Novel Method and Device for Fully Non-Invasive Cerebrovascular Autoregulation Monitoring

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[1]***Abstract*—The novel method and the device for non - invasive cerebrovascular autoregulation (CA) status monitoring without using the arterial blood pressure (ABP) measurement channel are presented. This fully non-invasive CA monitor is based on the ultrasonic time-of-flight measurement of cerebral blood volume pulsations within the brain parenchyma, extraction of informative and reference slow and respiratory volumetric waves and calculation of CA estimating indexes without using any additional ABP measurements.**

For demonstrating the applicability of the proposed method, the CA status was monitored on 11 traumatic brain injury patients simultaneously by using the novel fully non-invasive monitor and compared to the CA status representing indexes calculated from the invasively measured intracranial pressure (ICP) and ABP slow waves. The total monitoring time was about 22 hrs. The correlation factor between the invasively and non-invasively obtained CA data showed significant agreement (r=0.751) between the two methods.

The proposed innovative CA real-time monitoring method gives us new possibilities to perform estimation of the CA status from the intracranial waves only as well as to exclude the ABP line's errors and artifacts from the measurement results.

***Index Terms*—Cerebrovascular autoregulation, intracranial pressure waves, medical diagnosis, patient non-invasive monitoring.**

I. INTRODUCTION

Cerebrovascular autoregulation (CA) is a protective mechanism of the brain to regulate its blood supply by expanding or narrowing arterioles, while maintaining stable cerebral blood flow when cerebral perfusion pressure (CPP) is changing within physiological ranges [1], [2]. The human brain is at risk of a secondary injury, especially when this function fails [3], [4]. The autoregulation is effective when the CPP is approximately within the physiological limits from 50 mmHg to 150 mmHg. The CPP above the upper limit of autoregulation can cause cerebral oedema or hyperaemia. The CPP below the lower threshold causes disturbed supply of the blood flow and, as a result, cerebral ischemia. A brain injury can lead to vasomotor paralysis when autoregulation is impaired and cerebral blood flow depends entirely on CPP [5].

The impairment of CA has a strong impact on the traumatic brain injury (TBI) patients' outcome, therefore, it is essential to know the real-time status of CA [4], [6]. The consensus was already achieved that the cerebral blood flow (CBF) autoregulatory state of TBI patients has to be monitored and the individualized treatment strategy should be re-valuated regularly over the time course of the CBF autoregulation status [7], [8].

Several approaches of CA status estimation are known based on the measurement and analysis of cerebral perfusion pressure and cerebral blood flow velocity slow fluctuations [6], [9]–[11], and measurement of cerebral vascular resistance in relation to the change in CPP [11], [12]. However, more clinically practical method for continuous CA assessment is the method of calculation of pressure reactivity index (PRx) as a Pearson correlation coefficient (or moving correlation coefficient r) between slow arterial blood pressure (ABP) and intracranial pressure (ICP) [9], [13]–[15]. The slow ABP waves as a reference signal and the slow ICP waves as an informative signal within the frequency range 0.005 Hz – 0.035 Hz were proposed to be used for continuous PRx calculation [15]–[17].

The limits of PRx are from -1 to +1. The cerebral blood flow autoregulation mechanism is intact CA when PRx is negative. When the cerebral blood flow autoregulation mechanism is disturbed, PRx becomes positive and it indicates decreased cerebrovascular response to ABP

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changes. The critical value is PRx = +1, which means total impairment of the CA status [13]–[16]. The PRx value of 0 indicates no correlation between slow ABP and ICP fluctuations, with changes in cerebrovascular resistance fully compensating for changes in ABP so that a constant cerebral blood flow is maintained [15].

The implementation of non-invasive assessment of CA status is possible by performing cerebral blood flow velocity fluctuations measurement by using transcranial Doppler (TCD) technology and applying these fluctuations for calculation of PRx instead of ICP (or CBF) waves [9], [14]. The CBF and non-invasive ABP slow wave monitoring technology has been proposed together with PRx calculation for the CA continuous monitoring [9], [11], [14]. However, for the implementation of the non-invasive CA monitoring method based on the slow waves application there are a few limitations.

Firstly, the limitation of the slow wave moving correlation monitoring method is the intermittent nature of slow waves. Small slow waves or their absence cause a misleading estimation of the CA status thus, leading the shift of PRx index close to zero value (which means no correlation between ICP and ABP). The discrete clinical tests, e.g., the cuff leg test has been introduced in order to raise temporal changes of ICP and ABP values allowing to make assessment of the CA status [11]. However, this did not provide the continuous monitoring data needed for the continuous real-time CA estimation and optimal treatment.

The problem related to small ICP waves might be solved by using the respiratory waves. The main advantage of the natural or ventilator-supported respiratory wave application [18]–[21] for the CA assessment is the possibility of continuous uninterrupted CA monitoring with up to 10 times shorter monitoring data delay time compared with the slow wave method.

The second limitation of the slow wave based CA monitoring method is the necessity to apply the invasive or non-invasive ABP sensor. Although non-invasive ABP measurement technique (Finapres plethysmograph) might be used for CA assessment [22], the invasive ABP sensors are more often used in clinical practice. The disadvantages of the use of the invasive ABP sensor are:

– implantation of the ABP sensor in the artery is a complex and risky procedure,

– it is necessary to replace the ABP sensor periodically in order to avoid mortification of the body parts,

– artifacts caused by the body movements often distort the results of ABP measurements and give misleading evaluation of the CA status.

Moreover, the artifacts caused by the body movements often distort the results of ABP measurements and give misleading evaluation of the CA status. A short artifact lasting for a few seconds in the ABP channel can distort PRx value for ~5 min…10 min (depending on the length of time window used for calculation of moving correlation coefficient).

We have found that the reference slow or respiratory waves might be extracted after demodulation of the non-invasively (or invasively) measured ICP pulse waves and used instead of the reference ABP waves [19], [20]. It means that ABP waves might be rejected from PRx calculation and only one channel of the non-invasively measured intracranial waves, i.e. slow, respiratory and pulse waves might be used for estimation of the CA status [19], [20].

II. Implementation of Novel Cerebrovascular Autoregulation Electronic Monitoring Method

The possibility to estimate non-invasively the CA status without using any additional ABP measurements is to use a new ultrasonic "time-of-flight" technique [19], [20], [23], which enables to perform continuous non-invasive monitoring of slow, respiratory and pulse intracranial waves. The non-invasive ultrasonic "time-of-flight" (TOF) method for intracranial blood volume measurement is based on the transmission of short ultrasonic pulses from one side of the skull to the other and on dynamic measurements of the TOF of ultrasonic pulses [19]. The TOF depends on the acoustic properties of intracranial blood, brain tissue and cerebrospinal fluid. The changes in the volume of any of these components will change the TOF.

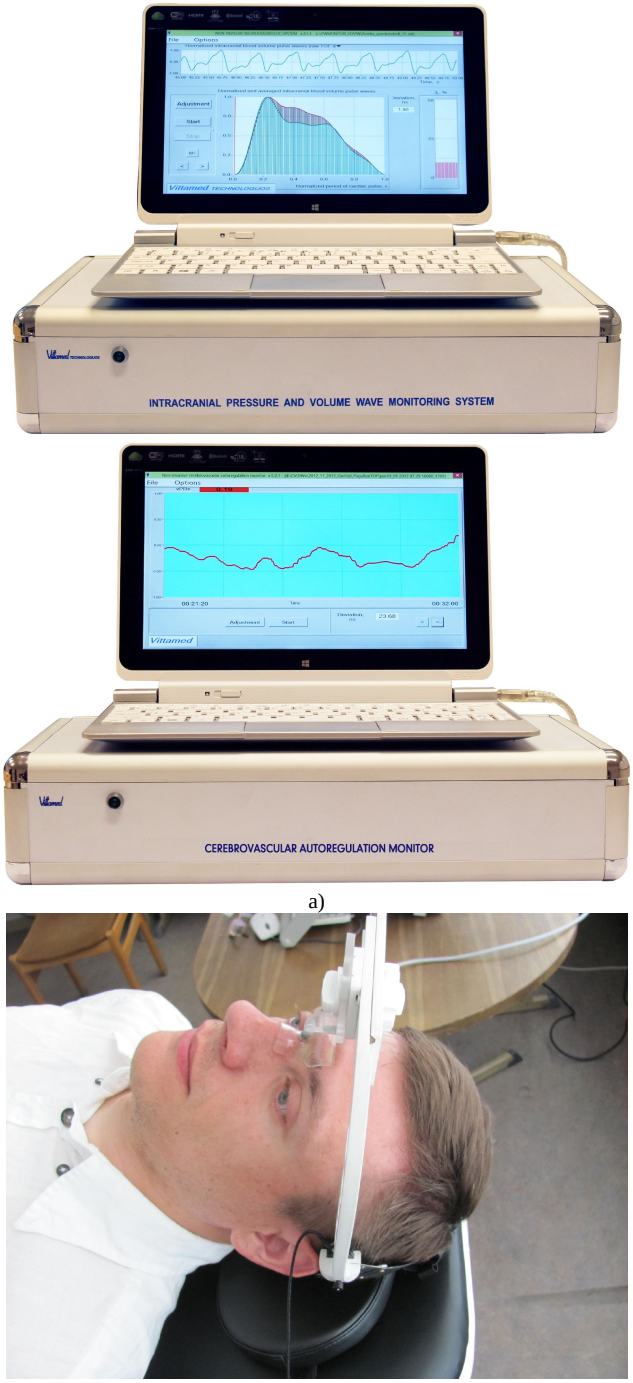
It is shown experimentally [23]–[25] that the slow, respiratory and pulse ICP waves are the consequences of the variations of the intracranial blood volume (IBV). The ultrasound speed in blood is higher than in other intracranial components [19], therefore the increase of blood volume during each heart beat cycle will result in the increase of averaged relative ultrasound speed $\Delta C(t)/C0$ which is inversely proportional to TOF, i.e., $\Delta C(t)/C0 \sim 1/TOF(t)$.

So, all IBV waves can be monitored continuously, non-invasively and in real-time by using the TOF technique [23], [25]. By using this technique, the invasive ICP slow, respiratory and pulse wave monitor can be replaced by the non-invasive monitoring of the relative speed $\Delta C/C0$ of the ultrasound passing through the volume of brain parenchyma, which also reflects the variations of the intracranial blood volume.

The IBV slow, respiratory and pulse waves are the consequence of the physiological fluctuations in ABP signal (reference signal) in corresponding frequencies of these waves. The latencies of IBV slow, respiratory and pulse waves with regard to these waves in the reference ABP signal are different and, moreover, can reflect the information on the CA status.

In the case of the intact CA status, the IBV slow wave (informative) and ABP slow wave (reference) have almost opposite phase due to the existing latency at low frequency (0.005 Hz–0.033 Hz). In this case, the phase shift between these waves is about 180 degree due to the autoregulatory properties of cerebral vasculature. In the case of a degrading CA, the phase shift between these waves decreases and is close to zero when CA is totally impaired. For the respiratory waves (0.1 Hz–0.3 Hz) the latency between IBV and ABP waves is close to the time constant of the autoregulation mechanism and the phase shift between these waves might vary within 70 degrees–30 degrees when the autoregulation is intact and is close to zero when the autoregulation is lost. For the fast pulse waves (0.5 Hz–2 Hz), the latency between IBV and ABP waves is small,

because the time constant of cerebral blood flow autoregulation is normally 3 s–7 s, i.e. a few times higher than a typical period of the pulse wave. Because of this, the latency between IBV and ABP pulse waves is negligibly small and, moreover, is not affected by the CA status.



a)

b)

Fig. 1. The non-invasive monitor for continuous real time monitoring of intracranial volumetric waves and cerebrovascular autoregulation (a) and also the mechanical frame mounted on the volunteer's head in order to fix the ultrasonic transducers in the position ensuring ultrasound wave transmission through the brain parenchyma (b).

The pulse waves are not the informative waves, however, they can be used for extraction of the reference signal which exists in the envelope without latency. The envelope of intracranial pulse waves is modulated with the slow and respiratory waves. These waves can be extracted by applying a specially created amplitude demodulation algorithms. It can be used as a reference signal instead of ABP waves for calculating PRx index for CA status estimation [19], [20]. Therefore, it is no longer necessary to use the invasive or non-invasive extracranial ABP or the respiratory wave sensors in order to get the reference signals for CA status evaluation [19], [20]. In this case, all ABP monitoring errors and artifacts are removed from the CA status estimation results. The fully non-invasive ultrasonic CA monitor based on this methodology has been created in the Health Telematics Science Centre of Kaunas University of Technology, Lithuania (Fig. 1). This monitor allows the non-invasive "time-of-flight" measurement of the pulsating intracranial blood volume to be performed within small parenchymal arterioles which are responsible for cerebral blood flow autoregulation [24].

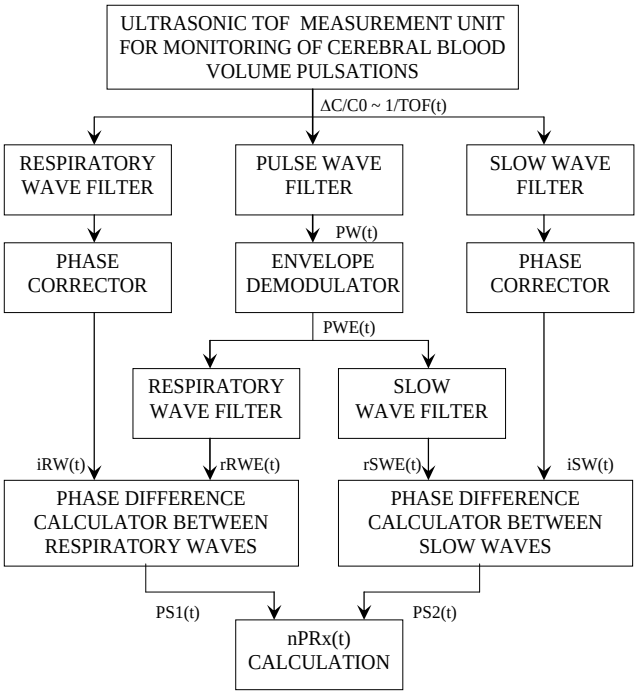


Fig. 2. The structural diagram of non-invasive monitor for continuous real time monitoring of cerebrovascular autoregulation.

A light and convenient head frame is mounted on the human's head in order to fix the ultrasonic transducers in a proper position for transmitting the ultrasonic pulses through the brain parenchyma (Fig. 1(b)).

The estimation of CA is performed by linear calculation of the phase shift between the reference slow (or respiratory) waves extracted from the pulse waves and the informative slow (or respiratory) ΔC/C0 waves. Non-invasive nPRx indexes are calculated using monitoring data of the corresponding phase shifts [19], [20]. The structural diagram of the non-invasive ultrasonic CA monitor device is shown in Fig. 2. The time-of-flight measurement unit is used to measure TOF(t) data with the resolution less than 60 ps. The TOF data are converted into the relative ultrasound values and split up into slow waves SW, respiratory waves RW and the pulse waves PW by using the corresponding band-pass filters. The envelope demodulator is used to demodulate the envelope of pulse waves PWE. The PWE data are filtered by using the band-pass filters in order to extract reference slow waves rSWE and reference respiratory waves rRWE.

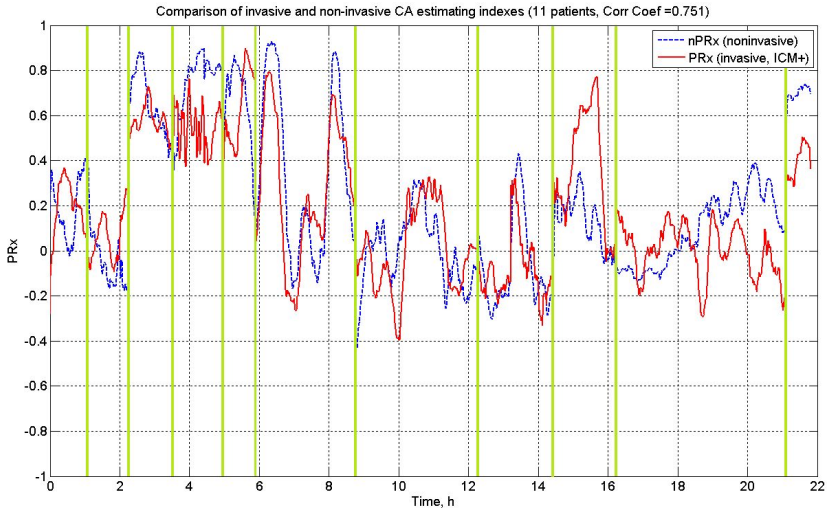


Fig. 3. The CA monitoring for 11 patients within 22 hours. The monitoring data of each patient are separated by solid vertical lines. Correlation factor between invasively measured CA index (PRx) and non-invasively measured (nPRx) is r = 0.751.

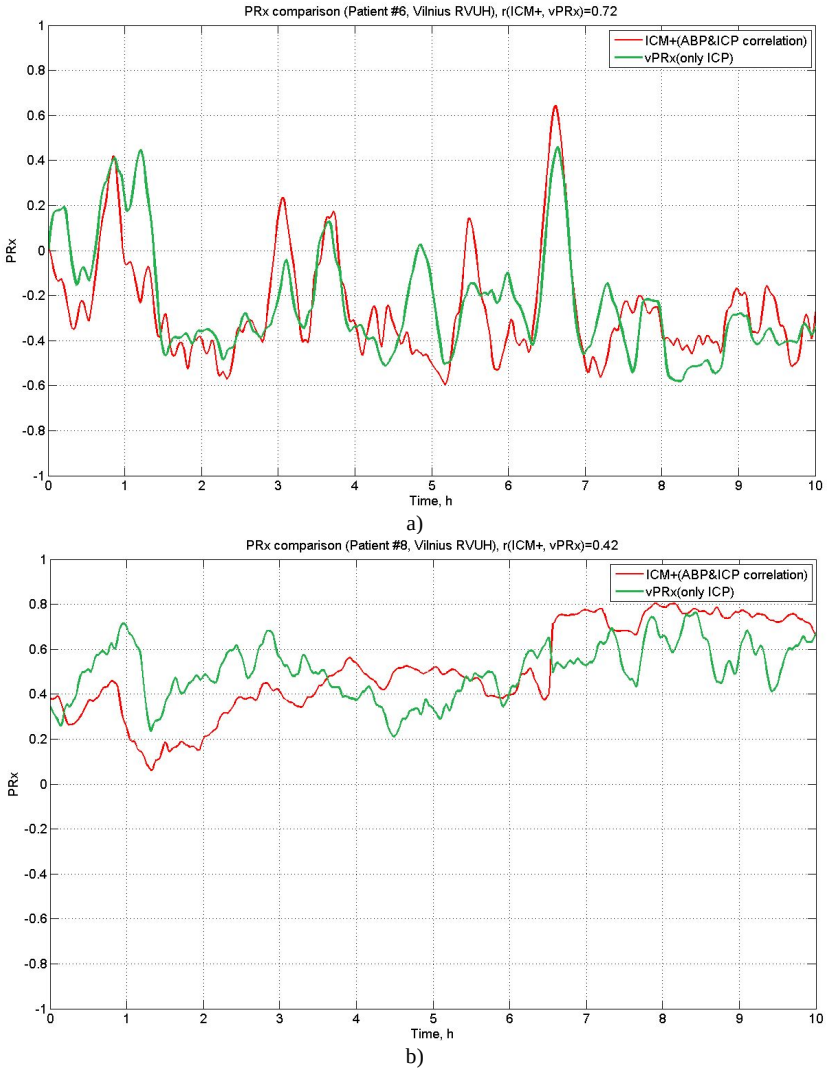


Fig. 4. Examples of 10 hour simultaneous invasive PRx and vPRx monitoring sessions: a) - CA is intact, b) - CA is impaired. PRx is CA index calculated by using ABP(t) and ICP(t) slow waves and ICM+ software (Cambridge, UK); vPRx is CA index calculated by using „Vittamed“ software without ABP reference signal monitoring.

Informative slow and respiratory waves: iSWE and iRWE, are processed additionally in order to compensate phase delay caused by the filtering reference waves with the pulse wave filter. Two calculators of phase difference in the slow and respiratory channels are used for continuous calculation of phase shifts PS1 between reference and informative respiratory waves and PS2 between reference and informative slow waves. Phase shift PS1 and PS2 are used to calculate the non-invasive indexes of cerebrovascular autoregulation index nPRx(t) which is

plotted on the screen of the CA monitoring device [19], [20].

III. RESULTS

11 traumatic brain injury patients (10 male and 1 female) in different pathophysiological states were monitored simultaneously invasively and non-invasively by using the invasive ICP monitor (Codman or Camino), the invasive ABP monitor (Datex) and the non-invasive "time of-flight" monitor (Vittamed). The monitoring data from the ICP monitor and the ABP monitor were processed in order to get slow ICP and slow ABP waves (from the frequency range 0.008 Hz–0.033 Hz). These slow waves were processed by using software ICM+ (Cambridge, UK) in order to calculate the moving correlation coefficient r(ICP; ABP) which was kept as a reference index of the CA status estimation

$$PRx = r\left[ABP(t); ICP(t)\right], \quad (1)$$

The monitoring data from the non-invasive "time of-flight" monitor (relative ultrasound speed) were processed in order to get informative slow waves (from the frequency range 0.008 Hz–0.033 Hz), informative respiratory waves (from the frequency range 0.1 Hz–0.3 Hz), reference slow and respiratory waves extracted from the envelope of the pulse waves and to calculate phase shifts PS1 and PS2. These phase shifts are used to calculate the non-invasive index of the CA status estimation

$$nPRx = -\cos\left[® - ~_1 * PS1(t) - ~_2 * PS2(t)\right], \quad (2)$$

where a1 and a2 are the weighting factors dependent on the amplitude of the pulse waves, slow waves and respiratory frequency; PS1 is the phase shift between the non-invasively measured informative and reference respiratory waves; PS2 is the phase shift between the non-invasively measured informative and reference slow waves.

In order to perform the comparison between the invasive and non-invasive CA data, these data obtained from 11 patients were joined into the time domain and plotted in Fig. 3. The total time of monitoring 11 patients was about 22 hrs. The correlation factor r = 0.751 between the invasive and non-invasive CA data was obtained. Such a value of the correlation factor shows that diagnostic information on CA dynamics reflected by non-invasive index nPRx is similar to information reflected by invasive index PRx. The important advantage of the nPRx index is the possibility to exclude invasive ABP line and to eliminate all the ABP measurement errors and artifacts from CA monitoring data.

IV. DISCUSSION

The application of the presented methodology of the non-invasive cerebrovascular autoregulation estimations without the ABP line can be extended exploring different methodologies of the CA status estimation. First, the CA status might be estimated by using the invasively measured ICP waves only. In this way the CA status might be evaluated by calculating the phase shifts between the reference slow or (and) respiratory waves extracted from the invasive ICP pulse waves and the informative slow or (and) respiratory ICP waves [23], [26]. Such approach is based on the assumption that the ABP pulse waves are modulated with the reference respiratory (and slow) waves which might be extracted from the envelope of the ICP pulse waves with a negligible delay. To test the possibility to evaluate the CA status by using the ICP data only, the present method was compared to the conventional method based on the PRx index calculation from the ICP and ABP slow waves. The analysis of the simultaneously recorded ICP and ABP data from 16 traumatic brain injury patients showed that both methods give similar information. The correlation coefficient between PRx (calculated from the ICP and ABP waves) and vPRx (calculated from ICP waves only) for all patients was r = 0.724 (the total time of all patients monitoring was 350 hrs). The examples illustrating the similarity between these two methods during the long term monitoring of traumatic brain injury patients under different CA conditions are shown in Fig. 4.

The next extension of the present method is the possibility of implementation of the fully non-invasive CA estimation measurements by introducing other non-invasive methods of intracranial wave measurements, such as TCD [6], [9], [10] or the near-infrared based [27] measurement methodology. The method presented in this article is based on developing the idea that the intracranial waves might be measured by using the non-invasive ultrasonic "time-of-flight" measurement methodology. The advantages of the presented novel non-invasive CA monitoring method are:

− the method does not require using an additional sensor for measurement of the reference waves, i. e. neither the ABP wave nor the lung (respiratory) wave measurement channel. This prevents additional phase-shift errors from the apparatus, thus increasing the accuracy of the proposed method. Moreover, the method is the ABP line's error and artifact-free,

− the method is fully non-invasive and it provides the new possibilities to apply the method for exploring the peculiarities of CA mechanism on various patients groups (TBI patients, hydrocephalus patients, cardiac surgery patients with cardiopulmonary bypass [28]) as well as on healthy volunteers [29],

− the increase of the informativeness and reliability of the method is obtained by combining simultaneous measuring of two phase shifts – the phase shift between the informative slow waves and the reference slow waves (PS1), and the phase shift between the informative respiratory waves and the reference respiratory waves (PS2) - in order to calculate an index representing the CA status.

V. CONCLUSIONS

The novel method and the device for non-invasive CA status monitoring without using the ABP measurement channel are presented. The comparative study performed on 11 TBI patients by using the novel non-invasive CA monitor and the conventional invasive CA estimation method based on PRx calculation showed significant agreement between these methods (r = 0.751), thus demonstrating for first time that it is enough to monitor and analyse the intracranial

blood volume dynamics non-invasively (or invasively) and it is not necessary to monitor the ABP dynamics in order to monitor the CA status.

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