Nonlinear Pressure-Flow Relationship Is Able to Detect Asymmetry of Brain Blood Circulation Associated with Midline Shift

Kun Hu,[1] Men-Tzung Lo,[1,2] C.K. Peng,[3] Vera Novak,[1] Eric A. Schmidt,[4]
Ajay Kumar,[5] and Marek Czosnyka[5]

Abstract

Reliable and noninvasive assessment of cerebral blood flow regulation is a major challenge in acute care monitoring. This study assessed dynamics of flow regulation and its relationship to asymmetry of initial computed tomography (CT) scan using multimodal pressure flow (MMPF) analysis. Data of 27 patients (38 ± 15 years old) with traumatic brain injury (TBI) were analyzed. Patients were selected from bigger cohort according to criteria of having midline shift on initial CT scan and intact skull (no craniotomy or bone flap). The MMPF analysis was used to extract the oscillations in cerebral perfusion pressure (CPP) and blood flow velocity (BFV) signals at frequency of artificial ventilation, and to calculate the instantaneous phase difference between CPP and BFV oscillations. Mean CPP-BFV phase difference was used to quantify pressure and flow relationship. The TBI subjects had smaller mean BP-BFV phase shifts (left, 8.7 ± 9.6; right 10.2 ± 8.3 MCAs, mean $\pm$ SD) than values previously obtained in healthy subjects (left, 37.3 ± 7.6 degrees; right, 38.0 ± 8.9 degrees; $p < 0.0001$), suggesting impaired blood flow regulation after TBI. The difference in phase shift between CPP and BFV in the left and right side was strongly correlated to the midline shift ($R = 0.78$; $p < 0.0001$). These findings indicate that the MMPF method allows reliable assessment of alterations in pressure and flow relationship after TBI. Moreover, mean pressure-flow phase shift is sensitive to the displacement of midline of the brain, and may potentially serve as a marker of asymmetry of cerebral autoregulation.

Key words: blood flow velocity; blood pressure oscillations; multimodal pressure flow analysis; traumatic brain injury

Introduction

DYNAMIC CEREBRAL AUTOREGULATION (dCA) adjusts cerebral perfusion pressure (CPP) in response to arterial pressure fluctuations on a beat-to-beat basis within a relatively short time, ranging from 6 to 12 sec (Aaslid et al., 1991). Impairment of autoregulation is observed after traumatic brain injury (TBI) (Enevoldsen and Jensen, 1977; Overgaard and Tweed, 1974), and it is one of the mechanisms rendering the brain vulnerable to secondary ischemia and leading to fatal outcomes (Czosnyka et al., 1996, 1997; Schmidt et al., 2003). Reliable assessment of cerebral autoregulation is clini-

cally important for monitoring of patients requiring neurological intensive care.

Continuous monitoring of blood flow velocities (BFV) using transcranial Doppler ultrasound enables assessment of autoregulation from relationship between blood pressure (BP) and BFV signals in both steady-state (Diehl et al., 1995; Czosnyka et al., 1996; Novak et al., 2004; Chen et al., 2006) and dynamic conditions (Novak et al., 1998, 2003; Tiecks et al., 1995; Panerai et al., 2001; Asil et al., 2007). Nonstationarity of physiological recordings can mask already complex BP-BFV relationship and pose a challenge for reliable assessment of dCA. The multi-modal pressure flow method (MMPF) that

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[1]Division of Gerontology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.
[2]Research Center for Adaptive Data Analysis, National Central University, Chungli, Taiwan, ROC.
[3]Division of Interdisciplinary Medicine & Biotechnology and Margret and H.A. Rey Institute for Nonlinear Dynamics in Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts.
[4]Department of Neurosurgery, Hopital Pourpan, Toulouse, France.
[5]Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge, United Kingdom.

assesses instantaneous BP and BFV phase shift without the assumption of stationary signals can potentially overcome these limitations (Novak et al., 2004; Lo et al., 2008). Studies have shown that the MMPF can reliably assess blood flow regulation and its alteration in stroke, hypertension and type 2 diabetes (Novak et al., 2004; Hu et al., 2008a,b). Moreover, the MMPF can use respiration-driven or spontaneous fluctuations of BP/BFV to estimate autoregulation, and the MMPF measure is highly correlated to the value obtained from the intervention-induced BP and BFV oscillations (Hu et al., 2008a,b; Lo et al., 2008).

In the present study, we tested (1) whether the MMPF method can reliably estimate cerebral blood flow dynamics in head-injured patients, using ventilation-driven BP and BFV fluctuations; and (2) whether the MMPF derived measures of autoregulation correlate to midline shift on computed tomography (CT) after brain injury. These questions may open a way for novel clinical applications in patients with evolving acute asymmetry of brain structures due to brain edema, including poor grade stroke patients.

Methods

Patients

This study utilized the existing de-identified databases at Neurocritical Care Unit (NCCU) at Addenbrooke's Hospital in Cambridge, United Kingdom. Subjects analyzed in this study included 27 patients (18 men and nine women, mean age 38 years, age range 16–69 years) with acute TBI who were admitted to Addenbrooke's Hospital with a mean GCS score of 6 (range, 3–13; Table 1) (Schmidt et al., 2003). The protocol approval was obtained in agreement with Neurocritical Care User Committee at the Addenbrooke's Hospital. This subgroup of patients was selected according to the midline shift seen on admission or subsequent CT scan. None of them had craniotomy to evacuate mass lesion during data collection. The midline shift (i.e., displacement of the brain's midline)

was measured on the CT film and transposed in actual size (mm) according to the scale on the CT scan. We give a positive value of the midline shift for displacement of the brain's midline from the right to the left, and negative value for displacement from the left to the right.

The patients were paralyzed, sedated, and ventilated at 12–22 breath cycles per minute to achieve mild hypocapnia (PaCO$_2$ 30–35 mm Hg). Spontaneous declines in BP that reduced CPP below 60 mm Hg were managed with alternating colloid and normal saline infusions, with supplementary inotropic agents if necessary (constant infusion of dopamine at 2–15 μg/kg per min). If ICP rose to >25 mm Hg, boluses of mannitol (200 mL of 20% for ≥20 min) were administered.

Data acquisition

Signals were monitored during periods of stable respiratory parameters, free from physiotherapy, tracheal suction, and other disturbances. Arterial blood pressure (ABP) was monitored directly in the radial or dorsalis pedis artery (System 8000, S&W Vickers Ltd.; or Solaris 3000, Marquette). Intracranial pressure (ICP) was monitored continuously using a microtransducer (Codman & Shurtleff, Raynham, MA) inserted intraparenchymally into the frontal region. CPP was obtained from ABP and ICP (i.e., CPP = ABP – ICP). Both middle cerebral arteries (MCA) were insonated daily, for 20 min to 2 h, starting from the day of admission until discharge or day 8 after head injury, to record bilateral BFVs in MCA using Neuroguard Doppler Ultrasound Unit (Medasonics, Fremont, CA) or Multidop 4X (DWL, Sipplingen, Germany). Analog outputs from the pressure monitors and the TCD unit (maximal frequency envelope) were connected to the analog-to-digital convertor (DT 2814; Data Translation) fitted into an IBM AT laptop computer (Amstrad ALT 386 SX). Data were sampled at a sampling frequency of 30 Hz and were stored on the hard disk with the software for the waveform recording (WREC, W. Zabolotny, Warsaw University of

TABLE 1. DEMOGRAPHIC AND PHYSIOLOGICAL CHARACTERISTICS OF STUDY POPULATION

	TBI group	TBI, <5 mm midline shift	TBI, ≥5 mm midline shift	P-value, ANOVA	P-value, Wilcoxon
Group (n)	27	14	13		
Age (years)	37.8 ± 15.2	33.1 ± 13.7	42.1 ± 15.8	NS	NS
Sex (M/F)	18/9	9/4	9/5		
Glasgow Coma Scale	6.3 ± 2.9	5.1 ± 1.9	7.5 ± 3.2	0.03	0.04
Glasgow Outcome Scale	3.0 ± 1.5 (3 unknown)	3.3 ± 1.5	2.6 ± 1.3	NS	NS
ICP (mm Hg)	18.2 ± 6.8	19.7 ± 7.7	16.8 ± 5.9	NS	NS
ABP (mm Hg)	95.1 ± 10.3	97.1 ± 9.8	93.3 ± 10.8	NS	NS
CPP (mm Hg)	76.9 ± 7.4	77.3 ± 8.3	76.6 ± 6.7	NS	NS
Heart rate (beats/min)	82.3 ± 17.3	86.1 ± 17.8	78.9 ± 16.8	NS	NS
Left BFV (cm/sec)	64.6 ± 31.8	53.4 ± 17.3	75.0 ± 38.8	0.08	0.08
Right BFV (cm/sec)	59.4 ± 27.5	49.6 ± 25.9	68.5 ± 26.6	0.07	0.08
Midline shift (mm), Absolute value	5.4 ± 4.1	2.3 ± 1.1	8.2 ± 3.7	<0.0001	<0.0001
Left-right difference in BP-BFV phase shift (degrees) Absolute value	5.1 ± 4.4	2.4 ± 1.7	7.3 ± 4.8	0.0038	0.002

Data were presented as mean ± SD. The p-values for comparison between TBI patients with midline shift of <5 mm and patients with ≥5mm were obtained from analysis of variances (ANOVA) and non-parametric Wilcoxon tests.

TBI, traumatic brain injury; NS, not significant; ICP, intracranial pressure; ABP, arterial blood pressure; CPP, cerebral perfusion pressure; BFV, blood flow velocity; BP, blood pressure.

Technology). Digital signals were then processed with software developed in-house (ICMplus; *www.neurosurg.cam.ac.uk/icmplus*).

Computed tomography analysis

The displacement of the midline of the brain (midline shift) was measured on the CT admission scan and then followed by subsequent scans. TCD data was acquired daily and analyzed as long as midline shift was present. In none of the patients was decompressing craniotomy performed (i.e., in most of the cases, midline shift was not caused by a lesion requiring surgery).

Outcome of patients

Glasgow Outcome Scale (GOS) was assessed 6 months after discharge to quantify outcome of patients (Jennett and Bond, 1975). In the five-point GOS, grade 5 indicates good outcome; grade 4, moderate disability; grade 3, severe disability; grade 2, persistent vegetative state; and grade 1, death.

Multimodal pressure-flow method

To assess cerebral blood flow regulation, we applied a computational method called multimodal pressure-flow (MMPF) analysis (Novak et al., 2004; Hu et al., 2008a,b) to quantify instantaneous phase interactions between ventilation-induced oscillations in BFV and CPP. Recordings were divided into 5-min segments. In each segment, BFV and CPP signals were decomposed into multiple empirical modes using the ensemble empirical mode decomposition (EEMD) algorithm (Wu and Huang, 2005) that is based on Hilbert-Huang transform (Huang et al., 1998). Each mode represents an intrinsic frequency-amplitude modulation at a specific time scale so that a specific physiologic influence on both CPP and BFV can be separated. The mode corresponding to ventilation-induced oscillations (0.1–0.3 Hz) was identified and extracted. To quantify the phase interactions between CPP and BFV oscillations, the Hilbert transform was applied to calculate instantaneous phases of each signal (Gabor, 1946). In this study, we focused on mean BP-BFV phase shift derived from the MMPF method that was calculated as the average of instantaneous differences of BFV and CPP phases. For each subject, the MMPF measures obtained from all available 5-min segments were averaged.

Receiver operating characteristic analysis

To test the performances of the MMPF in predicting midline shift, we used the receiver operating characteristic (ROC) analysis (Zweig and Campbell, 1993) to study the sensitivity and specificity of the MMPF-derived measures (absolute side difference in BP-BFV phase shift) in distinguishing subjects with large (≥ 5 mm) and small (< 5 mm) midline shift. The value of 5 mm was chosen because a previous study showed that poor outcome after TBI is associated with a midline shift of ≥ 5 mm (Valadka et al., 2000). Briefly, this ROC method (1) chooses a discrimination threshold for side difference in BP-BFV phase shifts; and (2) assigns subjects with the MMPF measure above the chosen threshold to the group with large midline shift, and subjects with smaller side difference (below the chosen threshold) to the other group. The sensitivity is the percentage of subjects with midline shift of ≥ 5 mm correctly identified using the above criteria; and the specificity is the percentage of subjects with midline shift of < 5 mm correctly identified. By choosing different values of the discrimination threshold, the sensitivity as the function of the specificity can be obtained. The plot of sensitivity versus 1-specificity (ROC curve) is used to illustrate the performance of a method, and the area under the curve is a simple parameter to quantify the performance. If the sensitivity and specificity are equal (the area under the curve = 0.5), then the method cannot detect subjects with midline shift of ≥ 5 mm and thus has the worst performance. The area value of > 0.5 and closer to 1.0 indicates a better discriminator between the groups with small and large midline shifts, and a better performance of the method.

Statistical analysis

One-way analysis of variance (ANOVA) and non-parametric Wilcoxon test were used for the comparison of MMPF results between TBI patients with ≥ 5 mm midline shift and with < 5 mm midline shift. Linear regression method was applied to study the relationship between midline shift and left-right difference in MMPF autoregulation indices, and the relationship between measures in the left and right sides. Multivariable analysis of variance (MANOVA) with sides (left vs. right MCA) as repeated measures was performed to explore the correlations between MMPF indices and outcomes.

Results

MMPF measures: Mean BP-BFV phase shifts

For all 27 patients with brain injuries, we identified well-pronounced oscillations in CPP and BFV signals at ventilation frequency (0.1–0.3 Hz; Fig. 1). Mean phase shifts between CPP and BFV oscillations in the left (8.7 ± 9.6 degrees; mean $\pm$ SD) and right side (10.2 ± 8.3) were highly correlated ($R = 0.7$, $p = 0.0001$). These values of phase shifts in TBI patients were much smaller than those previously found in healthy subjects (left side 37.3 ± 7.6 degrees; right side 38.0 ± 8.9; $p < 0.0001$) (Hu et al., 2008b).

Midline shift and asymmetry in MMPF measures

Ranging from -14 mm (left to right) to 14 mm (right to left), the midline shifts in TBI patients obeyed a normal distribution ($p = 0.77$ for rejecting the hypothesis of a normal distribution), and the absolute values of the shifts were 5.4 ± 4.1 mm (mean $\pm$ SD). The difference in mean BP-BFV phase shift between left and right sides (absolute difference 5.1 ± 4.4 degrees) was positively correlated to the midline shift ($R = 0.78$; $p < 0.0001$), i.e., positive midline shift (displacement of the midline to left) corresponded to positive left-right difference in BP-BFV phase shift (larger BP-BFV phase shift in the left side), and negative midline shift corresponded to negative left-right difference in BP-BFV phase shift (Fig. 2). Consistently, the subjects with midline shifts ≥ 5 mm had much larger left-right differences in BP-BFV phase shift (6.7 ± 4.2 degrees) compared to other patients (2.5 ± 1.7 degrees; $p = 0.0045$) but did not differ in other parameters (Table 1).

Receiver operating characteristic analysis

The receiver operating characteristic analysis showed that the area under the sensitivity-specificity curve for side
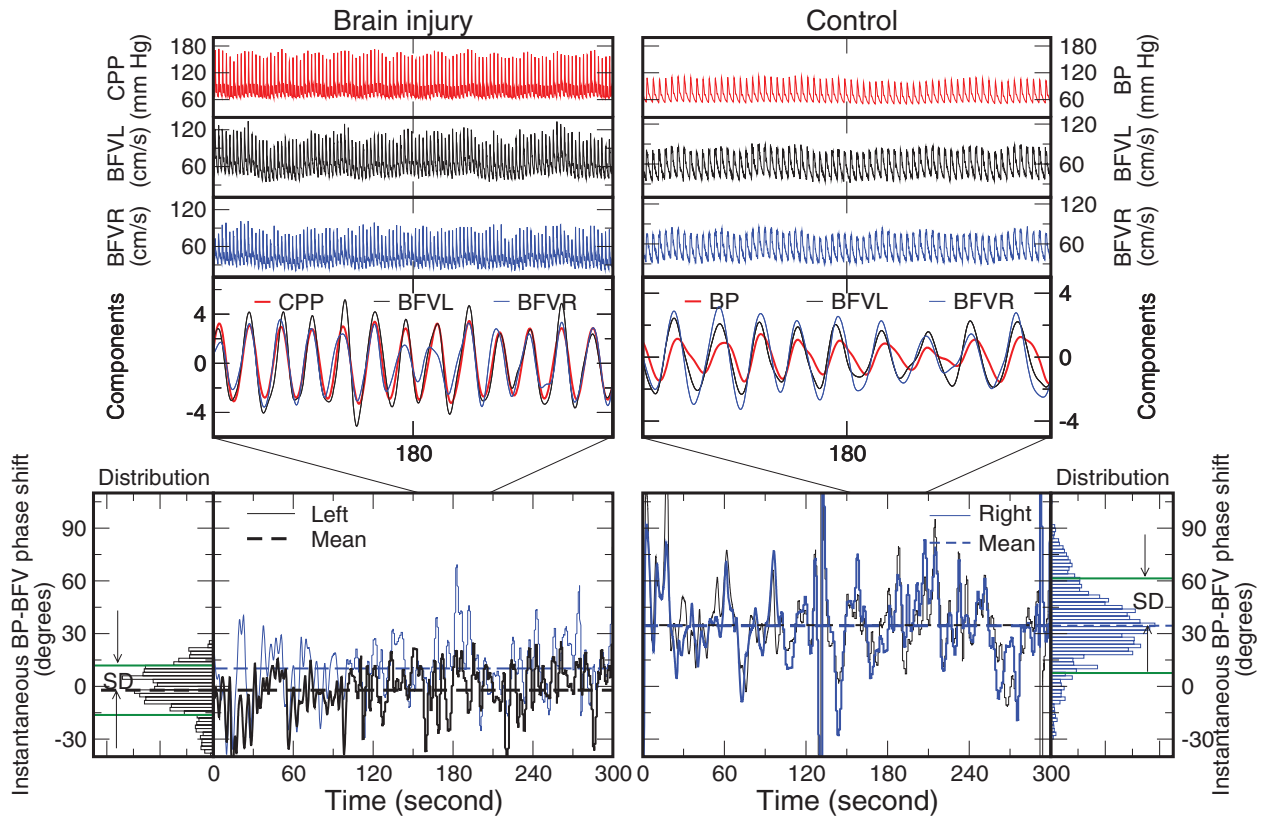
FIG. 1. Oscillations in blood pressure (BP) and blood flow velocities (BFVs) in the right (BFVR) and left (BFVL) middle cerebral arteries (MCA) signals of a 55-year-old patient with traumatic brain injury (TBI) at ventilation frequency (**left**) and a 65-year-old healthy subject at respiratory frequency (**right**). Cerebral perfusion pressure (CPP) was used for the TBI patient, and blood pressure measured from finger was for the healthy subject. Each signal (BP/CPP, BFVL, BFVR) was decomposed into different modes using ensemble empirical mode decomposition (EEMD). Oscillations at the frequency of artificial ventilations or respiration were extracted and used to calculate instantaneous phases. The mean and standard deviation of phase shifts were obtained from instantaneous phases of BP/CPP and BFV oscillations.

difference of BP-BFV phase shifts is 0.87 ± 0.07 (Fig. 3). The optimal value of side difference for distinguishing subjects with midline ≥ 5 mm and others is ~ 3 degrees, and the corresponding sensitivity and specificity are 85% and 82%, respectively. The value of the area under the ROC curve is much greater than 0.5 and close to 1.0, indicating the MMPF measures may serve as a sensitive biomarker of midline shift.

Discussion

Asymmetry of cerebral hemodynamics associated with midline shift

Asymmetry of cerebral hemodynamics can be caused by the lesion located in one side of the brain that leads to an alteration in cerebral microcirculation, asymmetry of brain swelling, and/or non-uniform ICP in different brain regions. Cerebral blood flow regulation is not necessarily a homogeneous all-or-none phenomenon and severity of its impairment after TBI may vary among brain regions. Previous studies showed that a midline shift of >5 mm is associated with poor outcome after TBI and that asymmetry in autoregulation is associated with death (Valadka et al., 2000; Schmidt et al., 2003). We could not find these associations in this study,
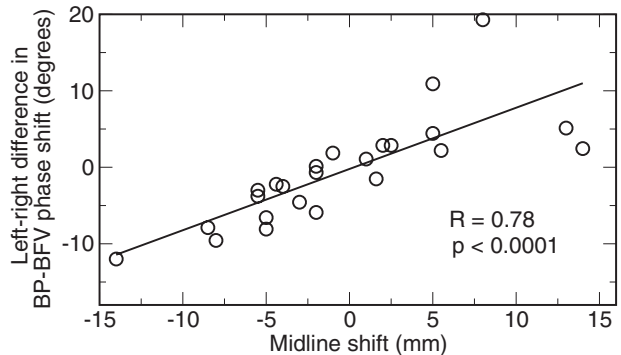

FIG. 2. Association between the midline shift and left-right difference in blood pressure/blood flow velocity (BP-BFV) phase shift. A positive value of the midline shift indicates displacement of the brain's midline from the right to the left, and negative value indicates displacement from the left to the right. The difference in BP-BFV phase shifts between the right and left hemispheres was positively correlated to midline shift of the brain.
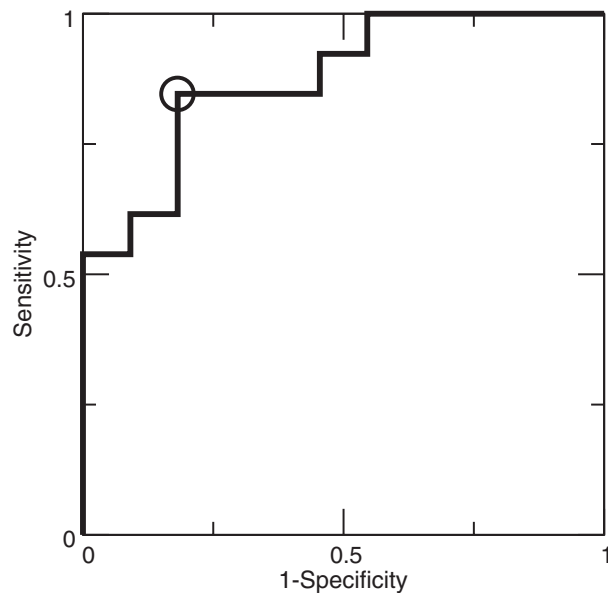
FIG. 3. Receiver operating characteristic curve for the prediction of midline shift _5 mm using absolute side difference of BP-BFV phase shift. The *x*-axis, 1-Specificity, indicates the probability of incorrectly identifying a subject with absolute midline shift <5 mm. The *y*-axis is sensitivity, indicating the probability of correct identifying a subject with absolute midline shift ≥5 mm. Area under curve = 0.87 ± 0.07 (mean ± SD), and the optimal value of side difference for distinguishing subjects with midline _5 mm and others is ~3 degrees (corresponding to the circle point).

which may be due to the sample size. One of our substantial findings was the positive correlation between left-right difference in BP-BFV phase shifts and the midline shift. This association is much stronger than reported previously by Kumar et al. (2005), between critical closing pressure and midline shift (correlation about 0.5), or asymmetry of autoregulation and midline shift (correlation around 0.42) reported by Schmidt et al. (2003). Specifically, the midline shifts from the side with a smaller BP-BFV phase shift to the other side. Since a smaller BP-BFV phase shift indicates a more passive BP influence on BFV associated with a worse blood flow regulation, our finding is consistent with a previous study (Schmidt et al., 2003) and supports that the midline shift on the CT can indicate a left-right asymmetry of autoregulation.

Application of the MMPF to continuous monitoring of blood flow

The MMPF method can potentially be used to continuously monitor BP-BFV phase interaction in clinical studies. Two related concerns about this application are (1) the CPU time for performing the MMPF and (2) the minimum signal length and sampling frequency for the MMPF to yield a reliable estimation of autoregulation. The significant time-consuming step of the MMPF is the decomposition of BP-BFV signals. For a faster performance of the decomposition, it is preferred to apply the decomposition algorithm on segments with shorter length and fewer data points (low sampling frequency). For 5-min recordings, it may take 2–20 min to obtain mean BP-BFV phase shift, depending on several factors such as

(1) sampling rate of recordings, (2) number of divided segments, and (3) number of simulation iterations for the decomposition. Our current and previous results indicated that 5-min recordings are enough for reliable estimation of mean BP-BFV phase shift (Hu et al., 2008a,b; Lo et al., 2008). Further systematic studies are necessary to determine optimal values of the three factors for a reliable assessment of BP-BFV phase relationship.

Cerebral blood flow regulation after brain injury

Quantification of relationship between changes in BP and BFV enables assessment of cerebral autoregulation. Physiological signals such as BP and BFV exhibit nonstationary temporal structures with spontaneous fluctuations at different time scales. Therefore, new methods without the assumption of stationarity are needed for reliable assessment of autoregulation. The MMPF analysis was recently implemented to quantify phase interactions between spontaneous and induced BP and BFV fluctuations (Novak et al., 2004; Hu et al., 2008a,b; Lo et al., 2008). A smaller BP-BFV phase differences indicate dependence of BFV on systemic pressure and, thus, suggests an impaired autoregulation. In this study, we found that mean BP-BFV phase shifts obtained by the MMPF were significantly smaller in TBI patients than in previously studied healthy subjects. These findings indicate that mean BP-BFV phase shift derived from the MMPF can serve as a biomarker of cerebral blood flow regulation after TBI. We note that TBI subjects in this study were paralyzed, sedated, and ventilated. This physiological condition of TBI subjects was dramatically different from supine resting conditions for healthy subjects in previous studies. Thus, the influences of the physiological condition on cerebral blood flow regulation need to be elucidated in future studies.

Autoregulation was generally believed to be more active at frequency <0.1 Hz based on many studies using transfer function analysis. Since BP/BFV oscillations in this study were mostly greater than 0.1Hz, the reduced BP-BFV phase shift at ventilation-induced frequency in TBI patients may also reflect different mechanisms of cerebral flow regulation than autoregulation. For instance, the asymmetry of BP-BFV phase shift at <0.1 Hz might carry information on the passive properties of cerebral parenchymal shift, being caused by midline shift and pressure gradients within the skull and independent of the influences on cerebral autoregulation. Further carefully designed studies are necessary to test this hypothesis and to determine the other mechanism(s) underlying the association between midline shift and BP-BFV phase relationship at frequency >0.1 HZ. On the other hand, nonlinear approaches in recent studies indicated that at high frequencies there are also alterations in BP-BFV relationship under pathological conditions associated with impaired autoregulation such as stroke, hypertension, and diabetes (Chen et al., 2006; Hu et al., 2008b; Lo et al., 2008). Thus, it is also possible that the active frequency range of autoregulation estimated from different techniques may be different, and it is important for further studies to check the sensitivity of methods for the assessment of autoregulation.

Nevertheless, our finding of the strong association between the displacement of midline of the brain and the left-right difference in mean flow-pressure phase shift is very intriguing. It indicates that the MMPF measure may

be used to monitor changes in midline shift between CT scans. In situations when clinical status is unstable, continuous non-invasive monitoring is possible, without subjecting patient to additional doses of radiation. From previous studies we know that patients with midline shift have greater mortality rate than those presenting symmetrical CT (35% with midline shift versus 15% without; $p < 0.05$) (Hiler et al., 2006). However, to promote such a novel clinical application, prospective clinical trial is needed.

Limitations

This is preliminary and retrospective study performed in rather limited material. Patients with midline shift and without surgical intervention (craniectomy, rising of bone flaps) are quite uncommon. Surgery to avoid detrimental consequences of intracranial hypertension is more frequent nowadays. Therefore this group is quite unique. Midline shift values of this group range from -14 to 14 mm and obey a normal distribution, which can enable a reliable assessment of association between the midline shift and the MMPF measures. However, this group of TBI patients did not have typical GCS and GOS distributions and, thus, is not suitable for the analysis of the TBI outcome and its association with MMPF measures. There is a hope that the technique described can be used in patients with acute brain edema from other reasons than TBI (like poor grade stroke) to detect brain structural shifts.

Comparison of healthy volunteers to anesthetized patients is always quite risky because of unknown effect of anesthesia on cerebral autoregulation. In most of cases in our group moderate dose of propofol was used, which reportedly does not affect autoregulation (Steiner et al., 2003). It will be better to compare TBI patients with subjects with normal autoregulation during the similarly sedated and paralyzed conditions. However, data of such subjects are not available in the current study.

Author Disclosure Statement

ICM (www.neurosurg.cam.ac.uk/icmplus) is a software licensed by University of Cambridge, Cambridge Enterprise Ltd and M.C. has financial interest in a fraction of licensing fee. C.K.P. is a shareholder of DynaDx Corporation, which plans to develop the MMPF method into a commerical software.

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Address reprint requests to:
Kun Hu, Ph.D.
Beth Israel Deaconess Medical Center
Harvard Medical School
330 Brookline Avenue, Stoneman 812
Boston, MA 02215

E-mail: khu@bidmc.harvard.edu