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Analysis of Cerebrovascular Autoregulation Reactivity Index Electronic Monitoring Methods

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Introduction

Pathophysiological processes in the injured human brain proceed quickly and are very risky for human life. Human brain cerebrovascular autoregulation is a vital protective function of the cerebral vasculature. Human brain is at risk of secondary injury especially when this function fails. Innovative methods and technologies for continuous monitoring of injured brain have been designed in order to minimize the disability or mortality rate of such patients.

Continuous monitoring of the absolute values and time dependences of intracranial pressure (ICP), arterial blood pressure (ABP) and cerebral perfusion pressure (CPP), also continuous monitoring of brain compliance and cerebrovascular autoregulation (CA) are very important for treating brain injuries [1].

The concept of preventing secondary insults after traumatic brain injury (TBI) involves maintaining of sufficient oxygen delivery to the intracranial neural tissues and preventing tissues from cerebral hypoxia. This implies that cerebral blood flow (CBF), arterial oxygen saturation and hemoglobin concentration in a specific patient must be adequate.

Impairment of CBF autoregulation has a strong impact for TBI patients outcome. It is not enough to monitor ICP, ABP and CPP in order to optimize the TBI treatment decisions. So, it is essential to know the real-time status of CBF autoregulation [2–18].

Consensus was already achieved [11] that the 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 CBF autoregulation status. The Brain Trauma Foundation (USA) also sees the CBF autoregulation monitoring as an only tool for fine-tune individual patient CPP optimization and treatment optimization goals [10]. Electronic CBF autoregulation monitoring methods have to be developed for that purpose.

Cerebrovascular autoregulation electronic monitoring methods

The idea of cerebrovascular autoregulation monitoring is based on the phenomenon of the phase shift between slow (or B type) CPP and CBF waves [3,4,6,9]. In the case of intact autoregulation such phase shift can be up to 180° and in the case of impaired CA the phase shift is close to zero degrees.

Intact CA can be demonstrated by negative correlation between slow waves of CPP and CBF. Impaired autoregulation - which can be referred to as a state of pressure intracranial vasculature passivity - results in positive correlation between slow waves of CPP and CBF [3, 4, 9]. But correlation in this case is used as a method to convert the phase shift between CPP and CBF into some CA estimation index. Pressure reactivity index PRx [5] which is Pearson's correlation coefficient has been proposed for that purpose.

It is possible to monitor CPP = ABP - ICP invasively. But it is impossible to monitor CBF non-invasively or invasively. Because of that CBF is replaced by surrogate measure – cerebral blood flow velocity (CBFV) which is measured using transcranial Doppler technology (TCD) in clinical practice. CPP is also sometimes replaced by surrogate reference measure – ABP [5,6]. Intracranial blood volume (IBV) waves can be monitored non-invasively using ultrasonic time-of-flight technology [2,17,18]. Because of that IBV can also be used as an informative surrogate of CBF in CA monitoring systems [2, 6, 16–18].

TCD and non-invasive ABP slow wave monitoring technology has been proposed together with PRx calculation for CA continuous monitoring [2, 12].

ABP and ICP B waves within frequency range 0.005 Hz – 0.035 Hz are also proposed as a reference signal and an informative signal for CA monitoring [13–15].
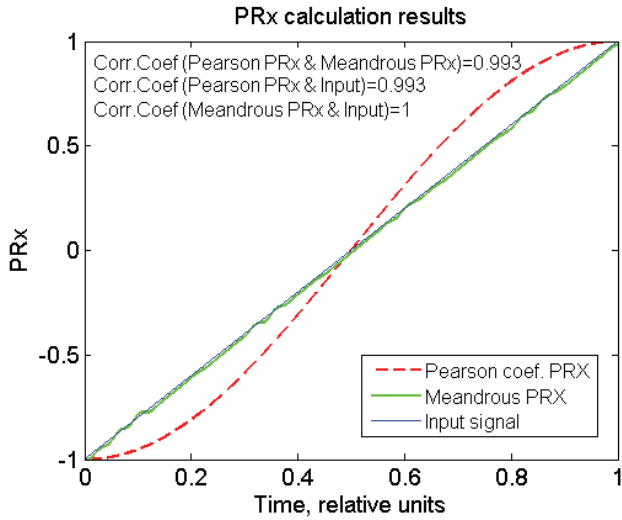

Fig. 1. Imitation of the human brain quasistatic cerebrovascular autoregulation (CA) linear change versus time between intact CA (PRx = -1.0) and impaired CA (PRx = +1.0) states: thin line – linear detection of the phase shift between ABP and ICP slow waves; thick line – cross correlation of ABP and ICP waves converted into rectangular signals rect(t) in order to eliminate non-linear distortions of PRx(t) calculation; dashed line – Pearson's correlation of slow ABP and ICP waves

The limitation of the slow B wave moving correlation monitoring method is the intermittent nature of B waves. The moving average of low amplitude B wave monitoring data in order to reduce the uncertainty of CA estimation is the cause of 3-10 min or even much longer instrumental delay between actual CA changes and the reflection of such changes in CA monitoring [13]. Such data delay time can be too big in the cases of aggressive treatment decision making. 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 [2,17,18] 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.

Electronic technologies for PRx monitoring

Pressure reactivity index (PRx) could be monitored and calculated from invasively measured ABP and ICP slow waves [13,14,15]. But conventional invasive ICP measurement techniques require surgical passage through the skull bone into the brain ventricles, parenchyma or the region between the skull and dura matter to implant a measuring transducer. Placement of the catheter may be difficult if there is ventricular effacement or displacement due to brain swelling or intracranial mass lesions. Furthermore, subdural fluid filled catheters are reasonably accurate below 30.0 mmHg. So, such invasive techniques, however, are undesirable, as damage to the sensitive brain tissues may result. Moreover, due to the invasive nature of
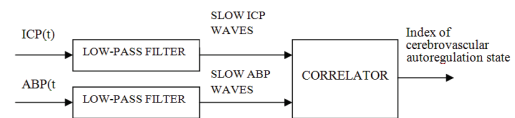
the procedures, infections may be caused despite precautions, which infections can be serious or even deadly [1].

Another possibility to measure ICP and ABP slow waves for calculating PRx is to use new ultrasonic "time-of-flight" technique [2], which allows continuous non-invasive monitoring of slow, respiratory and pulse ICP waves. 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 dynamic measurements of the TOF of ultrasonic pulses. The TOF depends on the acoustic properties of intracranial blood, brain tissue and cerebrospinal fluid. Changes in the volume of any of these components will change the TOF. It is proved experimentally [2,6,16,17,18], that slow, respiratory and pulse ICP waves are the consequences of the variations of intracranial blood volume (IBV). So, all IBV waves can be monitored continuously, non-invasively and in real-time using TOF technique [2]. Using this technique, the invasive ICP slow wave monitor could be replaced by the non-invasive monitoring of the relative speed $\Delta C/C0$ of the ultrasound passing 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 also slow $\Delta C/C0$ 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 (ICP; ABP) and non-invasive ($\Delta C/C0$; ABP) coefficients PRx [16].

It is known [7] that correlation of rectangular signals rect(wt) and rect(w(t-τ)) is linearly dependent on the delay time τ or the phase shift between two rectangular signals when $0 \leq \tau \leq T$. Pearson's correlation coefficient is non-linearly dependent on the phase shift difference between two harmonic signals (Fig. 1).

Comparing TOF technique with existing invasive techniques, the steps of PRx calculation are almost identical (Fig. 2). Here "limiter" means a double amplitude limiter for conversion of slow harmonic ICP and ABP waves into synchronous rectangular signals according to the conversion rules $A_{ICP}(t)\sin w_B t \rightarrow rect_{ICP}(w_B t)$ and $A_{ABP}(t)\sin w_B(t-\tau) \rightarrow rect_{ABP}(w_B(t-\tau))$, where w_B is angular frequency of ABP and ICP slow B waves.
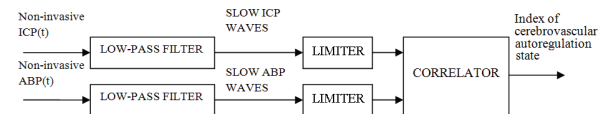

Fig. 2. Invasive and non-invasive PRx index monitoring techniques

Experimental results of PRx monitoring

In order to compare slow wave PRx monitoring technology with innovative [17,18] CA monitoring technology we used 250 hour invasive ICP and ABP data from three TBI patients' monitoring in Leuven (Belgium) University hospital.

Comparison of existing slow wave ICP and ABP monitoring data based PRx calculation technology with innovative ICP wave analysis based [17,18] PRx calculation technology is showed in Fig 3.

CA monitoring on TBI patients (Fig.3) with two different monitoring technologies - ICM+ (Cambridge Enterprise, UK) and proposed in [17,18] (Telematics Sc. Lab., Kaunas University of Technology) shows typical for traumatic brain injuries time course and fluctuations of PRx index.
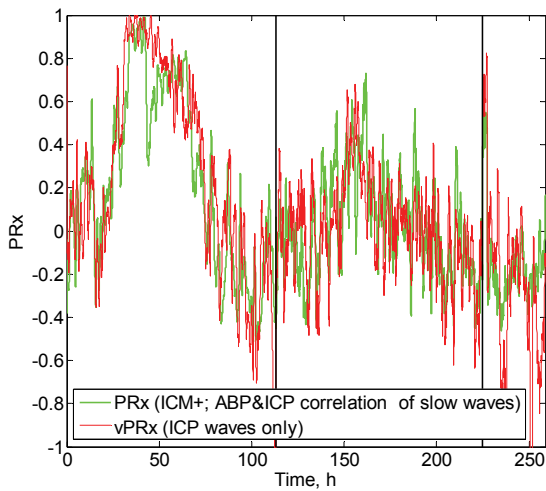

Fig. 3. 250 hours of PRx monitoring on 3 TBI patients: grey line - ICP and ABP slow wave monitoring data based PRx calculation using ICM+ software tool; black line – PRx calculated using ICP wave analysis software developed by Telematics Sc. Lab. (Kaunas University of Technology, Lithuania); individual patients' data are separated with vertical lines

Experimental results (Fig. 3) show that an innovative method proposed in [17,18] gives the same diagnostic information on PRx dynamics as ICM+ method. The monitoring data of both methods under comparison are highly correlated (R=0.843).

We hypothesized that the differences between two methods under comparison (Fig.3) could be caused by non-linear distortions of PRx(t) value calculation if PRx(t) has been calculated as a Pearson's correlation of slow ICP and ABP waves (Fig. 2). Application of transformation of ABP and ICP slow harmonic waves into rect(t) type signals is at the first time proposed in this work for elimination of PRx(t) non-linear distortions. Such transformation before Pearson's correlation coefficient calculation (Fig. 2) is well known in the other fields of measurements [7] as a linear phase shift estimation method.

Non-linear distortions of PRx(t)

Pressure reactivity index (or PRx(t)), in statistics also

named as the Pearson product-moment correlation coefficient or Pearson's correlation is obtained by dividing the covariance of two variables by the product of their standard deviations. It is widely used as a measure of the strength of linear dependence between two variables - X and Y.

So, if two variables – X and Y - is defined as the random gauges, and their averages are μ_X and μ_Y, the correlation of them could be written

$$\rho_{X,Y} = \frac{\text{cov}(X,Y)}{\sigma_X \sigma_Y} = \frac{E[(X-\mu_X)(Y-\mu_Y)]}{\sigma_X \sigma_Y}, \quad (1)$$

where cov(X,Y) is the covariation of variables X and Y. Because, $\mu_X = E(X)$ and $\sigma_{X2} = E(X^2) - E^2(X)$, also $\mu_Y = E(Y)$ and $\sigma_{Y2} = E(Y^2) - E^2(Y)$, the correlation of two variables X and Y could be written

$$\rho_{X,Y} = \frac{E(XY) - E(X)E(Y)}{\sqrt{E(X^2) - E^2(X)}\sqrt{E(Y^2) - E^2(Y)}}. \quad (2)$$

An equivalent expression gives the correlation coefficient as the mean of the products of the standard scores. Based on a sample of paired data (X_i, Y_i), the sample Pearson correlation coefficient is expressed as

$$r = \frac{1}{n-1} \sum_{i=1}^{n} (\frac{X_i - \bar{X}}{s_X})(\frac{Y_i - \bar{Y}}{s_Y}), \quad (3)$$

where $\frac{X_i - \bar{X}}{s_X}$ - standard score of X and Y, $\bar{X}$ and $\bar{Y}$ - sample means; s_X and s_Y - sample standard deviations.
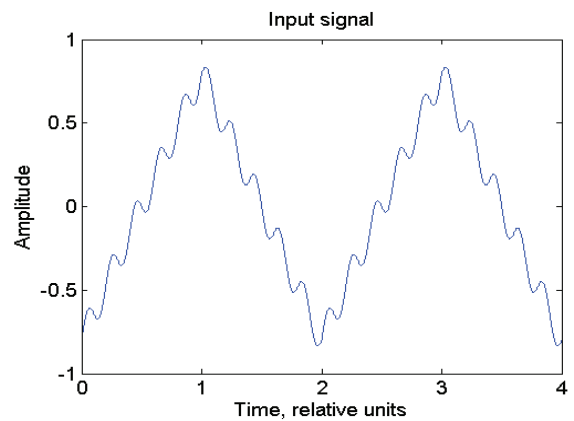

Fig. 4. Input signal for Pearson's correlation coefficient calculation non-linearity modeling: the sum of sinus and triangular signals

It is necessary to note, that Pearson's correlation is defined only if both of the standard deviations are finite and both of them are nonzero [5]. The values between −1.0 and 1.0 in all other cases indicates the degree of linear dependence between the variables X and Y. If the variables are independent, Pearson's correlation coefficient is 0, but the converse is not true because the correlation coefficient detects only linear dependencies between two variables.

However, in the special case when X and Y are jointly normal, existing of no correlation is equivalent to independence.
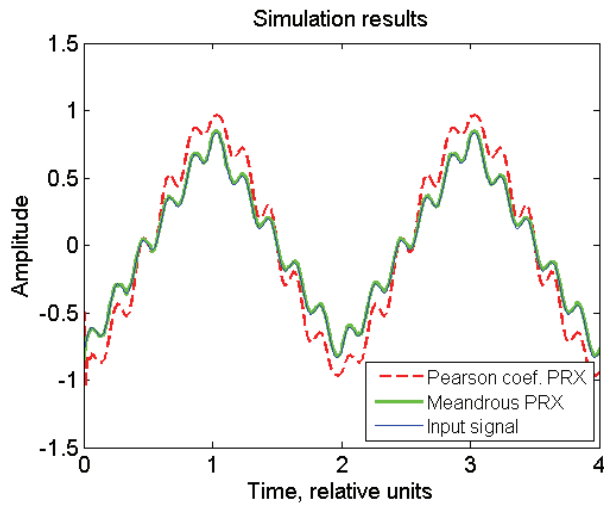

Fig. 5. Simulation results: thin line – input signal, dashed line - calculation of Pearson's correlation coefficient (PRx (t)), thick line – PRx (t) calculation without non-linear distortions

Invasively or non-invasively monitored slow ICP and slow ABP waves were modeled to perform the calculation of PRx in order to imitate CA dynamics adequately to physiological reality (Fig. 4). It was made an assumption, that slow ICP waves are sum of sinus and triangular shape waves. The input signal was simulated as shown in Fig 4.

The signal imitating periodical linear CA changes from intact to impaired states was processed by applying phase modulation with parameters of: $F_{carrier}$ = 125.0 Hz; F_{signal} = 20.0 kHz; modulation index = $\pi/2$. Modulated signal was multiplied by another cosines wave with the frequency - $F_{carrier}$. After filtering of high frequencies, it could be seen how non-linear phase demodulator equivalent to Pearson's correlation coefficient calculator brings non-linear distortion to the signal. Highest distortions appear when PRx values are closest to zero axis, and lowest - when PRx values are closest +1.0 or -1.0 axes (Fig. 5).

However, such non-linear distortions could be eliminated by using linear phase shift estimator of rectangular signals. In such case, highest signal fluctuations near PRx zero values could be eliminated, and the deviation of input signal in all amplitude values could be expressed without distortions (Fig 5, Fig. 6).

Existing Pearson's correlation coefficient calculation based CA estimation index PRx (t) is the result of non-linear phase shift demodulation which brings non-linear distortions in monitoring physiological processes of human brain cerebrovascular autoregulation. Imitation of the human brain quasistatic cerebrovascular autoregulation linear change versus time between intact CA (PRx = -1.0) and impaired CA (PRx = +1.0) states shows how signal correlation depends on different calculating methods.

Transformation of harmonic waves into rectangular signals before calculation of PRx(t) eliminates up to 20% - 25% non-linear distortions of CA dynamic estimation (Fig. 6, Fig. 7).
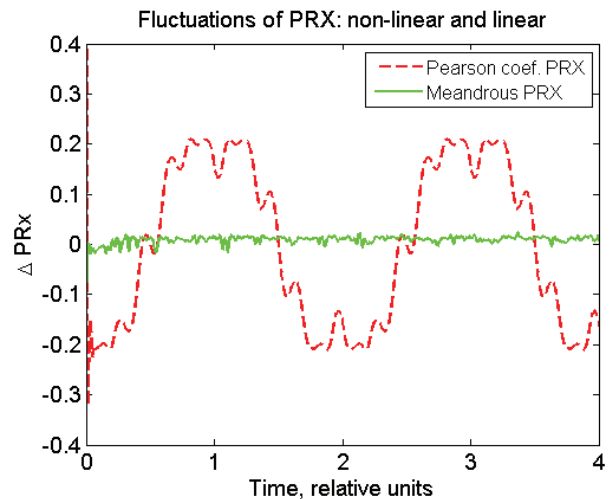

Fig. 6. Comparison of absolute bias of both PRx(t) calculation methods: dashed line – non-linear calculation of PRx(t), thick line –PRx(t) calculation without non-linear distortions
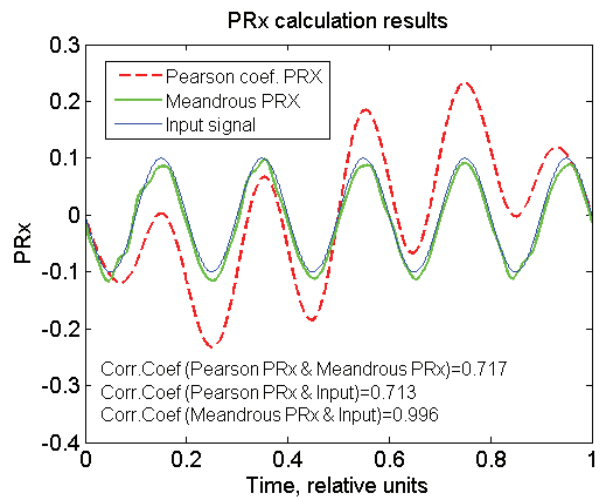

Fig. 7. Imitation of the human brain cerebrovascular autoregulation dynamic by PRx(t) sinusoidal variation versus time: thin line - linear detection of the phase shift between slow ABP and ICP waves; thick line - cross correlation of slow ABP and ICP waves converted into meandrous signals in order to eliminate non-linear distortions; dashed line - Pearson's correlation of slow ABP and ICP waves

Conclusions

It is essential to monitor CA continuously and to optimize the TBI patient treatment decisions according to the state of CA.

PRx as a CA estimation index is admitted by the European Society of Intensive Care Medicine to be the reliable indicator of the human brain vascular reactivity.

It was shown that existing PRx monitoring technology brings non-linear distortions in picturing physiological processes of human brain cerebrovascular autoregulation.

The calculation of PRx could be more precise and non-linear distortions could be eliminated by using linear phase shift estimation, realized by converting harmonic ICP(t) and ABP(t) slow waves into rect$_{ICP}$(t) and rect$_{ABP}$(t) type signals before calculation of the Pearson's correlation coefficient.

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A. Ragauskas, E. Kalvaitis, V. Petkus, G. Daubaris, B. Depreitere. Analysis of Cerebrovascular Autoregulation Reactivity Index Electronic Monitoring Methods // Electronics and Electrical Engineering. – Kaunas: Technologija, 2011. – No. 8(114). – P. 16–20.

Pressure reactivity index (PRx), which is a moving linear correlation (or Pearson's correlation) between slow waves of ABP and ICP is used as an estimator of the human brain cerebrovascular autoregulation state. Slow ICP and IBP waves were modeled and PRx was calculated by widely used calculation method. It was shown, that existing PRx calculation method gives non- linear PRx distortions comparing with phase shift of ABP and ICP slow waves. It was proposed PRx calculation method, which eliminates non-linear phase demodulator (Pearson's correlation coefficient calculator), brought in monitoring of human brain cerebrovascular autoregulation. Ill. 7, bibl. 18 (in English; abstracts in English and Lithuanian).

A. Ragauskas, E. Kalvaitis, V. Petkus, G. Daubaris, B. Depreitere. Cerebrovaskulinės kraujo spaudimo autoreguliacijos reaktyvumo indekso svarba ir naujo metodo taikymas spaudimo reaktyvumo indeksui apskaičiuoti // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2011. – Nr. 8(114). – P. 16–20.

Slėgio reaktyvumo indeksas (PRx), kuris apskaičiuojamas kaip lėtųjų ABP ir ICP bangų tiesinė koreliacija (arba Pirsono koreliacija), naudojamas žmogaus smegenų kraujotakos autoreguliacijos būsenų dinamikos stebėsenai. Lėtosios ICP ir ABP bangos buvo sumodeliuotos ir PRx buvo apskaičiuotas plačiai taikomais skaičiavimo metodais. Straipsnyje parodyta, kad plačiai taikomas PRx apskaičiavimo metodas nėra tikslus dėl netiesinės apskaičiuotų PRx verčių priklausomybės nuo ABP ir ICP lėtųjų bangų fazių skirtumo. Pasiūlytas naujas, tikslesnis, PRx apskaičiavimo metodas, kuris pašalina netiesinio fazinio demoduliatoriaus (Pirsono koreliacijos koeficiento skaičiuoklio) sukeliamus netiesinius fiziologinio žmogaus smegenų kraujotakos autoreguliacijos matavimo iškraipymus. Il. 7, bibl. 18 (anglų kalba; santraukos anglų ir lietuvių k.).