated ophthalmic artery segments are known and eliminated from the ICP = Pe balance data?
- How is externally added pressure (Pe) transferred to the ophthalmic orbit?
- How does the compliance of eye orbit depend on Pe?
- How does optic nerve sheat diameter (ONSD) respond to ICP change?

**Scientific-technological problem and work hypothesis**

In the cases of brain injury or in various areas of surgery (cardiosurgery, transplantology, neurosurgery, etc.), the main physiological parameters to be diagnosed, monitored, and controlled to achieve the best treatment outcome is arterial blood pressure (ABP)., intracranial pressure (ICP) and the state of cerebral autoregulation.

The scientific-technological problem: is it possible to develop non-invasive ICP measurement technology and CA monitoring technology which can satisfy clinical sensitivity requirements when cerebral autoregulation is active or impaired?

Working hypothesis: the technology based on the principle of pressure balance and technology for measuring the optical nerve subarachnoid space area can be developed into an ICP value meter required for the precision of clinical practise, and non-invasive TOF CA monitoring technology can be developed up to the sensitivity and specificity required for clinical practise.

## The aim and objectives of the research

The aim of the research is to carry out the missing experimental research of the non-invasive intracranial pressure absolute value measurements and the study of cerebral autoregulation monitoring systems as well as determine the ways and means providing the possibility to prove that by using these systems it is possible to apply precision medicine treatment concept by using the obtained data.

To achieve this aim, the following objectives were formulated:

1. To carry out the analysis of intracranial pressure measurement method as well as to identify the possibilities for improving the system. For that purpose, to develop and test the ophthalmic artery phantom and use it to study the method errors of measuring intracranial pressure using the pressure balance principle and a non-invasive method. The natural phantom designed for that purpose is non-existent. It is necessary to experimentally fill in the gaps which remained when developing the mathematical models for non-invasive ICP meter operating on the principle of pressure balance, since the aforementioned mathematical models describe the method as the interaction of pulsating ophthalmic artery segments with the applied pressures, but fails to describe the measurement errors of ultrasound Doppler parameters of blood flow. Also, to carry out experimental measurement research of the area of optic nerve subarachnoid space (ONSS) and optic nerve sheath diameter (ONSD) by using high frequency ultrasonic scanner and on the basis of the obtained data to determine the area differences between the measurements when a healthy volunteer is in a supine position and when turning the patient with his head down, when the ICP value and brain compliance values are changed. In addition, to apply external pressure Pe to the eye and the adjacent tissues seeking to raise intraorbital pressure and compress the optic nerve sheath for the sake of ICP value measurement.
2. To develop software designed to facilitate retrospective data analysis of the patients and carry out annotation. The data were collected from the patients with traumatic brain injury lying in an intensive care unit. After the analysis, based on the results obtained, to develop and to study the

machine learning algorithm designed for the automated classification of informative and non-informative signal episodes and to find the optimal value of cerebral perfusion pressure by using annotated data during the second stage of data analysis.

3. To analyse the cerebral autoregulation monitoring method and identify the possibilities for system improvement. For the first time, by means of non-invasive ultrasound technologies, to analyse the dynamics of cerebral autoregulation for the patients with normal tension glaucoma (NTG) and high tension glaucoma (HTG), as well as to compare with a healthy control group.

**Scientific novelty**

A unique phantom of ophthalmic artery blood flow having no analogues has been developed.

An innovative software providing the possibility to visually easier analyse physiological signals of the patients collected by means of the ICM+ equipment and to identify the links between physiological parameters.

The algorithm developed on the basis of machine learning and providing the classification of informative/non-informative episodes of the signals from the patients automatically.

For the first time after the aforementioned studies new empirical data was obtained, by means of which the possibilities for improving and developing non-invasive human brain blood flow monitoring methods were identified.

**Research methods and means**

By carrying out perspective and retrospective studies of patients with traumatic brain injuries, glaucoma patients, and healthy volunteers as well as studying the developed phantom of ophthalmic artery, the non-invasive intracranial pressure absolute value measurement and cerebral autoregulation monitoring systems developed at the Health Telematics Science Institute (KTU), were used.

The experiments with healthy volunteers and studies of ophthalmic artery phantom were carried out at Kaunas University of Technology Health Telematics Science Institute. The study of patients with traumatic brain injuries was carried out at Republican Vilnius University Hospital Intensive Therapy Department and at Kaunas Clinical Hospital of Lithuanian Health Sciences University. The study of glaucoma patients was carried out at Ophthalmic Clinical hospital, Lithuanian Health Sciences University.

In developing the software designed for the data analysis and annotation, the software package MatLab (version R202a) and IBM SPSS Statistics software packages were used.

## Practical importance of the research results

The ophthalmic artery phantom, which allows to demonstrate the operating principle of the non-invasive intracranial pressure measuring method based on the ophthalmic artery blood flow parameters in the internal and external segments and the balance of pressures is created and experimentally tested.

The software facilitating data analysis and annotation designed for the patients suffering from traumatic brain injury is developed. By using this software, a machine learning (ML) algorithm is developed and tested, and optimal brain perfusion pressure values individual for each patient are identified with a view to improve treatment methods based on precision medicine.

By means of non-invasive ultrasound technologies, the dynamics of cerebral autoregulation is analysed for patients suffering from normal and high tension glaucoma and the results are compared with the control group of healthy persons.

It is shown that the measuring technology for optic nerve subarachnoid space can be developed into a meter of the non-invasive intracranial pressure value.

## Statements presented for defence

1. A unique ophthalmic artery phantom was successfully created by means of which the operation of the pressure balance method based on parameter measurement of the blood flow in the internal and external segments of ophthalmic artery was demonstrated. For the first time it was shown that this method does not require calibration and can provide the necessary precision for clinical practise.
2. By using machine learning it is possible to improve the methods of precision treatment based on intracranial pressure (ICP) measurement and non-invasive monitoring of cerebral autoregulation (CA).
3. The perspective research results showed that impaired cerebral autoregulation is typical for patients suffering from normal tension glaucoma.
4. The technology for measuring the area of optic nerve subarachnoid space can be used to implement the method of non-invasive measurement of intracranial pressure, but on the condition that technical problems occurring during the experiment are solved and further research is continued.

## Approval of research results and publications

The research results of the dissertation are publicized in nine publications of the main list of Research Information Institute (ISI). The results were also publicized in the international conferences European Society of Neurosonology and Cerebral Hemodynamic (ESNCH), BrainIT, Bioelectrics in Czech Republic, Hungary, and Germany.

## Structure of the dissertation

The dissertation consists of an Introduction, seven chapters, the References list, and the list of the author's publications.

The first chapter presents a review of literature. The ICP and CA monitoring methods as used in the current clinical practise are presented. Also, innovative monitoring methods of these parameters are reviewed. Clinical situations, where the ICP and CA values are monitored are also considered.

Chapters 2 to 6 present descriptions of experiments and research methods used according to the aims and objectives of the work as well as the results obtained.

Chapter 7 provides the consolidation and conclusions of the results.

This dissertation consists of 104 pages; there are 37 figures and 9 tables; the references list contains 62 sources.

# I. ANALYSIS OF THE CHALLENGES AND POSSIBILITIES FOR THE DEVELOPMENT OF INTRACRANIAL PRESSURE AND CEREBRAL AUTOREGULATION

## 1.1. Analysis of the non-invasive measuring methods of intracranial pressure

Intracranial medium consists of approximately 80% of brain tissue, 10% blood, and 10% of cerebrospinal fluid. The volume of these three elements is balanced inside the skull, so that the pulsating blood flow in the arteries and bleeding in the veins are created and proper oxygen provision for brain tissue is ensured. Therefore, measuring intracranial pressure, which for a healthy person ranges from 7 to 15 mmHg depending on body position and several other factors, provides relevant information on the functional state of the cerebral system. Currently, monitoring of the intracranial pressure is precise enough, however, conventional measuring methods in clinical practise are invasive, since to identify cerebral pressure, it is necessary to drill a hole in the skull and insert a catheter.

The non-invasive methods for intracranial pressure measurement were developed and are being improved at the Health Telematics Science Institute of Kaunas University of Technology headed by prof. Ragauskas. When additional external pressure is applied to a patient's closed eye, simultaneously measuring the parameters of cerebral dynamics in two segments (internal and external) of the ophthalmic artery, and using ultrasonic Doppler technology external pressure inside the eye orbit is gradually increased, the measured cerebral parameters in the external and internal segments of the ophthalmic artery change unequaly because the external segment is affected by added pressure through the apple of the eye, and the internal segment is affected by intracranial pressure. Finally, a pair of equal cerebral parameters is found, where the externally applied pressure is equal to the intracranial pressure. This measuring technique is completely safe and does not require specific conditions.

The non-invasive ICP meter is defended in 11 USA patents, by prof. Ragauskas and co-authors. These patents are expanded into European and national patents in selected EU countries and Japan. ICP meter apparatuses (Vittamed 205) are manufactured by UAB VITTAMED (Kaunas, Lithuania), they are awarded EU CE signs and their clinical tests are carried out in Lithuania (Kaunas and Vilnius), Finland, Switzerland, USA, and Great Britain (Fig. 1.).

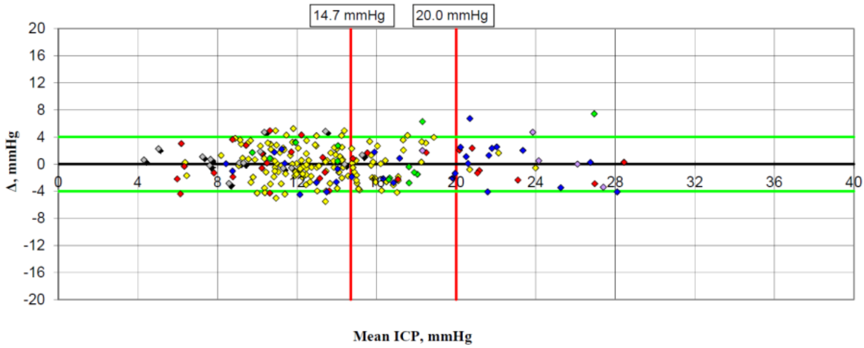


**Fig. 1** Bland and Altman plot of independent paired data points of simultaneous non-invasive absolute ICP value measurements and invasive ICP measurements: yellow points – Kaunas (Lithuania) study of 127 neurological patients, 139 independent paired data points ("gold standard" invasive ICP is measured via lumbar puncture); red points – on-going Vilnius (Lithuania) study of eight TBI patients , 30 independent paired data points (invasive ICP is measured using Codman microsensor parenchymal catheter kit with ICP sensor REF 82-6631); green points – on going Turku (Finland) study, five TBI patients, 13 independent paired data points (invasive ICP is measured using Codman microsensor ventricular catheter kit with ICP sensor REF 82-6653); blue points – Umea (Sweden) double blinded study, 11 patients, 29 independent paired data points ("Likvor Celda" reference ICP device and dynamic infusion via lumbar puncture test methodology has been used); violet points – Baylor CM (Houston, USA) double blinded study, six patients, six independent paired data points ("gold standard" invasive ICP is measured via lumbar puncture), grey points – on-going Aarau (Swiss) study with five TBI patients, 15 independent paired data points (invasive ICP is measured using Codman microsensor parenchymal catheter kit with ICP sensor). Here: Δ – absolute difference (absolute error) of paired non-invasive and invasive ICP data; Mean ICP is a mean value of invasively and non-invasively measured absolute ICP values; green lines – absolute error Δ corridor (±4.0 mmHg) caused by sampling step of externally applied pressure Pe, which is equal to 4.0 mmHg; vertical red lines show two clinically important ICP thresholds: neurological patients' general critical ICP threshold of 14.7 mmHg and severe TBI patients' critical ICP threshold of 20.0 mmHg

The clinical studies of 162 patients with a traumatic brain injury showed (Fig.1) that the Vittamed 205 apparatus measures non-invasively with a negligible systematic error (0.12 mmHg) and does not require calibration. Its SD of random errors is 2.52 mmHg.

By performing the analysis of 2,946 available patents according to the meaningful words „intracranial pressure“, „noninvasive intracranial pressure“ and „non-invasive intracranial pressure“ it was found that the balance method of two pressures –ICP and Pe added to a closed eye lid – offered by prof. Ragauskas, when the intracranial (internal) segment of the eye artery and intraorbital (external) segment used as a natural pressure sensor have had no analogues so far. All other offered and patented non-invasive ICP measurement methods are based on the correlation between some intracranial biological object parameters and ABP or are based on a mathematical object relating ICP to arterial blood pressure and cerebral blood flow inside the cerebral artery (Niddle cerebral artery). All of these methods, unfortunately, require system calibration “patient-non-invasive ICP meter”, which is impossible, since the reference non-invasive ICP meter is non-existent.

### 1.2. Analysis of cerebral autoregulation

Brain Trauma Foundation defines traumatic cerebral injury (TBI) as “a sudden trauma caused by the blow to the head which leads to cerebral injury”. Cerebral trauma can often cause the impairment of CA function, which means that the brain cannot maintain proper fluid pressures within the upper and lower autoregulation limits according to the Lassen curve. Since the operating mechanisms to prevent that are non-existent, CPP can easily fall below the lower limit of brain hypofusion, which can rapidly cause brain ischemia. For the state of ischemia, brain lacks oxygen and nutrients, so secondary injuries of cerebral tissues increase and the probability of functional recovery decreases.

The possible consequences of CA impairment after cerebral injury are presented in Fig.2. The green curve represents healthy functioning CA, which remains rather constant within the upper and lower CA limits because CPP and mean arterial pressure (MAP) vary. The red dotted line illustrates impaired CA function which can cause ischemia and oedema as well as other secondary injuries.

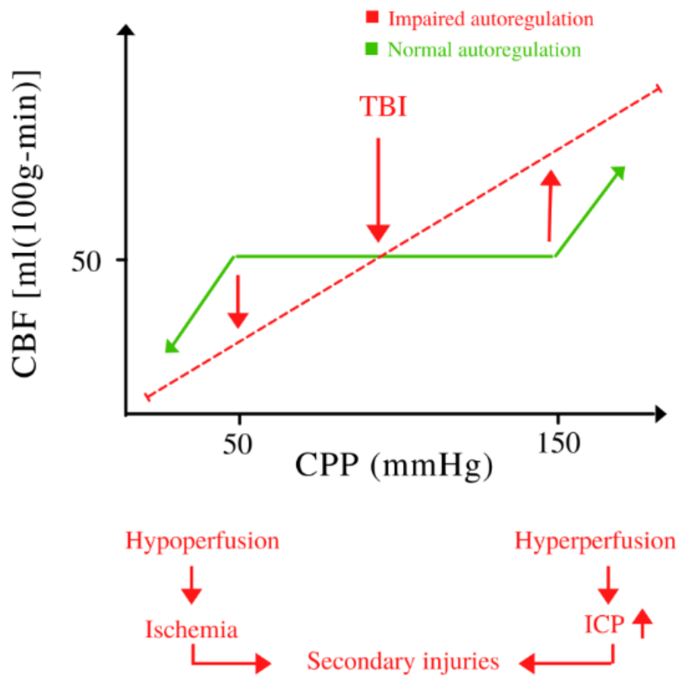

**Fig. 2** Lassen curve for the operating and impaired cerebral autoregulation

## 1.3. Analysis of monitoring methods of cerebral autoregulation

Over the past 20 years, different CA monitoring and evaluation methodologies and equipment were developed and used, such as transcranial Doppler (TCD), functional near infrared radiation spectroscopy (fNIRS), brain tissue oxygen saturation, parenchymal ICP monitors, etc. Alongside with each of these monitoring methods the indexes for CA evaluation were developed, such as mean flow index (Mx), volumetric reactivity index (VRx), oxygen reactivity index (ORx) and pressure reactivity index (PRx). Today clinical practice employs PRx to evaluate CA, which is considered as a clinical standard.

PRx describes the ability of cerebral blood vessels to change their diameter while reacting to the ABP fluctuations by retaining a stable cerebral blood flow (CBF). This index is calculated as the Pearson correlation coefficient between the slow waves of ABP and ICP. Slow waves are the fluctuations which can be found in ICP and ABP signals and which are longer than those which are stimulated by physiological reactions of breathing or heart work. The waves can be classified as slow waves, as the signal component vary at the frequency limit ranging from 0.05 to 0.0055. Rhythmic changes of CBF directly influence the form of the ICP slow wave where the increased slow wave amplitude shows CA response.

## 1.4. Analysis of ophthalmic artery blood flow phantom

After analysing previous scientific works, a single publication on the attempt to create an ophthalmic artery blood flow phantom was found. That was at the Pereira Technologies University in Columbia. By analysing the phantom structure, the used technological solutions, and results it was stated that the described phantom is not suitable to study the operating principle of non-invasive intracranial pressure measurement. The phantom described in the publication did not have the individual internal and external segments of eye artery which can be affected individually by different pressures. Also, it proved impossible to generate an appropriate pulse waves form.

Due to these reasons, it was decided to create a unique phantom of ophthalmic artery blood flow appropriate for the solution of the problem.

## 1.5. Analysis of machine learning algorithms and artificial intelligence methods

Supervised Machine Learning is the application of artificial intellect when the machine or computer are learning from the available data including the results (input data) to make future predictions (output data) according to the supplied new data for artificial intellect algorithm. To perform this task, the system learns from the supplied set of data referred to as learning data. This chapter describes the usage of machine learning algorithms with a teacher by carrying out data analysis and processing patients with traumatic brain injuries and by identifying the optimal values of cerebroperfusion pressure.

The machine learning methods have already been included in the studies of patients with traumatic brain injuries, such as support vector machines, decision trees and artificial neural networks. These studies were firstly based on the identification of features of patients with traumatic brain injuries from radiological pictures and long-term prediction for patients after discharge from hospital. Most studies analysing the application of machine learning methods in the case of traumatic brain injuries made a conclusion that the model of support vector machine is the best classifier and provides a better prediction precision than other models. Other studies showed that the artificial neural network model is the best classifier in the case of traumatic brain injuries and in analysing mortality prediction.

## II. DEVELOPMENT AND STUDY OF A UNIQUE PHANTOM OF THE OPHTHALMIC ARTERY BLOOD FLOW

A unique ophthalmic artery blood flow phantom reflecting two, external and internal, eye artery segments, was developed where simultaneous measurement of blood flow dynamics parameters and their dependence on the external pressure added by using Doppler technology. In addition, operating mechanisms allowing to measure the pressure in each chamber, the tension of fluid imitating blood and fluid system resistance at its end (hydrodynamic resistance) were integrated independently. This enables adequate imitation of hemodynamic processes in the eye artery and adjacent tissues as well as tests the operation principle of non-invasive intracranial pressure measurement method. Fig. 3 represents the principal diagram of the developed phantom.

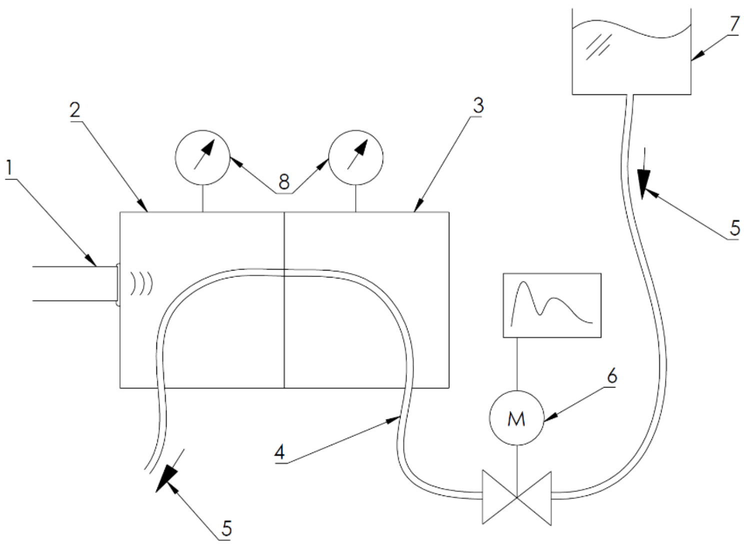


**Fig. 3** Principal diagram of the ophthalmic artery blood flow phantom

To study the operating principle of non-invasive intracranial pressure measuring method, the developed phantom of ophthalmic artery blood flow was tested. The scope of the test was 100 independent measurements with the aim to identify the tension in the chamber imitating the internal eye artery segment. The tension varied in the range of 4 to 40 mmHg with the tension step of 4 mmHg. This way, 10 different tension values given in advance were measured in the internal chamber with the tension values of 4, 8, 12, 16, 20, 24, 28, 32, 36, and 40mmHg. For each identified tension value, 10 measurements were made.

After the linear regression analysis, it was found that 94% of errors of all the measurements fall into the error corridor of ±4 mmHg interval. It is to be noted that the errors of not all measurements with the established 36mmHg pressure value in the internal chamber fall into the expected ±4 mmHg interval error corridor. Later the reason of this phenomenon was established to be that during measurement the internal chamber imitating intracranial pressure was depressurized and the proper pressure of 36mmHg was not maintained. The results of the linear regressive analysis are presented in Fig. 4.

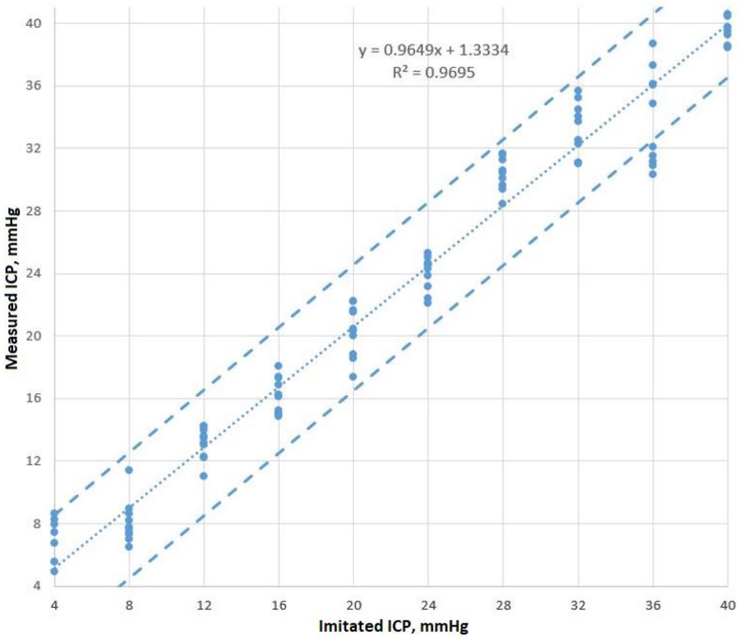


**Fig. 4** Results of linear regressive analysis. A dotted blue line marks the ±4 mmHg corridor of measured pressure errors. A dotted blue straight line marks the regression curve with the straight-line coefficients a=0.9649 and b= 1.3334, and R2 = 0.9695. Each blue dot marks the values of measured and imitated intracranial pressure obtained during every experiment

## III. STUDY OF THE OPTIC NERVE SHEATH AND OPTIC NERVE SUBARACHNOID SPACE

The aim of the study is to carry out an experimental pilot study of the ONSD and ONSS measurements by using a high frequency ultrasound scanner, and by means of the obtained data to establish the differences of optic nerve sheath diameter and optic nerve subarachnoid space between measurements, when a healthy volunteer is lying and when he is turned head down. External pressure Pe was applied to the apple of the eye and the surrounding tissues with the aim to increase the intraorbital tension and to compress the optic nerve sheath seeking to establish the value of absolute intracranial pressure.

This experiment involved 20 healthy volunteers. All of them are researchers of Biomedical Engineering and students of KTU Health Telematics Science Institute, 16 of which were men and 4 were women. The average age (±SD) was 34.1 years (±10.1) (range: 20–60 years).

Table 1 presents the results of each measured parameter (ONSD, ONSS1, ONSS2 sum). Here ONSD is diameter of optic nerve sheath and ONSS2 is optic nerve left and right subarachnoid space.

**Table 1** The calculated statistical mean, median, p (normal distribution) and P (similarity between groups) estimates

| Parameter | Body position | Mean | Median | p (normal distribution) | P (similarity between group) |
|---|---|---|---|---|---|
| **ONSD, mm** | Supine | 6.054 | 5.84 | 0.0254 | 0.0000048 |
| | 20mmHg | 6.396 | 6.3 | 0.512 | |
| **ONSS #1, mm2** | Supine | 4.441 | 4.425 | 0.552 | 0.00000229 |
| | 20mmHg | 5.366 | 5.19 | 0.374 | |
| **ONSS #2, mm2** | Supine | 4.912 | 5.255 | 0.176 | 0.0695 |
| | 20mmHg | 5.279 | 5.05 | 0.212 | |
| **ONSS sum** | Supine | 9.352 | 9.305 | 0.389 | 0.00000968 |
| | 20mmHg | 10.646 | 10.535 | 0.846 | |

# IV. STUDY OF CEREBRAL AUTOREGULATION OF PATIENTS WITH GLAUCOMA

During this study the cerebral autoregulation dynamics for patients suffering from normal tension glaucoma (NTG) and high tension glaucoma (HTG) was analysed for the first time by means of non-invasive ultrasonic technologies comparing it with a control group of healthy people. This prospective clinical study was carried out at the Eye Clinic of Lithuanian University of Health Sciences.

The study included patients suffering from normal and high tension glaucoma as well as healthy persons. The inclusion criteria were the following: the ophthalmologist confirmed clinical glaucoma diagnosis, the presence of optic nerve change and loss of view corresponding to glaucoma.

The measurement sample of this prospective clinical study was 28 persons who were divided into three groups: normal tension glaucoma patients (NTG), high tension glaucoma patients (HTG) and healthy persons. The NTG group consisted of 10 patients, nine of which were women and one was a man. The average age was 67.5 (SD = ±2.3) years. The HTG group consisted of eight patients, all of which were women, average age was 73.2 (SD ±2.7). The healthy persons' group was composed of 10 people, eight of which were women and two were men, average age was 71.1 years (SD = ±5.1).

Table 2 presents CA monitoring results. After the Shapiro-Wilk normal distribution law test according to VRx parameter, CA monitoring data did not show normal distribution, therefore, a comparison between groups was based on the Mann-Whitney test. The average VRx was -0.18 ± 0.22 for healthy persons, 0.06 ± 0.17 for the patients with NTG, and -0.07 ± 0.25 for patients with HTG. The VRx value for healthy persons was statistically significantly smaller than for patients with NTG ($p < 0.05$). Among healthy persons and HTG groups significant differences were not observed ($p=0.36$ and $p=0.24$, respectively).

LCAI duration average (when VR > 0) was 127 ± 66 sec for healthy persons, 281 ± 151 sec for patients with NTG and 231 ± 218 sec for patients with HTG. The average value of LCAI duration was statistically significantly smaller than for patients with NTG ($p < 0.05$). However, significant differences between healthy persons and patients with HTG and between patients with NTG and HTG were not observed ($p = 0.35$ and $p=0.10$, respectively).

LCAI duration average (when VRx > 0) was 13 ± 38 sec for healthy persons, 73 ± 59 sec for patients with NTG, and 42 ± 65 sec for patients with HTG. LCAI average duration for healthy persons was significantly lower than for persons with NTG ($p < 0.05$); however, significant differences between healthy persons and patients with HTG and between patients with NTG and HTG were not observed (p=0.20 and p=0.15, respectively).

**Table 2** The parameter averages of VRx, LCAI, when VRx > 0 and LCAI, when VRx > 0.4, standard deviations and the estimate P of group data normal distribution

| Parameter | HS, Mean ± SD | NTG, Mean ±SD | HTG, Mean ±SD | P |
|---|---|---|---|---|
| VRx | −0.18 ± 0.22 | 0.06 ± 0.17 | −0.07 ± 0.25 | 0.068 |
| LCAI, VRx>0 s | 127 ± 66 | 281 ± 151 | 231 ± 218 | 0.02 |
| LCAI, VRx>0.4, s | 13 ± 38 | 73 ± 59 | 42 ± 65 | 0.028 |

Here, HS is a group of healthy persons, NTG is a group of patients with normal tension glaucoma, and HTG is a group with high tension glaucoma.

## V. THE DEVELOPMENT OF CPPopt SOFTWARE AND THE STUDY OF MACHINE LEARNING AND ARTIFICIAL INTELLECT

This study involved a retrospective analysis of multimodal physiological monitoring data of 84 patients with traumatic brain injury with a view to use the obtained results for training a machine learning algorithm. The data was collected at the intensive care unit of Vilnius University Hospital as well as at Kaunas Clinical Hospital of Lithuanian Health Sciences University by carrying out clinical studies in 2013–2018. The monitoring data of high resolution 50hz continuous intracranial pressure (ICP(t), arterial blood pressure (ABP(t), brain perfusion pressure (SPS(t), as well as pulse reactivity index (PRx(t) were registered and calculated by means of the ICM+ Cambridge Software. ICM+ is software designed for scientific clinical research which offers a collection of high resolution data and real-time analysis from the patient's bedside monitoring sources. The intracranial pressure (IP) signals were monitored by using a Codman ICP monitor with an intraparenchymal catheter, and arterial blood pressure signals were monitored by means of photopletismogram with a Finapres NOVA blood dynamics monitoring system.

The CPPopt calculating software was developed by using the MATLAB (version R2020b, Math Works) software package. The principal aim of this tool was to illustrate and visually analyse the patient's physiological data accumulated by the ICM+software over a randomly selected monitoring window. Over the course of the research, it was noticed that the optimal length of the monitoring window is two hours as it was most convenient for the user. The software screen images are represented in Fig. 5 and Fig. 6.

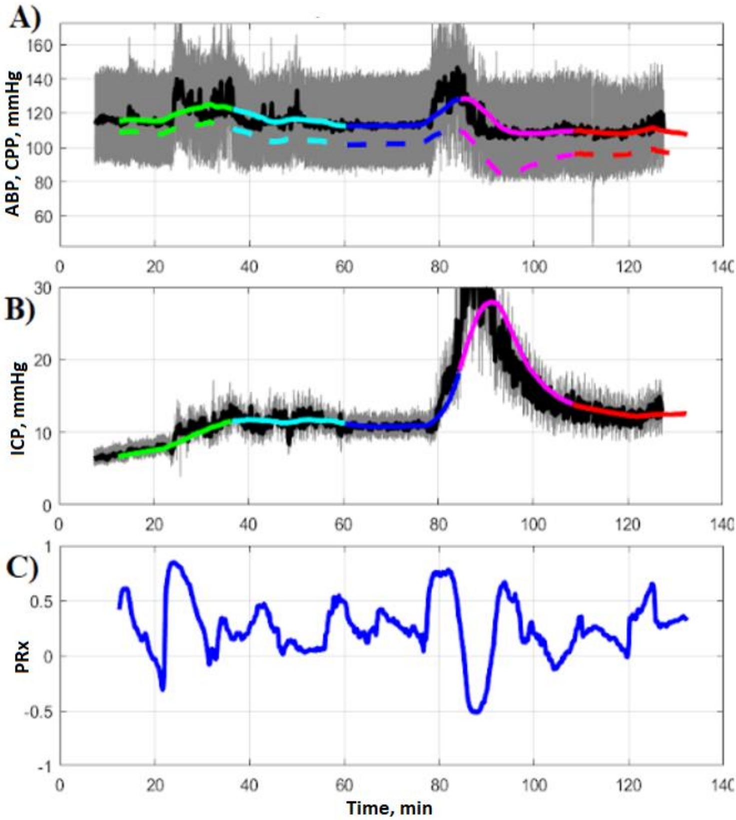


**Fig. 5** CPPopt software graphic user interface – patient's number 63, episode number 1 (left side of the screen shot)

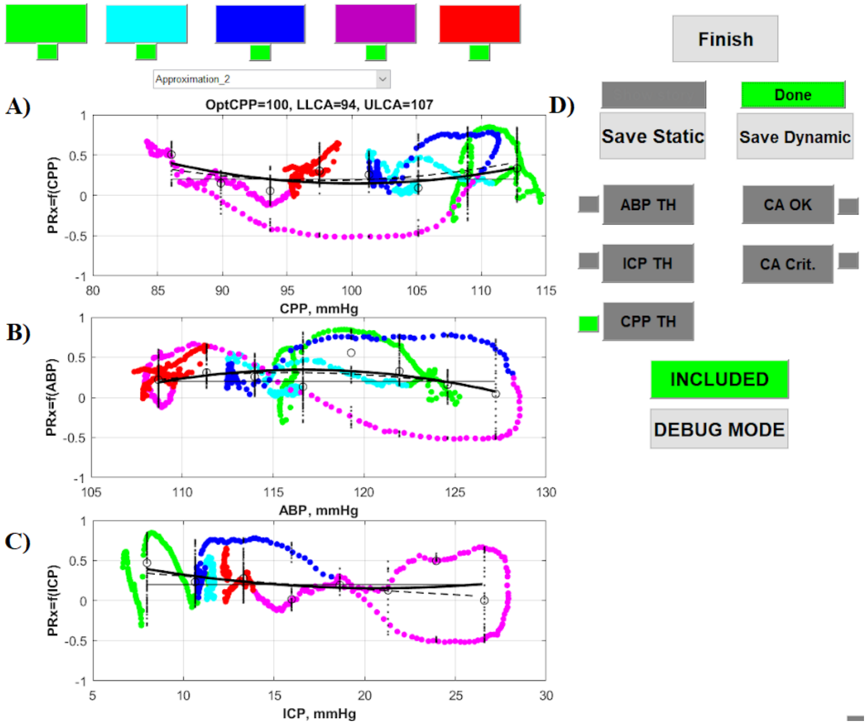


**Fig. 6** CPPopt software graphic user interface – patient's number 63, episode number 1 (right side of the screen shot)

The principal aim of this research was to develop and check the operation of the machine learning model algorithm providing the possibility to determine individual values of cerebroperfusion pressure for the patients with traumatic brain injury by using only the informative data. There was an attempt to use the possibility to identify optimal values of cerebroperfusion pressure in a shorter than 30 minutes time compared to a usual 4-hour monitoring window. This chapter presents the results of the offered algorithm, the analysis of productivity parameters, linear regression, correlation coefficients and standard deviations. The annotation results obtained with the CPPopt software are focussed on the ability of the machine learning model algorithm to correctly classify the groups and its precision in identifying individual optimal values of cerebroperfusion pressure.

The model (acc=68.8%) based on the support vector machine (SVM) method produced comparatively much better results compared to the artificial neural network model (acc=60.8%) in predicting informative and non-informative episodes. Therefore, a statistical analysis of the artificial neural network model was not included, and the attention was focused on the results of the model of the support vector machine.

The results of statistical analysis showed that the machine learning algorithm best improved prediction of the optimal value of brain perfusion pressure from the patient's informative physiological data compared to other clinical situations. However, in evaluating the operation of the algorithm, when it is used in the treatment strategies of high-risk patients, the equilibrium of sensitivity and specificity should be carefully considered. The study of the space under the ROC curve showed that the highest productivity of the algorithm was achieved when predicting clinical situations of critical and stable cerebral autoregulation. The regressive analysis failed to directly prove the added value of machine learning algorithm; however, it illustrates that the applied machine learning does not impede finding optimal values of brain perfusion pressure. In summary, it can be stated that statistical and regressive analysis together with standard deviation coefficients can help identify the possible applications and limitations of the machine learning model methods.

## CONCLUSIONS

The author's personal contribution to the publications proves that the dissertation material is original. All parts of the dissertation and the results obtained are patentable.

1. The study of 100 measurements sample by using the developed natural phantom showed that the ophthalmic artery blood flow phantom is suitable to test the precision and accuracy of the non-invasive intracranial pressure measurement method under idealized conditions. Random errors of the measurements fell into the identified error corridor of ±4 mmHg interval, and the linear regressive analysis estimate R2 equal to 0.9695 proved high precision of the non-invasive intracranial measurement method and linearity of the model. By means of the repeatability study analysis, statistical analysis error results were obtained, the identified pressure error average was equal to 1.331 mmHg, median was 1.33 mmHg, and the standard deviation estimate of only 0.722 mmHg confirms adequacy of the operation of the developed phantom.
2. The first experiment of external pressure application to the apple of the eye and surrounding tissues showed that the optic nerve sheath diameter decreased from 5.61 mm to 5.19 mm, when Pe measured inside the water chamber was increased from 0 mmHg to 45 mmHg. ONSD was affected by external pressure Pe, as expected. This experiment shows that the compression of ONSD by the external pressure principle and the intracranial pressure absolute value measurement idea in identifying balance "ICP is equal to intraorbital pressure" is potentially realizable. The measured optic nerve sheath diameter in a

horizontal position of the body was on average 5.767 mm, when intracranial pressure in such position approximately amounts to 10 mmHg. The measured optic nerve sheath diameter with the body turned head down at an angle calculated individually for the volunteer, thus increasing the ICP of the subject to approximately 30 mmHg, was on average 6.029. The difference of the optic nerve sheath diameter values obtained between different body positions was statistically significant (p=0.000138). The average difference between the sum values of the measured optic nerve subarachnoid space for the lying body position (the sum is 9.352mm2), and when the object's position was head down (sum was 10.646mm2), was statistically significant (p=0.00000968).

3. The application of machine learning increased the number of the optimal cerebral perfusion pressure identifications in limited duration episodes by 4.5% by comparing this number which was recieved without machine learning. In the cases when the patient's state is sensitive to minor changes of intracranial pressure and arterial blood pressure, this detection improvement of informative/non-informative episodes can upgrade the outcome results of the serious patients suffering from cerebral injury. The accuracy of the model operation was most efficient when identifying the limits of upper and lower cerebral autoregulation for the parameters of cerebral perfusion pressure (21% increase) and arterial pressure (20% increase).

4. The prospective clinical study results showed that the patients with normal tension glaucoma have impaired cerebral autoregulation, which can be diagnosed by carrying out non-invasive monitoring of cerebral autoregulation based on VRx index. In order to finally prove this hypothesis, further multicentre prospective clinical studies of a bigger number of samples according to the concept of precise medicine must be carried out.

## LIST OF SCIENTIFIC PUBLICATIONS ON THE SUBJECT OF THE DISSERTATION

1. [S1; US; OA] Hamarat, Yasin; Deimantavicius, Mantas; Dambrauskas, Vilius; Labunskas, Vaidas; Putnynaite, Vilma; Lucinskas, Paulius; Siaudvytyte, Lina; Simiene, Evelina; Stoskuviene, Akvilė; Januleviciene, Ingrida; Petkus, Vytautas; Ragauskas, Arminas. Prospective pilot clinical study of noninvasive cerebrovascular autoregulation monitoring in open-angle glaucoma patients and healthy subjects // Translational vision science & technology. Rockville, MD : Association for research in vision and ophthalmology. ISSN 2164-2591. 2022, vol. 11, iss. 2, art. no. 17, p. 1-10. DOI: 10.1167/tvst.11.2.17. [Science Citation Index Expanded (Web of Science); Scopus; MEDLINE] [IF: 3,283; AIF: 3,192; IF/AIF: 1,028; Q2 (2020, InCites JCR SCIE)] [M.kr.: M 001, T 010, T 001] [Indėlis: 0,083]
2. [S1; CH; OA] Hamarat, Yasin; Bartusis, Laimonas; Deimantavicius, Mantas; Lucinskas, Paulius; Siaudvytyte, Lina; Zakelis, Rolandas; Harris, Alon; Mathew, Sunu; Siesky, Brent; Januleviciene, Ingrida; Ragauskas, Arminas. Can the treatment of normal-pressure hydrocephalus induce normal-tension glaucoma? A narrative review of a current knowledge // Medicina. Basel : MDPI. ISSN 1648-9144. eISSN 1010-660X. 2021, vol. 57, iss. 3, art. no. 234, p. 1-10. DOI: 10.3390/medicina57030234. [Science Citation Index Expanded (Web of Science); Scopus; MEDLINE] [IF: 2,430; AIF: 5,182; IF/AIF: 0,468; Q2 (2020, InCites JCR SCIE)] [M.kr.: M 001, T 010, T 001] [Indėlis: 0,090]
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4. [S1; CH; OA] Deimantavicius, Mantas; Hamarat, Yasin; Lucinskas, Paulius; Zakelis, Rolandas; Bartusis, Laimonas; Siaudvytyte, Lina; Januleviciene, Ingrida; Ragauskas, Arminas. Prospective clinical study of non-invasive intracranial pressure measurements in open-angle glaucoma patients and healthy subjects // Medicina. Basel : MDPI. ISSN 1648-9144. eISSN 1010-660X. 2020, vol. 56, iss. 12, art. no. 664, p. 1-8. DOI: 10.3390/medicina56120664. [Science Citation Index

Expanded (Web of Science); Scopus; MEDLINE] [IF: 2,430; AIF: 5,182; IF/AIF: 0,468; Q2 (2020, InCites JCR SCIE)] [M.kr.: M 001, T 001, T 010] [Indėlis: 0,125]

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8. [S1; LT; OA] Petkus, Vytautas; Vainoras, Alfonsas; Berskiene, Kristina; Navickas, Zenonas; Ruseckas, Rimtautas; Piper, Ian; Deimantavicius, Mantas; Ragauskas, Arminas. Method for prediction of acute hypotensive episodes // Elektronika ir elektrotechnika. Kaunas : KTU. ISSN 1392-1215. eISSN 2029-5731. 2016, vol. 22, no. 1, p. 44-48. DOI: 10.5755/j01.eee.22.1.13453. [Science Citation Index Expanded (Web of Science); Scopus; Computers & Applied Sciences

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2. [T1a; GB] Hamarat, Y.; Deimantavicius, M.; Zakelis, R.; Bartusis, L.; Preiksaitis, A.; Ragauskas, A. 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. Oxford : John Wiley & Sons. ISSN 1351-5101. eISSN 1468-1331. 2018, vol. 25, iss. S1, P54, p. 60. [Conference Proceedings Citation Index - Science (Web of Science)] [M.kr.: M 001, T 001, T 010]
3. [T1a; GB] 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. London : SAGE. ISSN 1747-4930. eISSN 1747-4949. 2017, Vol. 12, iss. 1S, p. 29. DOI: 10.1177/1747493017703913. [Science Citation Index Expanded (Web of Science)] [M.kr.: T 010]

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2. [T1e; CZ] Hamarat, Yasin; Deimantavicius, Mantas; Zakelis, Rolandas; Bartusis, Laimonas; Preikšaitis, Aidanas; Ragauskas, Arminas. A pilot study of non-invasive intracranial pressure monitoring // Bioelectrics 2018: 15th international bioelectrics symposium, September 23-26, 2018, Prague, Czech Republic. Prague : Institute of Plasma Physics of the CAS. 2018, P08, p. 56. [M.kr.: T 001, M 001, T 010]
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| | |
|---|---|
| 1999–2007 | Kaunas Martynas Mažvydas high school |
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| 2010–2014 | Kaunas University of Technology, Faculty of Informatics. Bachelor of Informatics, 2014. |
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| 2014–present | Junior researcher – Kaunas University of Technology, Health Telematics Science Institute |
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## REZIUMĖ

### Problemų svarba

Intrakranijinis slėgis apibrėžiamas kaip smegenų skysčio slėgis kaukolės ir stuburo kanalo viduje. Žmogaus galvos smegenų neuronai yra greičiausiai mirštančios ląstelės žmogaus organizme, kai jie nėra aprūpinami deguonimi ir maisto medžiagomis prisotintu krauju. Intrakranijinis slėgis (IKS) tiesiogiai veikia smegenų perfuzijos slėgį (SPS), kurio sumažėjimas žemiau individui būdingos fiziologinės ribos stabdo smegenų ląstelių metabolizmą joms reikalingomis medžiagomis ir gali sukelti greitą jų žūtį. Taip pat reikėtų pabrėžti, kad vos kelias minutes trunkantis neuronų aprūpinimo sutrikdymas negrįžtamai pažeidžia smegenų audinius. Sveiko žmogaus, priklausomai nuo kelių faktorių (kūno padėtis, fizinis aktyvumas ir pan.), fiziologinės intrakranijinio slėgio ribos yra nuo 7 iki 15 mmHg. 22 mmHg krizinis intrakranijinio slėgio slenkstis yra ta riba, kurią viršijus būtina imtis klinikinėje praktikoje apibrėžtų gydymo scenarijų, o 40 mmHg ir didesnė IKS vertė yra traktuojama kaip kritinė ir siejama su maža išgyvenimo tikimybe ar mirtimi. Intrakranijinio spaudimo padidėjimas virš individualiam pacientui kritinės ribos yra vertinamas kaip antrinis smegenų pažeidimas.

Pasaulinėje klinikinėje praktikoje intrakranijinis slėgis matuojamas tik invaziniais metodais. Tai sudėtingos, reikalaujančios aukštos kvalifikacijos neurochirurgų arba neurologų, brangios bei rizikingos procedūros. Dėl šių priežasčių intrakranijinis slėgis dažniausiai yra matuojamas tik pacientams, patyrusiems sunkią galvos traumą. Vis dėlto intrakranijinio slėgio matavimas būtų naudingas ir kitų ligų atvejais. Hidrocefalija, meningitas ir kitos infekcijos, glaukoma, hemoraginiai insultai ir kt. sukelia IKS pokyčius, kuriuos būtina matuoti ir stebėti siekiant individualizuoti ir optimizuoti gydymo sprendimus. Tam reikalingos neinvazinės IKS matavimo ir stebėsenos technologijos.

Smegenų kraujotakos autoreguliacija yra žmogaus organizme vykstantis automatinis procesas – gebėjimas reguliuoti kraujotaką, kuri stabilizuojama siekiant užtikrinti optimalų smegenū ląstelių – neuronų – metabolizmą. Intrakranijinio slėgio padidėjimas aukščiau kritinės ribos individualiam pacientui taip pat kaip ir kraujospūdžio padidėjimas ar sumažėjimas indivudualiam pacientui gali būti smegenų kraujotakos autoreguliacijos sutrikdymo priežastis. Sutrikus smegenų kraujotakos autoreguliacijai neuronai yra pažeidžiami arba miršta.

Per pastaruosius 20 metų buvo sukurta ir naudojama įvairi smegenų kraujotakos autoreguliacijos (SKA) stebėsenos ir vertinimo metodika bei įranga, pvz., transkranijinis dopleris (TCD), artimosios infraraudonųjų spindulių spektroskopija (NIRS), smegenų audinio prisotinimas deguonimi, parenchiminiai IKS monitoriai ir kt. Kartu su kiekvienu iš šių stebėjimo metodų buvo sukurti indeksai SKA vertinimui, pvz., vidutinis kraujo srauto indeksas (Mx), smegenų tūrinis reaktyvumo indeksas (VRx), deguonies reaktyvumo indeksas (ORx) ir intrakranijinio slėgio reaktyvumo indeksas (PRx). Šiandien klinikinėje praktikoje PRx plačiausiai naudojamas SKA būsenos vertinimui. Tačiau trūksta aukščiausio trečio lygmens įrodymų, kad PRx taptų invazinių autoreguliacijos būsenos vertinimo indeksu, pripažįstamu kaip klinikinis standartas.

Reikėtų pabrėžti, kad dažniausia smegenų kraujotakos autoreguliacijos sutrikimo ir padidėjusio intrakranijinio slėgio priežastis yra sunkios galvos smegenų traumos, kurios statistiškai pasaulyje yra dažnas įvykis. Vien 2010 m. Europos sąjungos šalyse buvo nustatyta beveik 3 mln. ir JAV beveik 2 mln. smegenų traumų atvejų, kurių gydymui buvo išleista daugiau nei 160 mlrd. JAV dolerių. CDC (*Centers for Disease Control*) duomenimis galvos smegenų traumos yra pagrindinė žmonių iki 45 metų amžiaus mirties ir negalios priežastis.

Pasaulinėje klinikinėje praktikoje siekiama, kad IKS ir SKA matavimai būtų atliekami įvairesnėms pacientų grupėms bei būtų taikoma precizinės medicinos koncepcija, reikalaujanti individualaus paciento organizmo pažinimo (genetinė analizė ir modernios diagnostikos procedūros) siekiant priimti optimalius ir efektyviausius įmanomus individualaus paciento gydymo sprendimus.

Šio darbo tyrimo objektai yra profesoriaus A. Ragausko idėjų pagrindu sukurtos neinvazinės IKS absoliutinės vertės ir SKA matavimo sistemos bei jų pritaikomumas precizinės medicinos koncepcijai įgyvendinti.

**Mokslinė-technologinė problema ir darbinė hipotezė**

Žmogaus galvos smegenų traumų atveju arba įvairiose chirurgijos srityse (kardiochirurgija, trasplantalogija, neurochirurgija ir kt.) svarbiausi fiziologiniai parametrai, kuriuos būtina diagnozuoti, stebėti ir valdyti siekiant geriausios gydymo baigties yra arterinis kraujospūdis (AKS), intrakranijinis slėgis (IKS) ir smegenų kraujotakos autoreguliacijos būklė.

Mokslinė technologinė problema: ar įmanoma sukurti IKS neinvazinio matavimo ir SKA stebėsenos technologijas, kurios tenkintų klinikinius jautrumo ir specifiškumo reikalavimus esant veikiančiai arba sutrikdytai smegenų kraujotakos autoreguliacijai?

Darbinė hipotezė: slėgių balanso principu veikianti technologija ir optinio nervo subarachnoidinio tarpo ploto matavimo technologija gali būti išvystytos iki klinikinei praktikai reikiamo tikslumo ir preciziškumo neinvazinio IKS vertės matuoklio, o neinvazinė TOF SKA stebėsenos technologija gali būti išvystyta iki klinikinei praktikai reikiamo jautrumo ir specifiškumo.

**Darbo tikslas ir uždaviniai**

Darbo tikslas – atlikti eksperimentinius neinvazinės intrakranijinio slėgio absoliutinės vertės matavimo ir smegenų kraujotakos autoreguliacijos stebėsenos sistemų tyrimus bei panaudojus gautus naujus mokslinių tyrimų duomenis nustatyti būdus ir priemones, leidžiančias įrodyti, kad naudojant šias sistemas yra įmanoma taikyti precizinės medicinos gydymo koncepciją.

Darbo tikslui pasiekti buvo suformuluoti tokie uždaviniai:

1. Atlikti intrakranijinio slėgio matavimo metodo analizę bei nustatyti šios sistemos tobulinimo galimybes. Tam tikslui sukurti ir išbandyti akies arterijos imitatorių bei jį naudojant ištirti intrakranijinio slėgio matavimo slėgio balanso principu ir neinvaziniu būdu metodo paklaidas. Atlikus patentinę paiešką buvo nustatyta, kad natūrinis tokiam tikslui skirtas imitatorius neegzistuoja. Jis reikalingas tam, kad būtų galima idealiomis sąlygomis eksperimentiškai atlikti tai, kas nebuvo padaryta kuriant neinvazinio IKS matuoklio, veikiančio slėgių balanso princupu, matematinius modelius (Džiugys Misiulis), kadangi matematiniai modeliai aprašo metodą, kaip pulsuojančių akies arterijos segmenų sąveiką su pridėtais slėgiais, bet neaprašo ultragarsinių doplerinių šių segmentų kraujotakos parametrų matavimų paklaidų. Taip pat atlikti eksperimentinius bandomuosius optinio nervo dangalo diametro (ONDD) ir optinio nervo subarachnoidinio tarpo (ONSE) matavimų tyrimus naudojant aukšto dažnio ultragarsinį skenerį ir gautais duomenimis nustatyti optinio nervo dangalo diametro ir optinio nervo subarachnoidinės erdvės skirtumus tarp matavimų sveikam savanoriui gulint ir pavertus tiriamąjį žemyn galva, kai tikslingai keičiama IKS vertė ir smegenų slankumo vertė. Taip pat akies obuoliui ir aplinkiniams audiniams taikyti išorinį spaudimą (Pe), siekiant padidinti intraorbitinį slėgį ir suspausti optinio nervo dangalą absoliučios IKS vertės matavimo tikslais.
2. Sukurti programinę įrangą, skirtą palengvinti retrospektyvinę pacientų duomenų analizę bei atlikti anotaciją rezultatų, kurie buvo surinkti iš sunkią galvos traumą patyrusių pacientų, gulinčių intensyviosios terapijos skyriuje. Atlikus duomenų analizę, pagal gautus rezultatus sukurti ir ištirti mašininio mokymo algoritmą, skirtą automatizuotam informatyvių ir neinformatyvių signalo epizodų klasifikavimui bei optimalios smegenų perfuzijos slėgio vertės radimui, panaudojant anotuotus duomenis antro duomenų analizės etapo metu.
3. Atlikti smegenų kraujotakos autoreguliacijos stebėsenos metodo analizę bei nustatyti šios sistemos tobulinimo galimybes. Pirmą kartą neinvazinėmis ultragarso technologijomis išanalizuoti smegenų kraujotakos autoreguliacijos dinamiką pacientams, sergantiems

normalaus akispūdžio glaukoma (NTG) ir aukšto akispūdžio glaukoma (HTG), bei palyginti su sveikų asmenų kontroline grupe.

**Mokslinis naujumas**

Sukurtas unikalus, neturintis analogų akies arterijos kraujotakos imitatorius.

Sukurta nauja programinė įranga, leidžianti vizualiai lengviau analizuoti fiziologinius pacientų signalus, surinktus ICM+ įranga, bei nustatyti ryšius tarp fiziologinių parametrų.

Sukurtas mašininiu mokymu pagrįstas algoritmas, leidžiantis klasifikuoti informatyvius / neinformatyvius pacientų fiziologinių signalų epizodus automatiniu būdu.

Atlikus tyrimo uždaviniuose paminėtas studijas pirmą kartą buvo gauti nauji empiriniai duomenys, kuriuos pasitelkus buvo nustatytos neinvazinių žmogaus smegenų kraujotakos stebėsenos metodų tobulinimo ir plėtojimo galimybės.

**Tyrimo metodai ir priemonės**

Atliekant sunkias galvos traumas patyrusių pacientų, glaukoma sergančių pacientų ir sveikų savanorių prospektyvines ir retrospektyvines studijas bei tiriant sukurtą akies arterijos imitatorių, buvo naudojamos neinvazinės intrakranijinio slėgio absoliutinės vertės matavimo ir smegenų kraujotakos autoreguliacijos stebėjimo sistemos, sukurtos Sveikatos telematikos mokslo institute (KTU).

Sveikų savanorių studija bei eksperimentai su akies arterijos imitatoriumi atlikti Kauno technologijos universitete, Sveikatos telematikos mokslo institute. Sunkias galvos traumas patyrusių pacientų studija atlikta Respublikinės Vilniaus universitetinės ligoninės intensyviosios terapijos skyriuje bei Lietuvos sveikatos mokslų universiteto Kauno klinikose. Glaukomos pacientų studija atlikta Lietuvos sveikatos mokslų universiteto ligoninėje, Akių ligų klinikoje.

Kuriant programinę įrangą, skirtą duomenų analizei, bei jų anotavimui buvo naudojamas „MatLab“ (versija R2020a) programinis paketas. Atliekant surinktų duomenų statistinę analizę buvo naudojama „MatLab“ (versija R2020a) ir „IBM SPSS Statistics“ programiniai paketai.

**Praktinė darbo rezultatų reikšmė**

Sukurtas ir eksperimentiškai ištirtas akies arterijos imitatorius, leidžiantis pademonstruoti intrakranijinio slėgio matavimo neinvaziniu būdu metodo veikimo principą, pagrįstą akies arterijos kraujotakos vidiniame ir išoriniame segmentuose parametrų matavimu ir slėgių balansu.

Sukurta programinė įranga, palengvinanti pacientų, patyrusių sunkią galvos traumą, duomenų analizę ir jų anotavimą, bei ją panaudojant, sukurtas ir išbandytas mašininio mokymo algoritmas nustatant optimalias smegenų perfuzijos slėgio vertes, individualias kiekvienam pacientui, siekiant patobulinti precizine medicina grindžiamus gydymo metodus.

Neinvazinėmis ultragarso technologijomis išanalizuota smegenų kraujotakos autoreguliacijos dinamika pacientams, sergantiems normalaus ir aukšto akispūdžio glaukoma, bei rezultatai palyginti su sveikų asmenų kontroline grupe.

Parodyta, kad optinio nervo subarachnoidinio tarpo ploto matavimo technologija gali būti išvystyta iki neinvazinio intrakranijinio slėgio vertės matuoklio.

**Gynimui teikiami teiginiai**

1. Unikalus akies arterijos imitatorius buvo sukurtas sėkmingai ir juo pademonstruotas intrakranijinio slėgio matavimo neinvaziniu būdu pasiekiamo slėgių balanso metodo veikimas, pagrįstas akies arterijos kraujotakos vidiniame ir išoriniame segmentuose parametrų matavimu. Pirmą kartą parodyta, kad šis metodas nereikalauja kalibravimo ir gali užtikrinti klinikinei praktikai reikiamą tiklumą ir preciziškumą.
2. Panaudojant mašininį mokymą galima patobulinti precizinės medicinos gydymo metodus, grindžiamus intrakranijinio slėgio matavimu ir smegenų kraujotakos autoreguliacijos stebėjimu neinvaziniu būdu.
3. Glaukoma sergančių pacientų perspektyvinio tyrimo rezultatai parodė, kad pacientams, sergantiems normalaus akispūdžio glaukoma, yra būdinga sutrikusi smegenų kraujotakos autoreguliacija.
4. Optinio nervo subarachnoidinio tarpo ploto matavimo technologija gali būti panaudota neinvazinio intrakranijinio slėgio matavimo metodui įgyvendinti, bet reikia išspręsti eksperimento metu iškilusias technines kliūtis ir pakartotinai atlikti tolesnius tyrimus.

**Darbo rezultatų aprobavimas ir publikavimas**

Darbo rezultatai disertacijos tema paskelbti 9 publikacijose mokslinės informacijos instituto (ISI) pagrindinio sąrašo leidiniuose. Darbo rezultatai taip pat buvo paskelbti tarptautinėse konferencijose „World Congress of Neurology“ Olandijoje, „European Society of Neurosonology and Cerebral Hemodynamics“ (ESNCH) Čekijoje, Vokietijoje, bei Vengrijoje, „BrainIT“ Belgijoje, „Bioelectrics“ Čekijoje.

**Disertacijos struktūra**

Disertaciją sudaro įvadas, septyni skyriai, naudotos literatūros sąrašas, autoriaus publikacijų sąrašas ir vienas priedas.

Pirmame skyriuje pateikiama literatūros apžvalga. Pristatomi dabartinėje klinikinėje praktikoje naudojami IKS ir SKA stebėsenos būdai. Taip pat apžvelgiami inovatyvūs naujausi šių parametrų stebėsenos metodai. Yra apžvelgiamos klinikinės situacijos, kuriose yra stebimi IKS ir SKA įverčiai.

Nuo antro iki šešto skyriaus pateikti pagal iškeltus darbo tikslus ir uždavinius atliktų eksperimentų ir tyrimų metodų aprašymai bei jų gauti rezultatai.

Septintame skyriuje yra pateikiama gautų rezultatų apibendrinimas ir išvados.

Disertacijos apimtis – 104 puslapiai, tekste pateikti 47 paveikslai ir 9 lentelės, literatūros sąraše nurodyta 60 šaltinių.

## IŠVADOS

Autoriaus asmeninis indėlis į publikacijas įrodo, kad disertacijos medžiaga yra originali. Visos disertacijos dalys ir gauti rezultatai yra patentabilūs.

1. Atlikus 100 matavimų imties tyrimą panaudojant sukurtą natūrinį imitatorių, parodyta, kad akies arterijos kraujotakos imitatorius yra tinkamas patikrinti intrakranijinio slėgio matavimo neinvaziniu būdu veikimo metodo tikslumą ir preciziškumą idealizuotose sąlygose. Matavimų atsitiktinės paklaidos pateko į nustatytą ±4 mmHg slėgio intervalo koridorių, o tiesinės regresinės analizės įvertis $R^2$, lygus 0,9695, parodė aukštą intrakranijinio slėgio matavimo neinvaziniu būdu veikimo metodo tikslumą ir modelio tiesiškumą. Atlikus atsikartojamumo tyrimo analizę buvo gauti statistinės analizės paklaidų rezultatai: nustatytų slėgių paklaidų vidurkis buvo lygus 1,331 mmHg, mediana 1,33 mmHg, o standartinio nuokrypio įvertis tik 0,722 mmHg. Tai patvirtina sukurto imitatoriaus veikimo adekvatumą.
2. Pirmasis išorinio slėgio Pe taikymo akies obuoliui ir aplinkiniams audiniams eksperimentas parodė, kad optinio nervo dangalo skersmuo sumažėjo nuo 5,61 mm iki 5,19 mm, kai Pe, matuotas vandeniu užpildytos kameros viduje, buvo didinamas nuo 0 mmHg iki 45 mmHg. Šis eksperimentas rodo, kad ONDD suspaudimas išorinio slėgio principu ir intrakranijinio slėgio absoliučios vertės matavimo idėja identifikuojant balansą „IKS yra lygus intraorbitiniam slėgiui“ yra potencialiai įgyvendinamas. Išmatuotas optinio nervo dangalo diametras horizontalioje kūno pozicijoje vidutiniškai buvo 5,767 mm, o intrakranijinis slėgis tokioje pozicijoje vidutiniškai siekia 10 mmHg. Išmatuotas optinio nervo dangalo diametras kūną pavertus žemyn galva apskaičiuotu individualiu savanoriui kampu ir taip padidinus tiriamojo IKS iki apytiksliai 30 mmHg vidutiniškai buvo 6,029 mm. Optinio nervo dangalo diametro reikšmių skirtumas, gautas tarp skirtingų kūno pozicijų, buvo statistiškai reikšmingas ($p = 0{,}000138$). Vidutinis skirtumas tarp išmatuotų optinio nervo subarachnoidinės erdvės plotų sumos verčių gulimoje kūno padėtyje (suma 9,352 $mm^2$) ir kai tiriamojo kūno padėtis buvo žemyn galva (suma 10,646 $mm^2$) buvo statistiškai reikšmingas ($p = 0{,}00000968$).
3. Mašininio mokymo taikymas užtikrino galimybę identifikuoti optimalaus smegenų perfuzijos slėgio vertes 4,5 % didesniame skaičiuje multimodaliosios stebėsenos ribotos trukmės epizodų, lyginant su epizodų, kuriuose pavyko nustatyti tas vertes nenaudojant mašininio mokymo algoritmo, kiekiu. Be to pavyko pademonstruoti galimybę sutrumpinti stebėsenos laiką, reikiamą optSPS vertei identifikuoti. Modelio veikimo preciziškumas buvo didžiausias nustatant viršutinę ir apatinę smegenų

kraujotakos autoreguliacijos ribas smegenų perfuzijos slėgiui (21 % padidėjimas) ir arteriniam kraujospūdžiui (20 % padidėjimas).

4. Prospektyvinio žvalgomojo klinikinio tyrimo rezultatai parodė, kad pacientai, sergantys normalaus akispūdžio glaukoma, turi sutrikusią smegenų kraujotakos autoreguliaciją, kurią galima diagnozuoti atliekant smegenų kraujotakos autoreguliacijos veikimo stebėjimą neinvaziniu būdu, pagrįstą VRx indeksu. Norint galutinai įrodyti šią hipotezę, reikia atlikti tolesnius didesnės imties multicentrinius prospektyvinius klinikinius tyrimus pagal precizinės medicinos koncepciją.

## INFORMACIJA APIE DISERTACIJOS AUTORIŲ

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**Išsilavinimas:**

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**Mokslinių interesų sritys:**

Neinvazinės žmogaus smegenų fiziologinių parametrų stebėsenos sistemos ir skaitmenins signalų apdorojimas**.**

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