

ASSESSMENT OF CEREBRAL HEMODYNAMICS IN TRAUMATIC BRAIN INJURY

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ABSTRACT

We employ complex continuous wavelet transforms to develop a consistent mathematical framework capable of quantifying both cerebrospinal compensatory reserve and cerebrovascular pressure–reactivity. The wavelet gain $\eta_{ABP}^{ICP}(f)$, defined as the frequency dependent ratio of time averaged wavelet coefficients of intracranial pressure (ICP) and arterial blood pressure (ABP) fluctuations, characterizes the dampening of spontaneous ABP oscillations. This gain is introduced as a novel measure of cerebrospinal compensatory reserve. For a group of 12 patients who died as a result of cerebral lesions (Glasgow Outcome Scale GOS =1) the average gain $\eta_{ABP}^{ICP} = 0.45$ calculated at $f=0.05$ Hz significantly exceeds that of 17 patients with GOS=2: $\eta_{ABP}^{ICP} = 0.24$ with $p = 4 \times 10^{-5}$ (Kruskal-Wallis test). We also study the dynamics of instantaneous phase difference $\Delta\phi(f)$ between the fluctuations of ABP and ICP. The time-averaged synchronization index $\gamma_{ABP}^{ICP}(f) = \langle \sin \Delta\phi \rangle^2 + \langle \cos \Delta\phi \rangle^2$, which depends upon frequency, yields information about the stability of the phase difference $\Delta\phi$ and is used as a cerebrovascular pressure–reactivity index. For both groups of patients the synchronization is strong. We hypothesize that in patients who died the impairment of cerebral autoregulation is followed by the breakdown of residual pressure reactivity. For example at $f=0.05$ Hz $\gamma_{ABP}^{ICP} = 0.70$ (GOS=1) and $\gamma_{ABP}^{ICP} = 0.58$ (GOS=2). While these two synchronization levels are not statistically different ($p=0.15$) the corresponding average phase difference for GOS=1 is equal to 10 degrees in sharp contrast to the mean value of 44 degrees for patients with GOS=2 ($p = 1 \times 10^{-4}$).

1. INTRODUCTION

In the last decade the list of clinical parameters employed in the management of patients with severe brain injuries has been steadily growing. Continuous measurement of ECG, arterial and central venous pressure, pulse oximetry (SpO₂), and end-tidal carbon dioxide provide standard assessment of systemic cardiovascular and respiratory functions. These physiologic signals may now be monitored concurrently with intracranial pressure (ICP), jugular venous bulb oxygen saturation (JvO₂), flow velocity in major cerebral arteries, regional brain tissue concentration of O₂, CO₂, pH, glucose, lactate, and pyruvate, see, for example, (Kett-White et al. 2002) and references therein. There is a consensus that the technology used to acquire such physiologically diverse time series has outpaced algorithms used to analyze them. For example, continuous ICP monitoring has been an integral component of the management of patients with traumatic brain injuries or intracerebral hemorrhages for over two decades. Until recently the main objective of such monitoring was confined to the maintenance of adequate cerebral perfusion pressure. Certainly, severe consequences of even transient cerebral ischemia to some extent provide justification for the status quo. Nevertheless, recent studies have clearly demonstrated the clinical significance of more sophisticated hemodynamic metrics derived from ICP waveforms.

For example, Czosnyka et al (Czosnyka et al. 1996b) used the moving correlation coefficient between the fundamental harmonic of ICP pulse wave and the mean ICP (RAP index) to assess pressure-volume compensatory reserve. In the same vein, another ICP-derived metric - the pressure-reactivity index (PRx) (Czosnyka et al. 1997) quantifies cerebrovascular pressure-reactivity with the strength of linear correlation between fluctuations of arterial blood pressure (ABP) and ICP. A negative value of PRx reflects a normally reactive vascular bed, as ABP waves provoke inversely correlated waves in ICP. Positive values of this measure are associated with a passive

Report Documentation Page

*Form Approved
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|--|------------------------------------|--|---------------------------------|
| 1. REPORT DATE 01 NOV 2006 | 2. REPORT TYPE N/A | 3. DATES COVERED - | |
| 4. TITLE AND SUBTITLE Assessment Of Cerebral Hemodynamics In Traumatic Brain Injury | | 5a. CONTRACT NUMBER | |
| | | 5b. GRANT NUMBER | |
| | | 5c. PROGRAM ELEMENT NUMBER | |
| 6. AUTHOR(S) | | 5d. PROJECT NUMBER | |
| | | 5e. TASK NUMBER | |
| | | 5f. WORK UNIT NUMBER | |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Institute of Physics, Wroclaw University of Technology, Wybrzeze Wyspianskiego 27, 50-370 Wroclaw, Poland | | 8. PERFORMING ORGANIZATION REPORT NUMBER | |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) | | 10. SPONSOR/MONITOR'S ACRONYM(S) | |
| | | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) | |
| 12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited | | | |
| 13. SUPPLEMENTARY NOTES See also ADM002075., The original document contains color images. | | | |
| 14. ABSTRACT | | | |
| 15. SUBJECT TERMS | | | |
| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT |
| a. REPORT unclassified | b. ABSTRACT unclassified | c. THIS PAGE unclassified | UU |
| | | | 18. NUMBER OF PAGES 8 |
| | | | 19a. NAME OF RESPONSIBLE PERSON |

behaviour of a non-reactive vascular bed. This index was reported to correlate with indices of autoregulation based on transcranial Doppler ultrasonography (Czosnyka et al. 1996a; Lang et al. 2002). Furthermore, abnormal values of both PRx and RAP indicate poor autoregulation or reduced cerebrospinal compensatory reserve, respectively. These abnormal values have been shown to be predictive of a poor outcome following head injury (Balestreri et al. 2004; Czosnyka et al. 1997; Czosnyka et al. 1996b; Steiner et al. 2002).

However, recent studies (Giller; Mueller 2003; Latka et al. 2005; Mitsis; Marmarelis 2002; Mitsis et al. 2002, 2006; Panerai et al. 1999) have emphasized nonlinear, non-stationary and multiscale aspects of cerebral hemodynamics. The goal of this paper is to present a novel perspective of the frequency-dependent, non-stationary aspects of intracranial pressure dynamics. We adopt and extend the mathematical framework of complex continuous wavelet transforms to analyze the dynamics of the instantaneous phase difference between the fluctuations of ABP and ICP (Latka et al. 2005). We hypothesize that the frequency dependent strength of synchronization between these two hemodynamic time series reflects pressure reactivity of the cerebrovascular bed. We also test whether wavelet gain which characterizes the dampening of spontaneous arterial blood oscillations within intracerebral space can quantify cerebrospinal compensatory reserve.

2. METHODS

The study, approved by the Opole Human Research Committee, comprised 37 patients (29 males and 8 females) treated at the Department of Neurosurgery of Regional Medical Center in Opole, Poland. The median age of subjects was 55 ± 15 years. In the cohort 19 patients were diagnosed with subdural haematoma, 7 with spontaneous intracerebral haemorrhage, and 6 with subarachnoid hemorrhage from ruptured aneurysm. There were 4 cases of cerebral contusions and a single case of traumatic subarachnoid haemorrhage. The written informed consent requirement was waived since only routinely monitored variables were used in this research.

All of the patients were unconscious at admission. Their initial neurological condition was assessed with Glasgow Coma Scale (GCS). 5 patients had GCS=3; 14 had GCS=4; 8 had GCS=5; 5 had GCS=6; 4 had GCS=7; and 1 had GCS=8. In all but four cases the invasive intracranial pressure monitoring followed neurosurgical procedures. The tip of the ICP strain gauge transducer (Codman) was implanted intraparenchymally into the frontal lobe, contralaterally to the cerebral lesion. The arterial blood pressure was continuously measured with the radial artery cannulation (Gabarith). The simultaneous

monitoring of ICP, ABP and ECG was performed for up to 7 days after ICP gauge implantation.

Postoperative treatment involved the mechanical ventilation and optional barbiturane administration. The cerebral perfusion pressure (CPP) was generally maintained above 70 mmHg. The treatment was scored with Glasgow Outcome Scale (GOS). 12 out of 37 patients died (GOS=1). For the other patients the scores were distributed as follows: 17 with GOS=2; 6 with GOS=3; 1 with GOS=4; and 1 with GOS=5. The statistical analysis was confined to the two largest subgroups, i.e., those with GOS=1 and those with GOS=2. The physiologic data acquired during monitoring of patients with better clinical condition (GOS > 2) were used for case studies.

Beat-to-beat average values of blood and intracranial pressures were calculated via waveform integration of the corresponding signals sampled at 100 Hz and digitized at 16 bits. In numerical calculations non-uniformly spaced time series were resampled at 2 Hz with the help of cubic spline interpolation.

The wavelet transform is an integral transform which employs basis functions, known as wavelets, localized in both time and frequency. Such wavelets are constructed from a single mother wavelet $\psi(t)$ by means of translations and dilations. The wavelet coefficient $W_s(a, t_0)$ is obtained by filtering the signal:

$$W_s(a, t_0) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} \psi^* \left(\frac{t-t_0}{a} \right) \cdot s(t) dt \quad (1)$$

and quantifies the similarity of the signal $s(t)$ to the wavelet dilated by scale a and centered at t_0 (the asterisk denotes complex conjugation). The instantaneous phase $\phi(t)$ associated with the signal $s(t)$ can be readily extracted by calculating its wavelet transform with a complex mother function to obtain

$$\phi(a, t_0) = -i \log \left[\frac{W_s(a, t_0)}{|W_s(a, t_0)|} \right] \quad (2)$$

The dual localization of wavelets makes it possible to associate a pseudofrequency f_a with the scale a :

$$f_a = \frac{f_c}{a\delta t} \quad (3)$$

where f_c is the center frequency and δt is the sampling period. Herein, we employ the complex Morlet wavelet:

$$\psi(t) = \frac{1}{\sqrt{\pi f_b}} e^{2\pi i f_c t} e^{-t^2 / f_b} \quad (4)$$

and set both the center frequency f_c and the bandwidth parameter f_b to 1. The detailed description of the numerical algorithms used in wavelet analyses may be

found in (Latka et al. 2003; Latka et al. 2005) and will not be reproduced here.

We quantify the interdependence of ABP and ICP time series fluctuations with the scale (frequency) dependent synchronization index:

$$\gamma_{ABP}^{ICP}(a) = \langle \sin \Delta\phi \rangle^2 + \langle \cos \Delta\phi \rangle^2 \quad (5)$$

where $\Delta\phi = \phi_{ICP} - \phi_{ABP}$ is the instantaneous phase difference between the ABP and ICP time series. The angular brackets denote averaging over time. The synchronization index lies in the interval $0 \leq \gamma \leq 1$. A vanishing index $\gamma = 0$ corresponds to a uniform distribution of the phase differences (no synchronization) while $\gamma = 1$ corresponds to perfect synchronization (phase locking of the two processes).

In the most straightforward approach we define the scale-dependent time-averaged wavelet gain η as

$$\eta_{ABP}^{ICP}(a) = \frac{\langle |W_{ICP}(a, t_0)| \rangle}{\langle |W_{ABP}(a, t_0)| \rangle}. \quad (6)$$

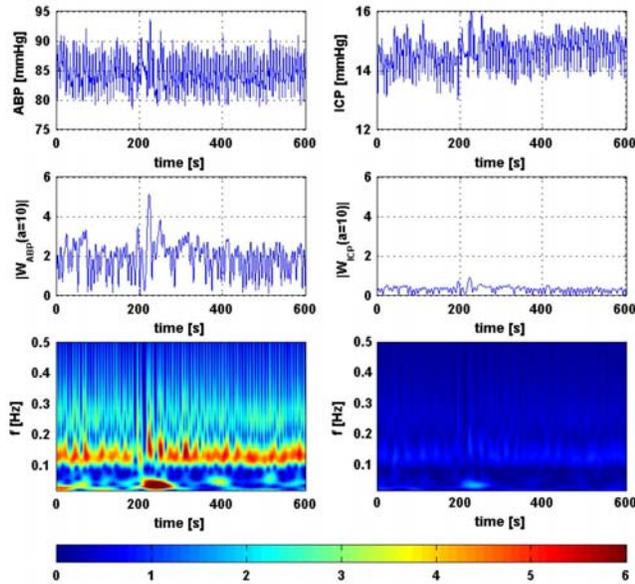


Fig. 1. Wavelet analysis of arterial (left column) and intracranial (right column) pressure fluctuations for a patient with mild hypertension. First row: The spontaneous fluctuations averaged over a cardiac beat. Second row: time evolution of the modulus of the wavelet coefficient for scale $a=10$ (this scale corresponds to pseudofrequency 0.2 Hz). Third row: the density plot of the modulus of the wavelet coefficients. The horizontal color bar at the bottom of the figure reveals the assignments of colors to values of wavelets coefficients. All coefficients with modulus greater than 4 are marked as dark brown. Strong damping of ABP fluctuations is characteristic of physiological cerebral hemodynamics.

The gain quantifies the damping of spontaneous ABP fluctuations. We hypothesize that the synchronization index γ is determined by reactivity of the vascular bed while the gain η may be used as a novel measure of cerebrospinal compensatory reserve.

3. DISCUSSION

It is apparent that the fundamental Fourier component of intracranial pressure waveform has a frequency equal to the heart rate. Czosnyka *et al* (Czosnyka et al. 1996b) argue that linear correlation between the amplitude of the pulse harmonic (AMP) and mean intracranial pressure provides information about accessible intracerebral space. More specifically, the relation between ICP and this volume is given by a nonlinear, sigmoid pressure-volume curve. At low ICP this curve is flat indicating good compensatory reserve. With increasing pressure the relation becomes exponential. The second flat zone, seen

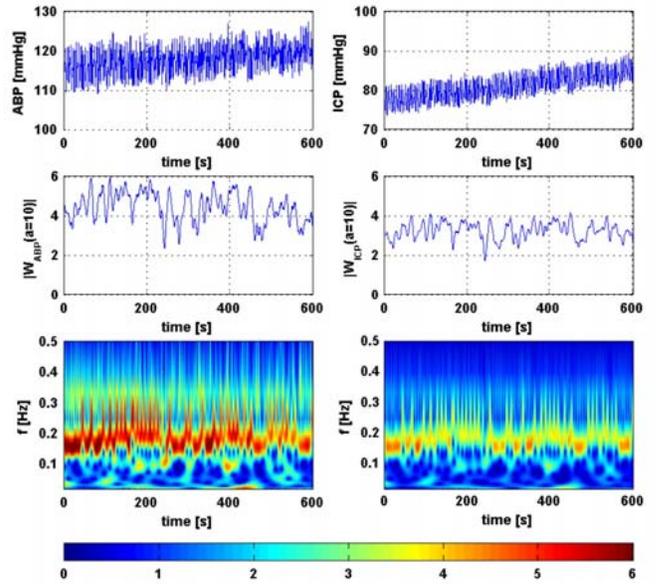


Fig. 2. Wavelet analysis of arterial (left column) and intracranial (right column) pressure fluctuations for a patient with severe hypertension. First row: The spontaneous fluctuations averaged over a cardiac beat. Second row: time evolution of the modulus of the wavelet coefficient for scale $a=10$ (this scale corresponds to pseudofrequency 0.2 Hz). Third row: the density plot of the modulus of the wavelet coefficients. The horizontal color bar at the bottom of the figure reveals the assignments of colors to values of wavelets coefficients. All coefficients with modulus greater than 4 are marked as dark brown. Weak damping of ABP fluctuations stems from severe cerebral swelling

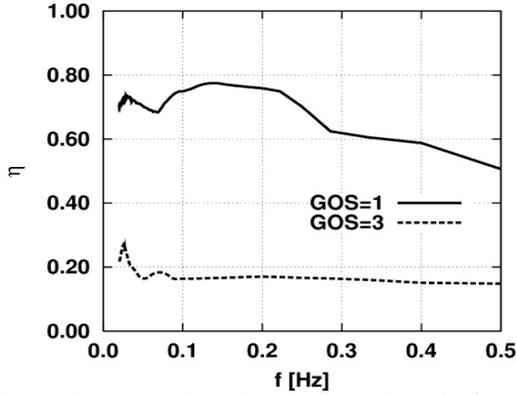


Fig. 3. Frequency dependence of wavelet gain for: a patient with mild (dashed line) and severe (solid line) cerebral hypertension.

at very high ICP reflects derangement of normal cerebrovascular responses. More specifically, they define the RAP index as the coefficient of correlation between 40 consecutive, time-averaged data points of AMP and ICP acquired over 6.4 s. The values of RAP close to 0 indicate good pressure-volume compensatory reserve at low ICP. Even though the simplicity and clinical relevance of the discussed approach is appealing, the fundamental question arises as to whether the response to changes in intracranial blood volume is frequency dependent.

In Fig. 1 and Fig. 2 we compare time evolution of the modulus of wavelet coefficients of ABP and ICP fluctuations for two patients with mild and severe cerebral hypertension respectively. On the basis of these case studies one can hypothesize that strong damping of spontaneous ABP fluctuations is characteristic of physiologic hemodynamics. Thus, the wavelet gain η which quantifies such attenuation is a plausible metric for pressure-volume compensatory reserve.

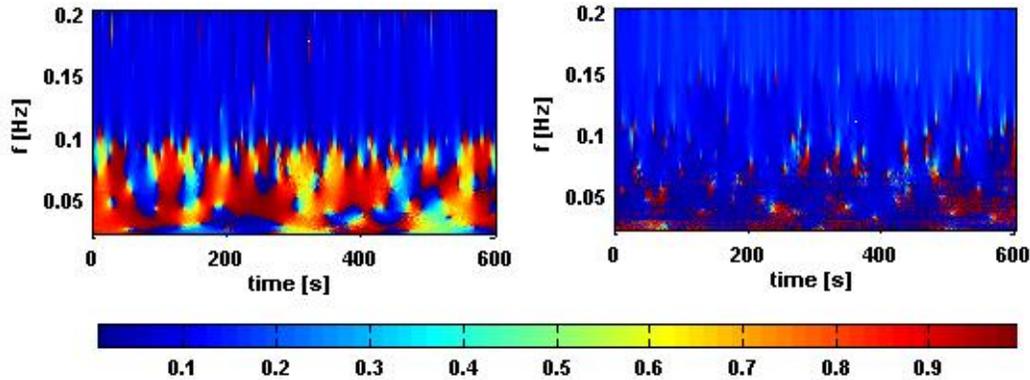


Fig. 5. Time evolution of frequency dependent normalized phase difference ($\Delta/2\pi$) between fluctuations of arterial and intracranial pressure fluctuations for a patient with: (a) mild hypertension (cf. Fig. 1) and (b) severe hypertension (cf. Fig. 2).

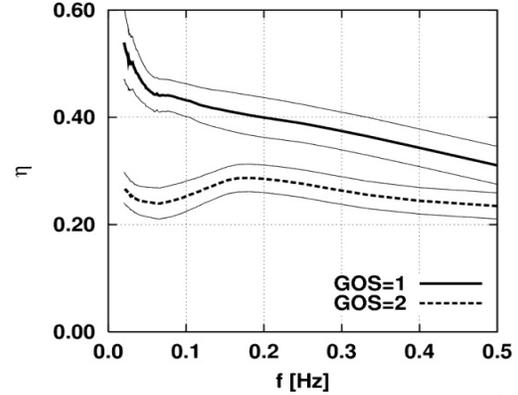


Fig. 4. Group averaged wavelet gain as a function of frequency. The thick solid line corresponds to the patients who died (GOS=1) and the dashed line to those with GOS=2. The thin lines represent the corresponding standard error of the mean.

In Fig. 3 we plot the gain as a function of frequency for the cases analyzed in Figs. 1 and 2. The elevated value of wavelet gain over the entire frequency range is evident for a subject with severe cerebral swelling. It is also worth pointing out that the damping of ABP fluctuations is significantly weaker (as indicated by higher values of gain) in low-frequency part of the spectrum. These conclusions are corroborated by the statistical analysis of the wavelet gain for two group of patients: those with GOS=1 and those with GOS=2 (cf. Fig. 4). With decreasing frequency, the mean gain for both groups starts to diverge at approximately 0.2 Hz. For example, for patients who died the average gain $\eta_{ABP}^{ICP} = 0.45$ calculated at $f=0.05$ Hz significantly exceeds that of patients with GOS=2: $\eta_{ABP}^{ICP} = 0.24$ ($p = 4 \times 10^{-5}$ obtained from the Kruskal-Wallis test).

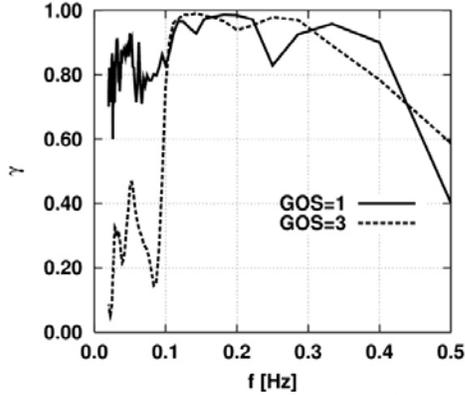


Fig. 6. Frequency dependence of synchronization parameter for: a patient with mild (dashed line) and severe (solid line) hypertension.

In the phenomenological description of cerebral hemodynamics, fluctuations of ABP, due to pressure reactivity of cerebral vessels, lead to fluctuations of ICP. The vascular origin of the ICP slow waves through intracranial blood volume variations is commonly accepted (Steinmeier et al. 1996). Nevertheless, the quantitative description of this clinically significant effect is the subject of ongoing research. To shed new light on the interplay of ABP and ICP we chose to employ complex wavelet transforms to study the time evolution of the instantaneous phase difference between the two time series. Fig. 5 exemplifies such an approach for two previously discussed case studies. Upon inspection of both density plots in this figure one finds that the presence of the horizontal multicolor strip for a subject with mild cerebral hypertension (Fig. 5a) is just a manifestation of low-frequency phase variability. Such variability is almost entirely lost during severe hypertension (Fig. 5b). Synchronization strength between fluctuations of ABP and ICP can be quantified with the help of synchronization parameter γ which in Fig. 6 is plotted as a function of frequency for both subjects. The very high values of γ for the patient with GOS=1 reflect pathological entrainment of ABP and ICP time series. Such entrainment can also be observed in Fig. 7 which shows the synchronization parameter averaged over both groups. For this hemodynamic metric the differences between the groups are not as strongly pronounced across the displayed frequency range as were the differences in wavelet gain (Fig. 4). At $f=0.05$ Hz we find $\eta_{ABP}^{ICP} = 0.70$ (GOS=1) and $\eta_{ABP}^{ICP} = 0.58$ (GOS=2). These two synchronization levels are not statistically different ($p=0.15$). In principle one might argue that for both groups cerebrovascular reactivity was compromised. However, strong phase-locking allows us to characterize cerebral hemodynamics also in terms of the time-averaged value of the phase difference between the ABP and ICP waveforms.

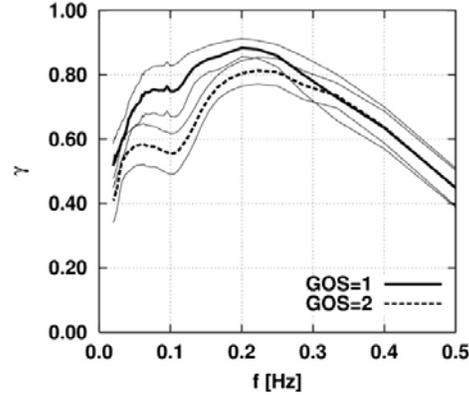


Fig. 7. Group averaged synchronization parameter as a function of frequency. The thick solid line corresponds to the patients who died (GOS=1) and the dashed line to those with GOS=2. The thin lines represent the corresponding standard error of the mean.

Fig. 8 shows the group averaged phase difference as a function of frequency. At $f=0.05$ Hz the corresponding difference for GOS=1 is equal to 10 degrees in sharp contrast to the mean value of 44 degrees for patients with GOS=2 (circular variant of the t-test (Batschelet 1981) yielded the value of $p=1 \times 10^{-4}$). The low-frequency variability of the phase difference between the spontaneous oscillations of ABP and blood flow velocity in major cerebral arteries is the hallmark of intact cerebral autoregulation (Giller 1990; Latka et al. 2005). Therefore, we hypothesize that in patients who died the impairment of cerebral autoregulation is followed by the breakdown of residual pressure reactivity. It is worth emphasizing that such insight is unique to the wavelet analysis. In the PRX approach the gradual loss of cerebrovascular bed pressure reactivity is manifested solely by the index's value approaching one.

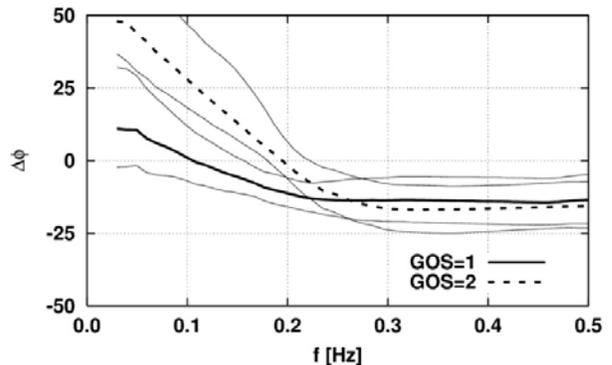


Fig. 8. The time averaged angle between ABP and ICP fluctuations for: patients with GOS=1 (thick solid line) and GOS=2 (thick dashed line). The thin lines delineate 95% confidence intervals.

In the pioneering studies of cerebrospinal fluid system Marmarou (Marmarou 1973) postulated an exponential volume-pressure relation. Such interdependence of variables underlies the PVI index which quantifies the

compliance over the whole physiological range of ICP. Miller *et al* (Miller et al. 1973) advocated the volume pressure response (VPR) as a measure of elastance (inverse of compliance) which is independent of functional relation between craniospinal volume and pressure. In both approaches, now commonly accepted as the gold standards, the corresponding indices are calculated from the pressure change resulting from volume injection or withdrawal of fluid from the CSF space. An exhaustive list of relevant references is given in (Reilly, Bullock 2005).

Physiological causes of elevated ICP may be broadly classified into vascular and non-vascular. Vascular mechanisms are associated with either passive or active vasodilation of the cerebrovascular bed. Active vasodilation may be brought about by increased concentration of CO₂ and/or, within the operating range of pressure autoregulation, decreased cerebral perfusion pressure. The list of non-vascular causes is long and includes increased: brain water content (edema), intracerebral, extradural or subdural mass as well as CSF outflow resistance (Reilly; Bullock 2005).

Marmarou *et al* demonstrated that in patients with severe head-injury elevated ICP can to a large extent be attributed to vascular mechanisms (Marmarou et al. 1987). Gray and Rosner determined that PVI and CPP may be linearly anticorrelated or correlated depending on whether the CPP range is beyond or within the autoregulating range (Gray; Rosner 1987a, 1987b). Detrimental influence of low CPP on intracranial compliance was recently corroborated by Portella *et al* (Portella et al. 2005). Interestingly enough, cerebrovascular compensatory reserve is also time-dependent. Anile, Portnoy, and Branch found that VPR indices derived from slow, medium and rapid bolus injection differ (Anile et al. 1987). The dif-

ferences result from the existence of two distinct components of craniospinal compliance. The short-time physical compliance is determined by such factors as spinal dura matter expansion while the time constant of physiological compliance associated with cerebrovascular alterations (e.g. venous outflow resistance) is significantly longer. Thus, to fully understand the intricate interplay of craniospinal volume and pressure, the dynamic and the viscoelastic properties of CSF, nervous tissue and vascular factors must all be considered.

To address this issue in the most straightforward way, in Fig. 9 the values of wavelet gain and synchronization index, averaged over the low frequency part of the spectrum, were used as the coordinates of points representing the overall hemodynamic condition. It comes as no surprise that the high-synchronization high-gain region of the cerebral hemodynamic state space to a large extent coincides with high values of intracranial pressure. Nevertheless, one can easily find cases with relatively high wavelet gain, moderate ICP and largely intact pressure reactivity of the vascular bed. Thus, further studies should explore whether the onset of severe cerebral hypertension is preceded by high-gain episodes. If such episodes are sufficiently long they could become the cornerstone of a ICP hypertension prediction algorithm. It also worth pointing out that overnight ICP monitoring may be used in the diagnosis of patients with hydrocephalus symptoms or shunt malfunctions (Czosnyka et al. 2004). The frequency dependent aspects of cerebrospinal fluid dynamics discussed herein give strong indications that such monitoring can provide more detailed assessment of patients' clinical conditions than do limited time infusion tests. From the clinical point of view, the studies of time evolution of the wavelet gain in patients with normotensive hydrocephalus, are particularly important.

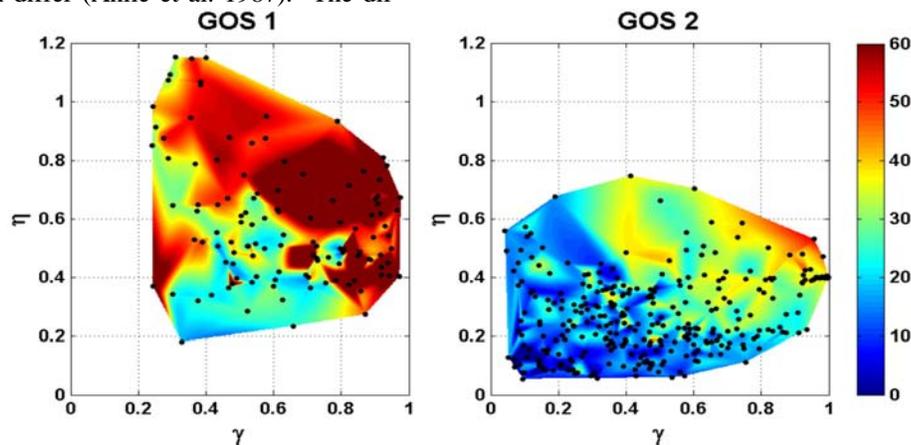


Fig. 9. The values of wavelet gain and synchronization index, averaged over the low frequency part of the spectrum (0.02-0.07 Hz), were used as the coordinates of points representing the hemodynamic condition of patients with GOS=1 (left plot) and GOS=2 (right plot). The vertical color bar shows the assignment of colors to values of intracranial pressure. Each dot corresponds to 15 minute monitoring interval.

4. CONCLUSIONS

Diverse approaches have been used to elucidate interrelations between intracranial pressure and other hemodynamic variables. Most of the research effort has been focused on propagation of the pulse wave from the arterial bed to the intracranial space (Aboy et al. 2003; Avezaat et al. 1979; Daley et al. 1995; Pettorossi et al. 1978; Portnoy; Chopp 1981; Portnoy et al. 1982). However, during the last decade the clinical significance of low frequency ICP waves has been repeatedly emphasized (Steinmeier et al. 1996). Herein we presented the mathematical framework capable of quantifying intrinsically non-stationary properties of cerebral hemodynamics across the broad range of physiologically relevant frequencies. We are convinced that optimal therapy management of patients with cerebral lesions hinges on thorough, qualitative assessment of their clinical condition. The further validation of the proposed assessment of compensatory reserve and pressure reactivity will involve the comparison with the gold standards (Diehl 2002; Reilly; Bullock 2005) as well as the methods which fairly recently gained clinical acceptance (Piper et al. 1999; Piper et al. 1990). This issue is the subject of our ongoing research.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the U.S. Army Research Office (Grant DAAD19-03-1-0349) and Polish Ministry of Science and Information Society Technologies (Grant 3 T11E 023 29).

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