

## Non-invasive Technology for Monitoring of Cerebrovascular Autoregulation

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### 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 haemoglobin concentration in a specific patient must 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, distinct 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. Impairment of CBF autoregulation is a strong predictor of TBI patients' outcome [1-3]. In order to optimize the TBI treatment decisions it is not enough to monitor ICP, ABP and CPP. In this case it is necessary to know the status of CBF autoregulation in real-time.

It is assumed that a negative correlation or the phase shift close to 180° in the time courses of "slow B waves" [4] (0.03 Hz to 0.008 Hz) of CBF and CPP reflects an

active change in cerebrovascular resistance and therefore an intact CA system [2,3,5].

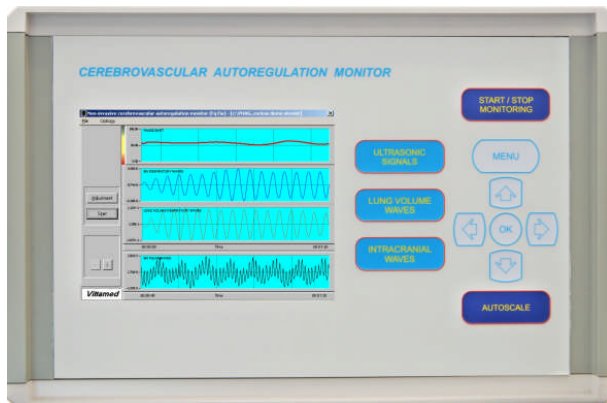
A positive correlation or the phase shift close to zero of CBF and CPP shows a non-reacting cerebral vessels and impaired CA system [2,3,5].

Control of CA in order to prevent secondary brain insults and to guide ICP / CA targeted therapy requires continuous uninterrupted and real-time CA monitoring. Transcranial Doppler (TCD) technology together with non-invasive ABP wave monitoring has been proposed for non-invasive CA assessment [5]. A convenient way to assess CA continuously under ICU conditions is to monitor the moving Pearson's correlation coefficient between invasively measured ABP and ICP waves [2,6] at B wave frequencies [4]. It is necessary to note that the moving Pearson's correlation coefficient in the case of CA monitoring reflects the cosine of phase shift between the waves under comparison (+1 is equivalent to 0 degrees phase shift, and -1 is equivalent to 180 degrees phase shift). The limitation of the slow B wave moving correlation method is the intermittent nature of B waves. The moving averaging of monitoring data to reduce the uncertainty of CA estimation is the cause of 3 min to 10 min instrumental delay between actual CA changes and the reflection of such changes in CA monitoring [2]. Such a data delay time can be too big in the acute patients' treatment. ABP and ICP respiratory waves are permanent and up to 10 times more frequent compared with slow B waves. The main advantage of natural or ventilator supported respiratory wave application for CA assessment is the possibility of continuous uninterrupted CA monitoring with up to 10 times shorter monitoring data delay time comparing with B wave method.

Slow, respiratory and pulse ICP waves are the consequences of the variations of intracranial blood volume (IBV). All IBV waves can be monitored continuously, non-invasively and in real-time by applying ultrasonic “time-of-flight” Vittamed technique [1,3,4,12,13].

Vittamed 505 CA monitor provides information about the blood volume dynamics in the smallest vessels responsible for cerebral blood flow autoregulation – small arterial vessels and arterioles. It is impossible to obtain such information using other known invasive or non-invasive technologies.

The Vittamed 505 CA monitor (Fig. 1) was tested in several intensive care units (ICU).



**Fig. 1.** Non-invasive cerebrovascular autoregulation monitor Vittamed 505

### Main technical parameters of Vittamed 505 CA monitor

The main technical parameters of Vittamed 505 CA monitor are as follows:

- Central frequency of transmitted ultrasonic pulse spectrum is 1.05 MHz.

- Duration of transmitted ultrasonic pulses is 2.86  $\mu$ s at a level of 0.5 of envelope amplitude, and its repetition frequency is 1.0 kHz.

- Acoustic output parameters are derated spatial peak, temporal-average intensity  $I_{SPTA,3} = 0.86 \pm 0.02$  mW/cm<sup>2</sup>; derated spatial-peak, pulse average intensity  $I_{SPPA,3} = 1.18 \pm 0.03$  W/cm<sup>2</sup>.

- Uncertainty of the time-of-flight measurements is  $U = \pm SD = 0.07$  ns, and the bandwidth of non-invasive intracranial pressure / volume pulse waves measuring channel is from 0.6 Hz to 5.0 Hz, sampling frequency is 50 Hz.

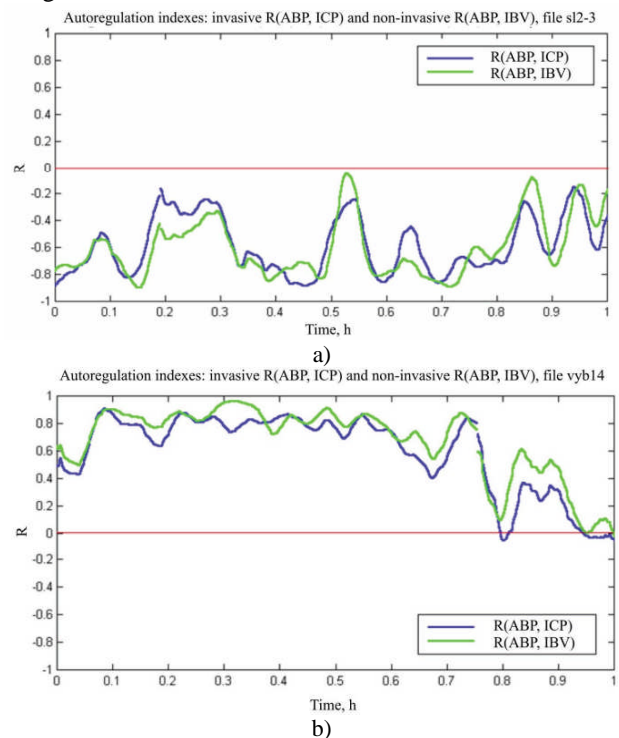
- Power supply is AC 100 V – 240 V, 1.5A, 47Hz – 63Hz.

- The device meets requirements of EN 60601-1, EN 60601-2-37 and EN 60601-1-2 standards.

Belt type respiratory effort transducer is used in order to generate the reference signal for Vittamed 505 monitor. This respiratory effort reference signal replaces ABP respiratory wave signal which is used in known invasive slow intermittent wave CA monitoring technology. Therefore, replacement it is not necessary to use invasive or non-invasive ABP monitoring channel together with

Vittamed volumetric respiratory wave channel in Vittamed 505 CA monitor.

The typical clinical results of simultaneous invasive and non-invasive monitoring of CA are illustrated in Fig. 2 a) and Fig. 2 b). It shows good agreement between invasive R(ABP, ICP) and non-invasive R(ABP, IBV) moving correlation coefficients. The individual variability between these coefficients during one hour invasive and non-invasive CA monitoring sessions was clinically insignificant.

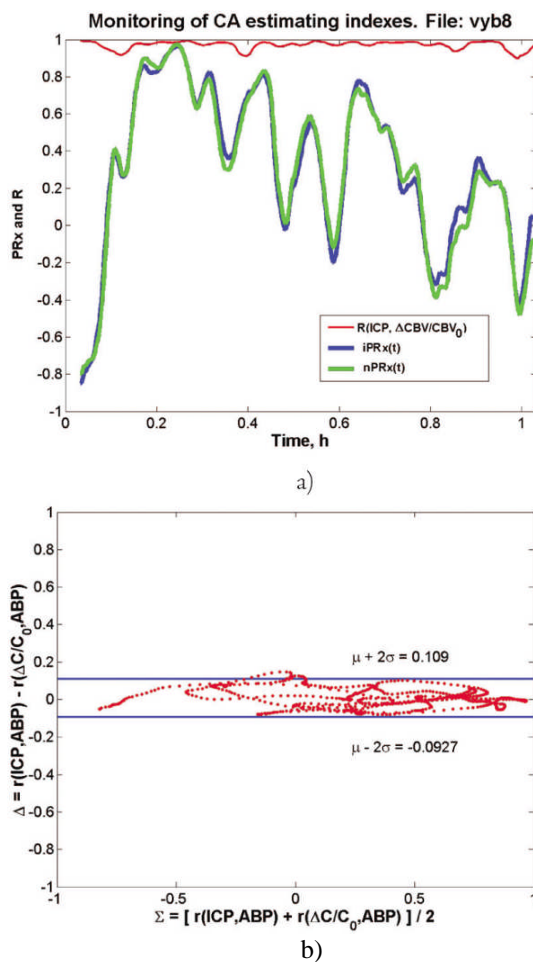


**Fig. 2.** Typical simultaneous invasive and non-invasive CA monitoring data (one hour monitoring sessions): a) variability of intact CA, b) variability of impaired CA

It was determined that the correlation coefficient  $R(ABP, IBV)$  exceeded 0.9 when the amplitude of ICP B waves was above 3 mmHg. Correlation coefficient between invasive and non-invasive CA monitoring data also exceeded 0.9 when the amplitudes of ICP B wave was above 3 mmHg and the amplitude of ABP slow wave was above 5 mmHg. To assess the similarity between the data of invasive ICP slow waves and non-invasive IBV slow waves, two types of data sets were evaluated for each monitoring session. The data sets of the first type that contain all measurement points were checked by calculating the standard deviation and mean of differences between the normalized invasive and non-invasive data and by applying the correlation analysis. The data sets of the second type that contain randomly selected data points were evaluated by performing  $t$  – test of the paired data. The values of  $t$  – criterion corresponding to each data set were calculated using normalized data. Normalization was performed dividing the original measurement data by standard deviation. The calculated values of  $t$ -criterion were checked in terms of inequality  $|t| < T_{crit}$  ( $\alpha = 0.05$ ,  $n = 50 \dots 70$ ), where,  $t$  is the calculated value of  $t$  – criterion of paired samples,  $T_{crit}$  is a critical value of  $t$  – statistics,  $\alpha$  is a significance level of the test,  $n$  is a number of

randomly selected points.  $N = 83$  samples of paired data were found which satisfied the condition of the accepted hypothesis on the equality of the mean values of measurements under comparison. The investigated number of samples was  $N = 87$ . The obtained proportion of samples with positive decision was higher than the proportion of interest ( $\pi = 0.95$ ) and that confirms the hypothesis on the coincidence of invasively and non-invasively measured slow waves  $\pi = N+/N = 0.954 > 0.95$ .

The Bland Altman evaluation of invasively and non-invasively measured slow B waves and the distribution of the differences between these waves show the good agreement between invasive and non-invasive data ( $SD = 0.089$ ,  $p < 0.0001$ ). The Bland Altman evaluation of invasive and non-invasive CA monitoring data also shows good agreement ( $SD = 0.05$ ,  $p < 0.0001$ ). Both invasive and non-invasive methods of CA monitoring seem to give the same diagnostic information about CA with the uncertainty of experimental data, which is not important for clinical practice.



**Fig. 3.** Cerebrovascular autoregulation study:

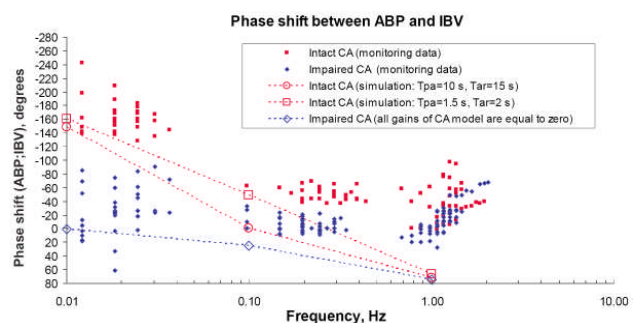
a) one hour simultaneous invasive and non-invasive monitoring of CA on TBI patient:  $iPRx$  is invasively measured correlation factor between slow intermittent ICP and ABP waves,  $nPRx$  is non-invasively measured correlation factor between slow intermittent intracranial volumetric waves (Vittamed 505 monitor) and ABP waves,  $R$  is correlation between invasively and non-invasively measured CA indexes  $iPRx(t)$  and  $nPRx(t)$ ;

b) Bland Altman plot of invasive and non-invasive CA indexes, obtained from Fig. 3 a)

## Relationship between ABP / IBV respiratory wave phase shift and CA

Our data suggest that the phase shift not only between slow intermittent B waves of ABP and IBV, but also the phase shift between permanent respiratory waves is able to differentiate between intact and impaired CA (Fig. 4). In order to support the clinical results, the phase shift between ABP and ICP waves was simulated on a computer using the mathematical model described in [15,16], with different values of autoregulation gains and time constants. The simulations were performed at the frequencies 0.01 Hz, 0.1 Hz and 1.0 Hz (Fig. 4). The different time constants of pial artery reactivity ( $T_{pa}$ ) and reactivity of arterioles ( $T_{ar}$ ) has been used in the case of intact CA. The impairment of CA was simulated by reducing all gains in CA model up to zero. Mathematical simulation shows that the phase shift between ABP and ICP or IBV respiratory waves under intact CA is higher than in the case of impaired CA in the wide range of  $T_{pa} = [1.5 \text{ s}; 10 \text{ s}]$  and  $T_{ar} = [15 \text{ s}; 10 \text{ s}]$  (Fig. 4). It is evident (Fig. 4) that the phase shift between ABP and IBV can be used as an estimator of CA impairment under ICU conditions when the frequencies of natural or ventilator supported patient respiration can change in the wide frequency band from 0.1 Hz to 0.45 Hz. This is an attractive alternative to slow B wave application for CA monitoring because natural or ventilator supported respiration is a permanent physiological process which can be monitored continuously, uninterruptedly and with the instrumental delay time of monitoring data up to 10 times less comparing with B wave method [4, 16].

ABP and IBV pulse wave phase shift clinical data shows no difference in the cases of intact and impaired CA (Fig. 4). That is in agreement with simulation data. Phase shift changes of permanent respiratory ABP waves and IBV waves also permit continuous non-invasive CA monitoring under ICU conditions without physical or pharmacological stimulations of CA system. Vittamed non-invasive monitor of CA (Fig. 1) in the case of respiratory wave application does not need invasive or non-invasive ABP respiratory wave monitoring.



**Fig. 4.** Phase shift between ABP and IBV waves in the cases of intact and impaired CA comparing with intact CA / impaired CA phase shift data of mathematical simulation:

$T_{pa}$  – time constant of pial arteries,

$T_{ar}$  – time constant of arterioles;

Slow B wave data are presented in the frequency band 0.01 Hz ... 0.04 Hz, respiratory wave data in the frequency band 0.1 Hz ... 0.45 Hz and pulse wave data in the frequency band 0.65 Hz ... 3.0 Hz.

In order to get information about ABP respiratory wave it is possible to use the information about the cause of mechanical respiration process – mechanical movement of the human breast. This mechanical movement is monitored applying non-invasive belt type respiratory effort transducer. In this case Vittamed monitor is only real – time CBF autoregulation monitor which is cost effective and absolutely non-invasive.

## Conclusions

1. The clinical study shows that the non-invasive technology could be applied for continuous monitoring of cerebrovascular autoregulation by using permanent intracranial wave methodology.

2. Coincidence of invasively and non-invasively measured ICP and IBV slow wave data has been statistically significantly proved ( $\pi > 0.95$ , 87 monitoring hours, 13 patients).

3. Phase shift changes of permanent respiratory ABP waves and IBV waves permit continuous non-invasive CA monitoring under ICU conditions without physical or pharmacological stimulations of CA system.

4. The new monitor Vittamed 505 has been created which uses both slow wave and respiratory wave methodology.

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New non-invasive ultrasonic technology for CA monitoring has been created which uses both intracranial slow wave and respiratory wave methodologies. The technology provides information about the intracranial blood volume dynamics in the smallest vessels responsible for cerebral blood flow autoregulation – small arterial vessels and arterioles. The clinical study shows that the non-invasive technology could be applied for continuous monitoring of CA by using slow intracranial wave or intracranial respiratory wave methodologies. Ill. 4, bibl. 12 (in English, summaries in English, Russian and Lithuanian).

**A. Рагаускас, Г. Даубарис, В. Петкус, Р. Райшутис, Р. Хомскис, Р. Шлитерис, В. Декснис, Й. Гузайтис, Г. Ленгвинас, А. Ругайтис. Технология неинвазивного мониторинга цереброваскулярной авторегуляции // *Электроника и электротехника*. – Каунас: Технология, 2008. – № 5(85). – С. 93–96.**

Создана новая ультразвуковая технология для мониторинга цереброваскулярной авторегуляции. Она основана на методологиях медленных интракраниальных волн и волн дыхания. Эта технология представляет информацию о динамике кровяного объема в мелких кровяносных сосудах, ответственных за авторегуляцию мозгового кровоснабжения. Клиническая студия новой неинвазивной технологии показала, что она может быть использована для мониторинга цереброваскулярной авторегуляции при использовании методологий как медленных интракраниальных волн, так и интракраниальных объемных волн дыхания. Ил. 4, библи. 12 (на английском языке; рефераты на английском, русском и литовском яз.).

**A. Ragauskas, G. Daubaris, V. Petkus, R. Raišutis, R. Chomskis, R. Šlitteris, V. Deksnys, J. Guzaitis, G. Lengvinas, A. Rugaitis. Cerebrovaskuliarinės autoreguliacijos neinvazinio monitoringo technologija // *Elektronika ir elektrotechnika*. – Kaunas: Technologija, 2008. – Nr. 5(85). – P. 93–96.**

Sukurta nauja ultragarsinė technologija cerebrovaskuliarinės autoreguliacijos monitoringui atlikti. Ji remiasi intrakranijinių lėtųjų bangų ir kvėpavimo bangų metodologijomis. Ši technologija teikia informaciją apie intrakranijinės terpės kraujo tūrio dinamiką smulkiausiuose kraujo induose, atsakinguose už cerebrovaskuliarinę autoreguliaciją – mažose arterinėse kraujagyslėse ir arteriolėse. Naujos neinvazinės technologijos klinikinė studija parodė, kad ši technologija tinka cerebrovaskuliarinės autoreguliacijos monitoringui atlikti taikant tiek intrakranijinių lėtųjų bangų, tiek intrakranijinių tūrinių kvėpavimo bangų metodologijas. Il. 4, bibl. 12 (anglų kalba; santraukos anglų, rusų ir lietuvių k.).