Non-invasive assessment of intracranial biomechanics of the human brain

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Abstract

This review paper describes innovative methods and technology for non-invasive human brain physiological monitoring based on measuring the acoustic properties of the brain parenchyma. The clinical investigation of new technology shows the similarity between the invasively recorded intracranial pressure (ICP) and non-invasively recorded intracranial blood volume (IBV) pulse waves, slow waves and slow trends under intensive care unit (ICU) conditions. Also, the applicability of the non-invasive IBV slow wave monitoring technique for long-term non-invasive cerebrovascular autoregulation monitoring is supported by theoretical and experimental studies. The paper also describes a new absolute ICP measurement method which does not need calibration. The new method is based on a two-insonation depth transcranial Doppler (TCD) technique for absolute ICP and external absolute pressure aPe monitoring technique for long-term non-invasive cerebrovascular autoregulation monitoring supported by theoretical and experimental studies. The clinical study shows that it is possible to measure ICP non-invasively without calibration of the system.

Key words: innovative non-invasive methods, human brain, physiological monitoring, ultrasonic technique

Introduction

The primary clinical objective after traumatic brain injury (TBI) is to prevent secondary insults including elevated ICP, a common sequel to the primary injury. The concept is to prevent cerebral hypoxia by maintaining sufficient oxygen delivery to the intracranial neural tissues. This implies that cerebral blood flow (CBF), arterial oxygen saturation and hemoglobin concentration in a specific patient need to be adequate.

Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring is recommended for severe TBI. There are several limitations of ICP and CPP monitoring: the ICP devices are invasive, discreet ICP and CPP target recommendations are uncertain and not specific for the individual patient, CPP is not equivalent to CBF and the relationship between CBF and CPP depends on the status of CBF autoregulation.

Additional causes of elevated ICP include shaken-baby syndrome, epidural and subdural hematomas, brain hemorrhage, meningitis, encephalitis, lead poisoning, Reye’s syndrome, hypervitaminosis A, diabetic ketoacidosis, water intoxication, brain tumors, blood clots in the cranioacavity, abscesses, stroke, hydrocephalus and dural synus and venous thrombosis. Elevated ICP is very serious pathology and may be life threatening. It require immediate treatment and continuous monitoring.

This review paper describes innovative methods and technology for human brain non-invasive physiological monitoring. The non-invasive methods of brain physiological monitoring and the prototype devices have been developed by the “Vittamed technologijos” team. This presented study is the implementation of the project, “Technological development and applied research of complex equipment and innovative non-invasive methods of human brain physiological monitoring” (BPD04-ERPF-3.1.7-03-05/0020), funded by EU structural funds as per the Scientific Research and Development activity area (applied research and technological development of Measure 3.1, Direct Support for Business). The need for this project was determined by worldwide demand for physiological measuring equipment that would monitor the human brain non-invasively. Currently such equipment is not available in a clinical practice. The clinical investigation of new technology shows the similarity between the invasively recorded intracranial pressure (ICP) and non-invasively recorded intracranial blood volume (IBV) pulse waves, slow waves and slow trends under intensive care unit (ICU) conditions. Also, the applicability of the non-invasive IBV slow wave monitoring technique


for long-term non-invasive cerebrovascular autoregulation monitoring is supported by theoretical and experimental studies.

The paper also describes a new absolute ICP measurement method which does not need calibration. The new method is based on a two-insonation depth transcranial Doppler (TCD) technique for absolute ICP and external absolute pressure aPe comparison using the eye artery (EA) as a natural “scales”. The clinical study shows that it is possible to measure ICP non-invasively without calibration of the system.

Materials, methods and results

1. State of the art of non-invasive ICP measurement

The arterial blood pressure (ABP) and intracranial pressure (ICP) are both fundamental physiological parameters that must be monitored in brain injured patients in order to determine their physiological state. The most important characteristics of brain cerebrovascular function are cerebral blood flow autoregulation (CA), cerebrospinal compliance (CS), cerebral perfusion pressure (CPP), which are all dependent on ABP and ICP [27, 9, 26, 5]. It has been technically possible to measure ABP non-invasively since 1904 [11] after the invention of Nobel prize (1944) winner Joseph Erlanger. Why is it still impossible to measure absolute ICP non-invasively?

There are several main problems limiting the ability to create a non-invasive ICP meter. The first problem is to find a physiological or biophysical characteristic of the cerebrospinal system that could be related to ICP, the parameters of which could be measured using non-invasive methods. These concepts for a non-invasive ICP measurement have been appearing since 1977 which have generated many patents, the authors of which attempt to find the objects or physiological characteristics of the cerebrospinal system that would be related to the ICP and monitor them non-invasively (Table 1) [31, 29, 2, 17, 3, 10, 20, 19, 12, 22, 35, 14, 15, 4, 21, 34]. Most of the proposed monitoring technologies are based on use of ultrasound and are capable of monitoring physiological properties such as blood flow in: intracranial [2, 17] or intraocular vessels [29, 3, 10], pulsations of the cerebral ventricle [20, 19], brain tissue [12, 22], cranial bone diameter [35], dura matter thickness [14, 15], acoustic properties of the cranium [4] or skull bones [21].

The second problem is to define the relationship between non-invasively measured characteristics of the craniospinal system and absolute ICP which includes all the key known influential physiological and physical factors. Such a relationship could be expressed using the generic equation:

\[ E_{ICP}(t) = F_x(t, ABP, ICP,...) + \Delta S(t, ABP,...), \] (1)

where: \( E_{ICP} \) is the non-invasively measured ICP, \( F_x \) is a non-linear function which relates \( E_{ICP} \) and ICP and which depends on many influential factors including time, ABP, cerebrospinal compliance, the state of cerebral autoregulation, the state of a patient’s individual demographic factors (gender, age, etc.), \( \Delta S \) is the systematic error which also depends on a series of influential factors.

The third problem that must be solved in order to implement the non-invasive ICP monitoring is the question how to calibrate non-invasively and individually to the patient the absolute ICP meter?

While exploring these problems and considering the work of J. Guiset [12], we have developed the ultrasonic time of flight technology for non-invasive intracranial blood volume monitoring [27, 31, 25].

Our technology is based on the following experimental findings:

- the acoustic properties of the brain parenchymal acoustic path are dependent upon the blood, cerebrospinal fluid and parenchyma tissue volume within this path;
- these acoustic properties can be measured or monitored non-invasively and in real-time;
- the measured values of ultrasound speed and attenuation across the intracranial acoustic path are correlated to the intracranial volume changes and waves which are the causes of the ICP changes and waves.

Using this approach, a new information about the human cerebrovascular system can be obtained while measuring the dynamics of the acoustic properties of brain parenchyma [27, 25, 24]. These include:

- the correlation coefficient between non-invasively measured slow waves (such as B waves) of the cerebral blood volume and the slow waves of the ABP is an indicator of the function of cerebral blood flow autoregulation;
- the changes of brain compliance due to the pathological changes in intracranial component volumes influences the cerebral blood outflow. These cerebrospinal compliance changes can be determined by measuring the parameters of cerebral blood volume pulse waves.

2. Non-invasive intracranial blood volume change monitoring method

The cause of ICP fluctuations and ICP waves (\( \Delta ICPIP(t) \)) are intracraniospinal volume (V) changes \( \Delta V(t) \) (Fig. 1) [18]. Fig. 1 shows the relationship between ICP, V, CSC, intracranial blood volume pulse waves \( \Delta V(t) \) and ICP pulse waves \( \Delta ICPIP(t) \). Our aim was to create non-invasive ultrasonic technology for monitoring the volume V changes and volume waves \( \Delta V(t) \) in order to study the dynamics underlying ICP change. The dynamics of the craniospinal axis have not been studied before because of the lack of non-invasive volumetric monitoring technology.

The non-invasive measurement of the changes of intracranial component volumes is based on the time-of-flight for transmission of ultrasonic waves through a human head [27, 24]. As all intracranial components (brain tissue, cerebrospinal fluid, blood) have different acoustic properties (ultrasound speed, frequency dependent attenuation), changes of their relative content inside the acoustic path will influence the total acoustic characteristics of intracranial media and thus the monitored parameters of the ultrasonic signal as well [27, 24].

The results of mathematical simulations [27, 24] of ultrasound pulse propagation through the human brain show the linear relationship between changes in the time-
Fig. 1. Relationship between ICP, V, CSC, intracranial blood volume pulse waves $\Delta V(t)$ and ICP pulse waves $\Delta ICP(t)$

of-flight of the ultrasound pulse with changes in a blood volume within the cerebral parenchyma. Because the intracranial blood volume changes are directly related to ICP and craniospinal compliance changes, it supports the use of the time-of-flight measurement to evaluate these physiological parameters.

### 2.1. Non-invasive monitoring of ICP trends

The basic concept underlying the non-invasive monitoring of cerebral blood volume, ICP pulse waves, respiratory waves, slow waves and trend evaluation is outlined below [27, 25, 28]:

- the intraventricular or supraventricular parenchymal acoustic path which crosses the human head is used as the volume under study (Fig. 2). The parenchymal acoustic path mainly consists of parenchymal tissue, relatively small blood vessels (arterioles, venules and capillary vessels) and a small amount of cerebrospinal fluid (CSF) (Fig. 2). The parenchymal arterioles are those mainly responsible for cerebral blood flow autoregulation. The speed of ultrasound within the parenchymal acoustic path mainly depends on the blood volume inside this path. Also, the attenuation of ultrasound inside this path mainly depends on the volume of parenchymal tissue inside this path,

- to measure the changes in ultrasound speed inside the parenchymal acoustic path, this path is insonated by broadband ultrasonic pulses and the time-of-flight measured,

- to compensate for the influences of the external tissue hemodynamics in real-time and in situ the same ultrasonic pulses and their echoes from internal surfaces of the skull are also measured,

- specially designed software is used to convert the measured data into both absolute and relative indices for ICP, CPP or into the status of cerebral blood flow autoregulation.

This method is the only existing technology for non-invasive monitoring of the volume dynamics of the cerebral parenchyma microvessels.

The non-invasive ultrasonic Vittamed monitor (Fig. 3) was designed and tested in several intensive care units (ICU). The display panels of the Vittamed monitor are shown in Fig. 4 a, b and c.

Fig. 2. State of the art methodologies for non-invasive ICP measurement
Fig. 3. Innovative, non-invasive intracraniospinal slow, respiratory and pulse volumetric wave monitor (Vittamed 105) and cerebrovascular autoregulation monitor (Vittamed 505): a - Vittamed 105 front panel, b - Vittamed 505 front panel, c - Vittamed 105 and Vittamed 505 rear panel, d - typical position of mechanical frame affixed on the human head.

Fig. 4. The display panels of the non-invasive Vittamed monitor: a - for pulse, respiratory wave and trend monitoring; b - for cerebrovascular autoregulation monitoring using slow intracranial wave methodology; c - for pulse wave shape analysis.
The simultaneous invasive ICP monitoring (Camino or Codman) with the non-invasive Vittamed monitor was performed for ICU coma patients with severe closed head injuries. The clinical results of simultaneous ICP pulse wave monitoring and long-term trend monitoring (1h...3h) are illustrated in Fig. 5 a, b, c, d and e.

The non-invasive ICP indices were calculated from the ultrasound time-of-flight data using linear conversion after the real-time and in situ compensation of the influence of the external tissue and skull bones on the measured time-of-flight data. In 18 head injured patients we demonstrated a linear relationship between the measured ultrasound speed in the cerebral parenchymal acoustic path and ICP. The test range was clinically relevant and covered a range from ICP = 0 mmHg up to ICP = 50 mmHg. This linear relationship covers the critical treatment level of ICP which is believed to be approximately 20 mmHg.

2.2. The concept of cerebrovascular autoregulation non-invasive monitoring

Slow waves of ICP are the consequence of slow variations of intracranial blood volume. The duration of slow B waves can vary between 30 s to 200 s [9].

In the case of normal autoregulation, the correlation coefficient between ICP and BP \( r(\text{ICP};\text{ABP}) \) is negative and opposite to that found with an impaired cerebral autoregulation (CA) which is has a positive correlation coefficient \( r(\text{ICP};\text{ABP}) \) [35, 36]. Under optimal autoregulatory conditions, \( r(\text{ICP};\text{ABP}) \) is close to −1. With functioning autoregulation, an increase in CPP (within the physiological limits) is accompanied by constriction of the cerebral arterioles (active vasoconstriction), i.e. their diameter decreases in order to keep the cerebral blood flow stabilised. In the case of impaired cerebral autoregulation (CA), an increase in ABP is accompanied by passive dilatation of the cerebral arterioles, i.e. their diameter and blood flow rate increases with the rise in CPP. Under worst case conditions for impaired CA the correlation between ICP and BP \( r(\text{ICP};\text{ABP}) \) tends towards +1.

For non-invasive monitoring, the invasive ICP slow wave monitor could be replaced by the non-invasive monitoring of the relative speed \( \Delta C/C_0 \) of ultrasound through a volume of brain parenchyma, which also reflects the slow variations of intracranial blood volume. Thus, the estimation of CA can be performed by calculating the correlation coefficient between slow ABP waves and slow \( \Delta C/C_0 \) waves (as a measure of B-wave activity due to fluctuations in the cerebral blood volume). The same ABP waves were used for calculation of both invasive \( r(\text{ICP};\text{ABP}) \) and non-invasive \( r(\Delta C/C_0;\text{ABP}) \) coefficients.

The concept of non-invasive CA monitoring has been demonstrated experimentally in studies conducted in the ICU. Twelve severely head injured patients under different pathophysiological conditions were monitored invasively and non-invasively using invasive ICP monitoring (Codman or Camino), invasive ABP monitoring (Datex) and non-invasive monitoring (Vittamed). The distribution for ICP and ABP ranged from 3 to 50 mmHg and 35 to 140 mmHg respectively. The average age of patients was 31.25 years. The youngest and oldest patients were 21 and 64 years old respectively. Fifty-five one hour sessions of invasive and non-invasive CA monitoring and 86 one hour sessions of ICP and \( \Delta C/C_0 \) simultaneous monitoring have been performed during clinical studies. We found that 40% of the total time of monitorings (86 hrs) the correlation coefficient between \( \Delta C/C_0 \) and ICP \( r(\Delta C/C_0;\text{ICP}) \) exceeded 0.9. About 80% of the total monitoring time \( r(\Delta C/C_0;\text{ICP}) \) was above 0.6. This indicates that invasive monitoring of ICP slow waves can be effectively replaced by non-invasive monitoring of the intracranial volume slow waves and that the correlation coefficient between ABP waves and the relative velocity change of ultrasound transmission \( r(\Delta C/C_0;\text{ABP}) \) can be reliably used for non-invasive estimation of the status of CA.

We also determined that the correlation coefficient \( r(\Delta C/C_0;\text{ICP}) \) exceeds 0.9 when the amplitude of CPP B waves is above 3 mmHg. Thus the threshold for reliable diagnosing of CA could be chosen to be close to 3 mmHg for slow waves in CPP, as as found in many pathophysiological cases, the amplitude of CPP slow waves are within the ranges of 3 to 30 mmHg. Furthermore, a minimum of a 3 mmHg amplitude CPP slow wave is typically found in infants as well.

An example of a one-hour session of simultaneous invasive and non-invasive monitoring of slow waves and cerebrovascular autoregulation is illustrated in Fig. 6. It shows a good agreement between invasive and non-invasive measurements \( r(\Delta C/C_0;\text{ABP}) \equiv r(\text{ICP};\text{ABP}) \). The correlation coefficient \( r(\Delta C/C_0;\text{ICP}) \) between \( \Delta C/C_0 \) and ICP slow waves was close to +1.0 while the state of CA was changing from intact CA \( r<0 \) to impaired CA \( r>0 \) (Fig. 6). Key unique feature of the using non-invasive CA monitoring technology is that our method of the correlation coefficient analysis does not require calibration procedures. Moreover, this technique appears insensitive to any drift or the absolute magnitude of the non-invasively measured data.

3. Ultrasonic method for absolute ICP measurement without calibration problem

Existing non-invasive ICP measurement methodologies share a common problem of calibration into absolute (aICP) data. This problem is the main factor limiting the effective implementation of non-invasive aICP measurement systems into clinical practice [30]. The only reliable solution for non-invasive aICP measurement system calibration we have found is to calibrate aICP measurement by the direct comparison of aICP with an extracranially applied pressure \( aP_e \) using a “physiological scales” methodology. The question is where are such “scales” suitable for aICP measurement in the human body?

One option is to use intracranial arteries as natural ICP sensors. The ophthalmic artery (OA) is a unique vessel with both intracranial (OI) and extracranial segments (OE) with almost similar anatomy. The pressure balance between the two segments can be achieved when the absolute value of external pressure \( aP_e \) applied to OE via the eye orbit, is equal to the aICP which affects the intracranial segment of OI [29]. When balanced \( aP_e = aP_c \) and the blood flow parameters in both OA segments (OE and OI) are almost equal and independent of: the absolute value of arterial blood pressure, hydrodynamic...
Fig. 5. Simultaneous invasive and non-invasive of ICP pulse waves a monitoring: a - ICP=80 mmHg, b - ICP=60 mmHg, c - ICP=40 mmHg, d - ICP=20 mmHg and e - long term 3 h monitoring.
resistance of the eye veins, the pressure inside the eye ball and the initial absolute value of the blood flow in both segments of the eye artery. Therefore, by designing a special two depth pulse wave transcranial Doppler device that can simultaneously measure both the intracranial (OI) and extracranial (OE) segments of the OA we have a technology that can identify this balance in the natural “physiological scales”. The absolute value of external pressure which needs to be applied to the orbit to effect this balance reflects the absolute ICP value.

In order to validate the proposed aICP measurement method we conducted a clinical study of simultaneous invasive and non-invasive aICP measurements performed under neurosurgical ICU conditions. The main goal of the study was to determine the systematic error of the non-invasive method compared with the invasive method. In order to minimize any systematic errors the simultaneous invasive (ICP Codman) and non-invasive aICP measurements (physiological scales method) were performed as soon as possible after implantation of invasive ICP transducers. The study population consisted of all closed severe traumatic brain injury patients, 57 male and 37 females with a mean age of 27.6 (18–70) years. All were implanted with invasive ICP transducers.

The results of the clinical study are summarized in Fig. 7. A Bland - Altman plot (Fig. 7) of the simultaneous invasive and non-invasive aICP measurements shows that the difference \( \Delta = \text{ICPi} - \text{ICPn} \) between simultaneous invasive and non-invasive aICP data has a negligible systematic error 0.939 mmHg. This systematic error (solid line in Fig. 7) does not depend on aICP over the tested aICP range. This data is evidence that the proposed non-invasive aICP measurement system does not need correction for systematic errors, e.g., does not need calibration. The random errors (Fig. 7) inherent with the clinical data (SD = 6.18 mmHg) are followed by both invasive and non-invasive measurement systems. The random error of the non-invasive aICP system is mainly due to the limited resolution and accuracy of the two depth TCD device. That is a new challenge for further development of the two depth TCD technology development [27].

**Acoustical output and safety parameters**

The derated acoustic intensity of transcranial Doppler device was approximately 50 mW/cm² at the depth of 38 mm, the sample volume was 3 mm.

The main technical parameters of Vittamed 105 pulse wave monitor and Vittamed 505 cerebrovascular autoregulation monitor are as follows:

- Central frequency of the transmitted ultrasonic pulse spectrum is 1.5 MHz.
- Duration of transmitted ultrasonic pulses is 800 ns at the level of 0.5 of the envelope amplitude, and its repetition frequency is 1.0 kHz.
- Acoustic output parameters are derated spatial peak, the temporal-average intensity ISPTA3 = 0.869 mW/cm²; derated spatial-peak, the pulse average intensity ISPPA3 = 1.181 W/cm² and the ultrasonic power WO = 25 mW.
- Resolution of measured time-of-flight or ultrasound velocity relative values is 1.25E-6, and the bandwidth of
non-invasive intracranial pressure/volume pulse waves measuring channel is 12 Hz.
- Power supply is AC 100 V - 240 V, 1.5A, 47Hz - 63Hz.
- The device meets the requirements of EN 60601-1, EN 60601-2-37 and EN 60601-1-2 standards.
- An electrocardiographic channel is used to associate the pulse wave recording with the cardiac cycle.
- When 10 intracranial pulse waves are averaged using the sampling frequency of 50 Hz, the time-of-flight measurement uncertainty is +/-0.07 ns (+/- standard deviation) in the frequency band from 0.6 Hz up to 5.0 Hz.

Conclusions

The comparative clinical studies outlined in this paper on the non-invasive ultrasonic Vittamed monitoring technology simultaneously with invasive ICP monitors conducted in the ICU show that:
- it is possible to achieve measurement accuracy better than +/-2.0 mmHg for long term non-invasive ICP monitoring using our the time of flight methodology over a clinically relevant range of ICP values from 0 mmHg to 50 mmHg and to achieve a high correlation \( r = 0.997 \) between invasively and non-invasively measured ICP data;
- the non-invasive time-of-flight technology Vittamed can also be applied for continuous cerebrovascular autoregulation monitoring based on correlation monitoring between BP and non-invasive ICP slow waves. The high correlation between invasively and non-invasively measured ICP and intracranial blood volume slow wave
data has been demonstrated in these clinical studies (p<0.95, 87 hours of monitoring in 13 patients);
- the amplitude and shape of non-invasively measured intracranial blood volume (IBV) pulse waves are also related to cerebrospinal compliance.

The innovative “physiological scales” method described in this paper for measurement of absolute ICP by non-invasive two depth TCD measurement, is the only known method for non-vasive measurement of absolute ICP without the need for individual patient to patient calibration.

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Zmogaus smegenų intrakraninės biomechanikos neinvazinė stebėsena

Rezimė

Apžvelgiam įvairių žmogaus smegenų neinvazinės fiziologinės stebėsenos metodai ir technologiją. Metodai remiasi smegenų paviršiaus akustiniių savybių matavimu. Klinikinių technologijų tyrimai parodė, kad panašumo tarp invazinio ir neinvazinio matavimo priklauso nuo smegenų sunkumo (IBV) ir kranio visumos. Aptartas absoliucijų intrakraninio slėgio (ICP) matavimo metodas, nereikalaujantis papildomo kalibravimo.