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Nonlinear Assessment of Cerebral Autoregulation from Spontaneous Blood Pressure and Cerebral Blood Flow Fluctuations

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Abstract

Cerebral autoregulation (CA) is an most important mechanism responsible for the relatively constant blood flow supply to brain when cerebral perfusion pressure varies. Its assessment in nonacute cases has been relied on the quantification of the relationship between noninvasive beat-to-beat blood pressure (BP) and blood flow velocity (BFV). To overcome the nonstationary nature of physiological signals such as BP and BFV, a computational method called multimodal pressure-flow (MMPF) analysis was recently developed to study the nonlinear BP–BFV relationship during the Valsalva maneuver (VM). The present study aimed to determine (i) whether this method can estimate autoregulation from spontaneous BP and BFV fluctuations during baseline rest conditions; (ii) whether there is any difference between the MMPF measures of autoregulation based on intra-arterial BP (ABP) and based on cerebral perfusion pressure (CPP); and (iii) whether the MMPF method provides reproducible and reliable measure for noninvasive assessment of autoregulation. To achieve these aims, we analyzed data from existing databases including: (i) ABP and BFV of 12 healthy control, 10 hypertensive, and 10 stroke subjects during baseline resting conditions and during the Valsalva maneuver, and (ii) ABP, CPP, and BFV of 30 patients with traumatic brain injury (TBI) who were being paralyzed, sedated, and ventilated. We showed that autoregulation in healthy control subjects can be characterized by specific phase shifts between BP and BFV oscillations during the Valsalva maneuver, and the BP–BFV phase shifts were reduced in hypertensive and stroke subjects ($P < 0.01$), indicating impaired autoregulation. Similar results were found during baseline condition from spontaneous BP and BFV oscillations. The BP–BFV phase shifts obtained during baseline and during VM were highly correlated ($R > 0.8$, $P < 0.0001$), showing no statistical difference (paired-t test $P > 0.47$). In TBI patients there were strong correlations between phases of ABP and CPP oscillations ($R = 0.99$, $P < 0.0001$) and, thus, between ABP–BFV and CPP–BFV phase shifts ($P < 0.0001$, $R = 0.76$). By repeating the MMPF 4 times on data of TBI subjects, each time on a selected cycle of spontaneous BP and BFV oscillations, we showed that MMPF had better reproducibility than traditional autoregulation index. These results indicate that the MMPF method, based on

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instantaneous phase relationships between cerebral blood flow velocity and peripheral blood pressure, has better performance than the traditional standard method, and can reliably assess cerebral autoregulation dynamics from ambulatory blood pressure and cerebral blood flow during supine rest conditions.

Keywords

Spontaneous oscillations; Instantaneous phase shift; Valsalva maneuver; Baseline resting condition; Stroke; Hypertension; Traumatic brain injury

Introduction

Cerebral autoregulation reflects the ability of cerebral microvasculature to adapt to systemic BP changes by adjusting the small vessel resistance to maintain relatively “stable” blood flow (Aaslid 1992; Panerai 1998). Hypertension and diabetes, that are the leading causes of stroke and dementia of elderly people, are associated with microvascular disease that compromises capacity to regulate perfusion in cerebrovascular bed (Lipsitz et al. 2000; Novak et al. 2003). Cerebral autoregulation compensating fluctuations of systemic BP is lost post-stroke (Eames et al. 2002; Novak et al. 2004; Immink et al. 2005) and after traumatic brain injury (TBI) (Czosnyka et al. 1997; Schmidt et al. 2003), rendering blood flow dependent on perfusion pressure. Furthermore, autoregulation failure has been associated with increased morbidity and mortality in these conditions. Therefore, monitoring of cerebral autoregulation is critically important in patients with acute brain trauma to avoid secondary insults to the injured brain due to hypoperfusion or brain edema (Schmidt et al. 2003; Czosnyka et al. 1997, 1996). Reliable and noninvasive assessment of cerebral autoregulation is a major challenge in medical diagnostics and post-stroke care. Conventional approaches model autoregulation with BP as input and blood flow as output (using blood flow velocity (BFV) measured by transcranial Doppler ultrasound and beat-to-beat peripheral BP) (Diehl et al. 1995, 1998; Olufsen et al. 2002; Carey et al. 2003) and assume that signals are composed of superimposed sinusoidal oscillations of constant amplitude and period at a presumed frequency range. However, BP and BFV signals recorded in clinical settings are often nonstationary, and are modulated by nonlinearly interacting processes at multiple time-scales corresponding to the beat-to-beat systolic pressure, respiration, spontaneous BP fluctuations, and those induced by interventions.

To overcome problems related to nonstationarity and nonlinearity, a novel computational method called multimodal pressure-flow (MMPF) analysis was recently developed to study the BP–BFV relationship during the Valsalva maneuver (Novak et al. 2004). The MMPF method enables evaluation of autoregulatory dynamics based on instantaneous phase analysis of BP and BFV oscillations induced by the intervention (sudden reduction followed by an increase in BP and BFV). Applying this technique, a characteristic phase lag between BFV and BP oscillations induced by the Valsalva maneuver was found in healthy subjects and this phase lag was reduced in patients with hypertension and stroke (Novak et al. 2004). These findings suggested that BP–BFV phase lag could serve as an index of cerebral autoregulation. In this study, we aim to address three important questions about the MMPF method.

1. Traditional approaches assess autoregulatory responses by challenging cerebrovascular systems using interventions such as the Valsalva maneuver, thigh cuff deflation and the head-up tilt (Carey et al. 2003; Panerai 1998; Novak et al. 1998; Tiecks et al. 1999; Dawson et al. 1999; Panerai et al. 2001; Novak et al. 2003). These intervention procedures induce large intracranial pressure fluctuations and require patients’ cooperation and, therefore, such procedures are limited for clinical evaluation of autoregulation. We hypothesize that the dynamics of cerebral

autoregulation can be evaluated from spontaneous BP–BFV fluctuations during supine rest. Similarly to BP and BFV oscillations introduced by the Valsalva maneuver, there should be phase delays between spontaneous BFV and BP oscillations during resting conditions. To test this hypothesis we compared the BP–BFV phase shifts obtained from BP and BFV oscillations introduced by the Valsalva maneuver and from spontaneous BP and BFV oscillations during supine baseline.

2. Cerebral autoregulation reflects alterations in small vessel resistance in order to maintain relatively constant cerebral blood flow (CBF) despite changes in cerebral perfusion pressure (CPP). Thus, cerebral autoregulation should be ideally quantified based on the relationship between CPP and CBF. CPP is calculated from intra-arterial (ABP) and intracracranial pressure (ICP) recordings (i.e., CPP = ABP−ICP). The MMPF, as well as other autoregulation analyses (Diehl et al. 1995; Tiecks et al. 1995; Panerai et al. 2006), quantified the BP–BFV relationship based on peripheral arterial blood pressure (ABP) due to the complicated and invasive experimental settings for ICP measurements. Though in normal condition the change in CPP is dominated by the change in ABP and many studies indicated that the ABP–BFV relationship can be used to identify the alteration and impairment in autoregulation, it is important to understand whether there is a difference between the autoregulation measures based on ABP and CPP. To address this issue, we compared the CPP–BFV and ABP–BFV phase relationships quantified by the MMPF using data collected in 30 patients with TBI.

3. Reproducibility is an important performance measure for noninvasive methods of assessing cerebral autoregulation. Here we compared MMPF estimates of autoregulation and standard autoregulation index (ARI) using coefficient of repeatability.

Methods

Subjects

This study utilized the existing de-identified databases at the Syncope and Falls in the Elderly (SAFE) laboratory at the Beth Israel Deaconess Medical Center, Boston, United States and at Neurocritical Care Unit (NCCU) at Addenbrooke's Hospital in Cambridge, United Kingdom. Subjects analyzed in this study included (Table 1): (1) 32 subjects (16 men an 16 women, mean age 46.7 range 25–65 years) including 12 control, 10 hypertensive, and 10 stroke subjects who underwent the experimental protocol in the SAFE laboratory at the BIDMC and all subjects signed the informed consent approved by the BIDMC Institutional Review Board; and (2) 30 patients (23 men and 7 women, mean age 36 range 17–69 years) with TBI who were admitted to Addenbrooke's Hospital suffering from head injuries with a mean Glasgow Coma Scale (GCS) score of 6 (range, 3–13) (Schmidt et al. 2003). The protocol approval was obtained in agreement with Neurocritical Care User Committee at the Addenbrooke's hospital. Daily assessment of autoregulation was a part of routine clinical management protocol and informed consent was not required at the time of data collection. The patients with brain injuries were paralyzed, sedated, and ventilated to achieve mild hypocapnia. Spontaneous declines in ABP that reduced CPP to < 60 mm Hg were managed with alternating colloid and normal saline infusions, with supplementary inotropic agents if necessary (constant infusion of dopamine 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

Experimental Protocol for Control, Hypertension and Stroke Subjects—For 12 control, 10 hypertensive, and 10 stroke subjects, the experiments were done in the morning or

> 2 h after the last meal. During baseline conditions, subjects were resting in the supine position and were breathing regularly at their normal respiratory frequency. The Valsalva maneuver was performed after a 5 min period of supine rest when the subject was asked to expire forcefully through a mouthpiece with a small air-leak, maintaining for 15 s a pressure of 40 mm Hg. Beat-to-beat BP was recorded with a Finapres device (Ohmeda Monitoring Systems, Englewood CO) from a finger that was kept in a constant temperature. Flow velocities were measured from right and left middle cerebral arteries (MCA) using transcranial Doppler ultrasonography system (MultiDop X4, DWL Neuroscan Inc, Sterling, VA). Data were continuously recorded at a sampling frequency of 50 Hz.

Experimental Protocol for Brain Injury Patients—For patients with brain injuries, ICP was monitored continuously using a fiber-optic transducer (Camino Direct Pressure Monitor, Camino Laboratories) inserted intraparenchymally into the frontal region. Arterial pressure was monitored directly in the radial or dorsalis pedis artery (System 8000, S&W Vickers Ltd). The MCA was insonated daily for 20 min to 2 h from the day of admission to discharge or day 8 after head injury, using the PCDop 842 Doppler Ultrasound Unit (Scimed, Bristol, UK). Signals were monitored during periods of stable respiratory parameters, free from physiotherapy, tracheal suction, and other disturbances. Analog outputs from the pressure monitors and the ultrasound unit (maximal frequency envelope) were connected to the analog-to-digital converter (DT 2814, Data Translation) fitted into an IBM AT laptop computer (Amstrad ALT 386 SX). Data were sampled and digitized at 30 Hz and stored on the hard disk with the software for the waveform recording (WREC, W. Zabolotny, Warsaw University of Technology). Digital signals were then processed with software developed in-house (ICMplus, http://www.neurosurg.cam.ac.uk/icmplus).

Multimodal Pressure-flow Method

To quantify the dependency between cerebral blood flow and blood pressure, we used the MMPF analysis (Novak et al. 2004) that has been implemented to calculate instantaneous phase-shifts between two non-stationary signals. The MMPF method, which does not make any assumptions about linearity or stationarity of the signals, is ideally suited for the analysis of the short nonstationary time-series (http://www.dynadx.com/MMPF/).

To extract the spontaneous oscillations in BP and BFV during baseline conditions and during Valsalva maneuvers, we applied the improved empirical mode decomposition (EMD), namely ensemble EMD (EEMD) technique, to decompose the BP and BFV signals to intrinsic modes. Each mode represents the frequency-amplitude modulation at a specific time scale corresponding to different physiologic influences. One problem with the original EMD algorithm is that, for signals with intermittent oscillations, an intrinsic mode could comprise of oscillations with various wavelengths at different temporal locations (Huang et al. 1998a). This mode-mixing artifact of EMD may affect MMPF analysis and therefore we selected the signals with (1) large-signal-to-noise ratio and (2) verifying visually selection of the corresponding modes for the BP and BFV decomposition. To this end, we used the Valsalva maneuver to amplify the BP and BFV oscillations, and also relied on the experienced operator to select the intrinsic modes on a case-by-case basis (Novak et al. 2004). Our improved MMPF algorithm has significantly overcome these issues (see Appendix). Therefore, it is now possible to study the BP and BFV fluctuations of smaller amplitude during baseline (supine rest) conditions, as well as to make the mode selection process semi-automated. Figure 1 shows the screen shot of the improved MMPF analysis of a healthy subject using a software package, developed by us.

In the next step of the MMPF analysis, we applied the Hilbert transform to the extracted BP oscillation to calculate its instantaneous phases. This phase was then used as a reference

coordinate for both BP and BFV signals. Unlike the Fourier transform, the Hilbert transform does not assume that signals are composed of superimposed sinusoidal oscillations of constant amplitude and frequency. Real-world biological fluctuations, such as BP and BFV, are not stationary and, therefore, are better described by analytical methods that can quantify variations of amplitude and frequency.

Mathematically, the first two steps of the MMPF algorithm can be summarized in the following way: Any complex signal $S(t)$ can be represented as the superimposition of more basic (simpler) components: $S(t) = \Sigma_k S_k(t)$, where S_k are empirical modes that fulfill certain criteria of the original signal (Huang et al. 1998a). For each empirical mode, its Hilbert transform is defined as:

$$S_{kH}(t)=\frac{1}{\pi}\int\frac{S_k(t')}{t-t'}\mathrm{d}t'$$

where the Cauchy principal value is taken in the integral. Instantaneous amplitude, $A_k(t)$, and instantaneous phase, $\varphi_k(t)$, can be calculated by

$$A_k(t)=\sqrt{S_{kH}^2(t)+S_k^2(t)}\ \text{and}\ \varphi_k(t)=\tan^{-1}(S_{kH}(t)/S_k(t)).$$

For simplicity of statistical analysis, we originally calculate the phase shift at the minimum and maximum of these two signals (Novak et al. 2004). To provide statistically more robust phase estimates, the BP–BFV phase shift for each subject can be calculated as the average of instantaneous differences of BFV and BP phases over the course of the Valsalva maneuver or spontaneous oscillations. The MMPF was applied to one selected cycle of BP and BFV oscillations (spontaneous oscillations during baseline or oscillations induced by the Valsalva maneuver).

For the comparison of the MMPF results during supine baseline and during the Valsalva maneuver, we extracted spontaneous oscillations in control, hypertensive and stroke subjects under supine condition at frequency similar to that of oscillations introduced by the Valsalva maneuver (~0.15–0.04 Hz, period ~7–25 s), i.e., spontaneous oscillations were chosen in the same EEMD modes as the oscillations induced by the Valsalva maneuver.

To test whether there is difference between the MMPF measures based on ABP and CPP, oscillations in the respiratory frequency were extracted from a 5-min recording for each patient with traumatic brain insult and were used to obtain the instantaneous phases and CPP–ABP phase differences. If CPP–ABP phase differences are very small (approaching zero), then the BP–BFV phase shift based on ABP will be similar to that based on CPP.

Autoregulation index

The autoregulatin index (ARI) was used for comparisons with MMPF phase calculations. ARI is based on the BFV changes in response to the BP fluctuations (Tiecks et al. 1995). Data segments of TBI patients, in which BP and BFV oscillatory cycles were extracted by the EEMD (see Sec. Multimodal pressure-flow method) were used. ARi was calculated using a second order model proposed by Tiecks et al (Immink et al. 2005).

Statistical Analysis

Descriptive statistics were used to summarize data. We used the linear regression method and the paired-*t* test for comparison of oscillation periods and BP–BFV phase shifts during the two tests (i.e., Valsalva maneuver and baseline), and for comparisons of ABP phases and CPP phases. To assess the group difference in MMPF measures (BP–BFV and CPP–ABP phase shift), we performed both one-way analysis of variance (ANOVA) for left and right MCAs separately, and multivariable analysis of variance (MANOVA) with MMPF measures for right and left MCAs as repeated measures. To test repeatability of MMPF autoregulation estimates, we repeated MMPF analysis four times on selected spontaneous BP and BFV oscillations in 30 subjects with brain injuries, and calculated the coefficient of repeatability as described proposed by Bland and Altman (Bland and Altam 1986) and described in Altman (1991). Ranging between 0 and 1, the larger coefficient indicates better reproducibility or repeatability of a measurement. We also compared the performance of MMPF and the standard autoregulation index (ARI).

Results

BP–BFV Phase Shifts During Baseline Conditions and During the Valsalva Maneuver (VM) Based on Noninvasive BP Measurements

For each subject, we extracted a spontaneous BP–BFV oscillation during baseline condition using the same empirical mode as that for the oscillation cycle introduced by Valsalva maneuver (Fig. 1). The frequency of chosen spontaneous oscillations (period: mean ± SD, 15.7 ± 9.2 s) was similar to that of VM oscillations (17.7 ± 7.9 s, pair *t*-test $P = 0.37$). Table 2 summarizes mean period and phase shift of VM and spontaneous oscillations for control, hypertensive and stroke subjects. BP–BFV phase shifts during spontaneous oscillations (ranging from ~−60 to 120 degrees) were highly correlated to those obtained from VM oscillations (left $R = 0.92$, $P < 0.0001$; right $R = 0.80$, $P < 0.0001$) (Fig. 2). Consistently, the paired-*t* test showed that the average BP–BFV phase shifts during baseline were statistically similar to the values during the Valsalva maneuver ($P > 0.47$). These results indicate that cerebral autoregulation can be assessed from spontaneous BP–BFV fluctuations using the MMPF method.

Effects of Hypertension and Stroke on MMPF Measures

During the Valsalva maneuver, normotensive subjects had larger BP–BFV phase shift compared to hypertensive (left MCA, $P = 0.01$; right MCA $P = 0.02$) and stroke subjects (left $P = 0.003$; right MCA, $P = 0.003$) (Fig. 2c, d). The group effect was confirmed by both t test (control vs. HTN: left $P = 0.01$, right MCA $P = 0.02$; control vs. stroke: left $P = 0.003$, right MCA $P = 0.003$) and ANOVA (left $P = 0.005$; right $P = 0.007$). The same group differences were observed also during baseline conditions (left MCA: control vs. HTN vs. stroke, $P = 0.01$; right MCA: control vs. HTN vs. stroke, $P = 0.02$). MANOVA confirmed that BP–PFV phase shifts were reduced in hypertensive and stroke groups (VM: $P = 0.005$; baseline: $P = 0.01$), and also showed no difference between the left and right MCAs. No effects of age, sex and height weight on BP–BFV phase shifts were observed.

Effects of Brain Injury on MMPF Measures

For all 30 patients with brain injuries, we identified well-pronounced continuous oscillations of ABP, ICP, CPP and BFV signals in the frequency range 0.1–0.3 Hz (i.e., period of each oscillation 3–10 s). These dominant oscillations were truly embedded in signals and represented the physiological influences of ventillation (Fig. 3a). In a parallel study we also extracted dominant spontaneous BP–BFV oscillations in control subjects at the similar frequencies (0.1–0.4 Hz) (results not shown here) (Hu et al. 2007b). BP–BFV phase shifts in

control subjects were 37 ± 12 degrees (mean ± SD) as shown by the red lines in Fig. 4. Here we found that the ABP–BFV phase shifts in brain injury patients were much smaller (left side 9.0 ± 11.1 degrees; right side 10.8 ± 16.7 degrees; $P < 0.0001$) and closer to zero (Fig. 4).

BP–BFV Phase Shifts Based on Cerebral Perfusion Pressure and Intra-arterial Pressure Measurements

The phases of ABP and CPP oscillations at frequency 0.1–0.3 Hz were highly correlated ($P < 0.0001$, $R > 0.9$) and the instantaneous phase differences between ABP and CPP were very small and close to zero (mean ± SD 2.1 ± 6.2 degrees; absolute difference 5.5 ± 2.8 degrees) (Fig. 3). The similar results were found at the frequency range of 0.03–0.07 Hz that is traditionally believed the active frequency range of cerebral autoregulation (ABP–CPP phase difference: 4.4 ± 9.8 degrees; absolute difference: 7.7 ± 6.1 degrees). Since the difference between ABP phases and CPP phases is equal to the difference between ABP–BFV and CPP–BFV phase shifts, small ABP–CPP phase differences indicate that the instantaneous BP–BFV phase shifts based on ABP and CPP were similar. Consistently, we found that there is a high correlation between ABP–BFV phase shifts and BFV–CPP phase shifts ($P < 0.0001$, $R = 0.76$). The paired-*t* test revealed that the mean CPP–BFV phase shift was slightly but significantly smaller than the mean BFV–ABP (MANOVA: $P = 0.02$).

Repeatability of BP–BFV Phase Shifts and Autoregulation Indices

We have measured instantaneous CPP–BFV phase shifts during selected spontaneous CPP fluctuations at baseline. For each 5-min recording of a subject with brain injuries, we repeated the MMPF 4 times, each time on the full cycle of a different spontaneous oscillation within the 5 min. In all trials, dominant oscillations of CPP and BFV were exacted in the similar frequency range (~0.1–0.3 Hz) (Table 3). The variance of CPP–BFV phase shift within subjects was much smaller than the variance between subjects in all trials (Table 3). Consistently we obtained the intraclass correlation coefficient $\rho \approx 0.58$ for the MMPF measure. The large value of the coefficient suggests that the MMPF can enable reasonable estimation of BP–BFV phase relationship based on data within a spontaneous oscillation cycle (3–10 s). In order to obtain more reliable results, it is always better to obtain the mean phase shifts from more cycles of oscillations, which can significantly reduced the variance within subjects. In contrary, the results of the ARI analysis based on the blood flow changes in response to the blood pressure fluctuations (Tiecks et al. 1995) showed a larger variance within subjects compared to the variance between subjects (see Table 3), and the intraclass correlation coefficient $\rho \approx 0.08$ is much smaller than that of the MMPF. We also repeated the ARI analysis 4 times using the data of control, hypertensive and stroke subject during the Valsalva maneuver (oscillation period 17.7 ± 7.9 s; MEAN ± SD), and we also found the small intraclass correlation coefficient $\rho \approx 0.07$, similar to that of TBI patients. These results indicated that the MMPF phase measure of autoregulation has much better repeatability/reproducibility than the traditional ARI.

Discussion

Noninvasive assessment of cerebral autoregulation dynamics has emerged as a major challenge in medical diagnostics and acute care post stroke and brain injury. To quantify the dynamical interaction between cerebral blood flow and systemic pressure, a novel computational method called multimodal pressure-flow (MMPF) analysis were recently developed. The MMPF method assesses the dynamics of autoregulation based on the calculation of phase relationships between BP and BFV. It has been shown that there is a phase shift between BP and BFV oscillations introduced by the Valsalva maneuver and that the BP–BFV shift was significantly reduced in hypertensive and stroke subjects, indicating impaired autoregulation (Novak et al. 2004). In this study we addressed three main issues regarding the assessment of cerebral autoregulation using the MMPF.

First, we showed that BP–BFV phase shifts quantified by the improved MMPF from spontaneous BP–BFV fluctuations during supine baseline were virtually identical to phase shifts obtained from BP–BFV oscillations during the Valsalva maneuver. The strong correlation between phase shifts of BP–BFV oscillations during baseline and during the Valsalva maneuver indicates that autoregulation can be estimated from baseline conditions using the improved MMPF method. These results support the notion that autoregulation is a dynamic process and is always engaged, even during rest conditions, to control blood flow redistribution in response to local perfusion and metabolic needs during increased neuronal activity as well as systemic demands. The assessment of autoregulation dynamics during *spontaneous* BP and BFV fluctuations is of clinical importance because the traditional approaches of using interventions introduce large fluctuations in BP and, thus, are not suitable for subjects with impaired cardiovascular and cerebral systems.

In this study, we selected spontaneous BP and BFV oscillations in the same empirical mode as the oscillations induced by the Valsalva maneuver to compare the BP–BFV phase shifts obtained from the two different physiological conditions in the same frequency range (~0.04–0.15 Hz). However, in order to obtain statistically more reliable and reproducible results, it is ideal to choose dominant BP and BFV oscillations according to specific physiological conditions so that noise-to-signal ratio is lower. During rest conditions, dominant oscillations are often entrained by respiration and, thus, the frequency of the dominant oscillations (0.05–0.4 Hz) might be higher than that of the VM-induced oscillations (Hu et al. 2007a, b). Thus, a challenging question is whether or not the dominant spontaneous oscillations at a higher frequency (e.g., entrained by respiration at < 0.1 Hz) can be used to assess cerebral autoregulation. It has been proposed that autoregulatory mechanisms act as a high-pass filter—cybernetic model (Diehl et al. 1995, 1998), being more active at low frequencies (< 0.1 Hz) and less effective at high frequencies (> 0.1 Hz). Many studies that are based on the transfer function analysis support the frequency dependence of cerebral autoregulation (Giller 1990; Giller and Iacopino 1997; Zhang et al. 1998; Hamner et al. 2004) though there is no established physiological neural pathway that can account for the high-pass filter mechanism. The transfer function analysis is based on Fourier transform that implicitly assumes stationary signals composed of sinusoidal oscillations of constant amplitude and period. However, during physiological recordings, BP and BFV signals are nonstationary and exhibit dynamic changes over time (Mitsis et al. 2004). Thus, a single transfer function may be not sensitive enough to identify the influences of cerebral autoregulation on BP–BFV nonlinear relationship at different time scales. Our studies based on the MMPF method added new information on the active frequency range of cerebral autoregulation. In a parallel study, we extracted dominant oscillations of BP and BFV in control subjects during rest conditions in the frequency range 0.1–0.4 Hz (Hu et al. 2007a, b). Similarly to the spontaneous oscillations at 0.04–0.15 Hz, the MMPF revealed also a specific phase shift between BP and BFV oscillations (37 ± 12 degrees) in this higher frequency range (Hu et al. 2007b). In the current study, we showed that the BP–BFV phase shifts in the similar higher frequency (0.1–0.3 Hz) is significantly reduced in subjects with traumatic brain injury (left side 9.6 ± 7.1 degrees; right side 12.2 ± 9.9 degrees; see Results), indicating that impaired autoregulation is associated with the alteration in BP–BFV phase relationship in the frequency > 0.1 Hz. Therefore, more studies are needed to further explore the mechanisms of cerebral autoregulation and its influences on BP–BFV relationship at different frequencies.

In this study, we also showed that ABP and CPP phases at frequency ~0.1–0.3 Hz and at frequency ~0.03–0.07 Hz were strongly linearly correlated and the instantaneous differences between them were very small in all patients with traumatic brain injuries, indicating that the similar phase shifts between BP and BFV should be obtained using ABP compared to the results using CPP. Note that there were slight but significant differences between BP and BFV phase shifts based on ABP and based on CPP, i.e., ABP–BFV phase shifts were slightly larger.

This difference may not be a major concern for group comparisons (e.g., control vs. pathological conditions) as long as either ABP or CPP is used for all subjects in a study. In addition, we observed that ABP–BFV (or CPP–BFV) phase shifts in these patients with brain injuries were much smaller than ABP–BFV phase shifts of control subjects during supine rest condition, indicating impaired autoregulation. These results support the hypothesis, presumed in many studies that cerebral autoregulation can be assessed using the BFV and ABP. However, it should be emphasized that the BP–BFV relationship was obtained in patients during a special clinical scenario, i.e., patients with brain injuries were paralyzed, sedated, and ventilated. This special physiological condition may complicate the interpretation of these findings. Therefore, further systematic studies are needed to test whether the observed relationship between autoregulation measures based on ABP and CPP remains in control subjects under normal physiological conditions. Furthermore, many studies of autoregulation used beat-to-beat arterial blood pressure measured from finger (Finapres, Ohmeda Monitoring Systems), which has been shown highly correlated to intra-arterial blood pressure but with the overestimation of low-frequency components (< 0.15 Hz) and a phase delay (7–10 degrees) in finger blood pressure at 0.025–0.17 Hz (Omboni et al. 1993; Novak et al. 1994; Pinna et al. 1996). However, it is still unclear whether there is any significant difference between MMPF measures based on Finapres and based on invasive intra-arterial blood pressure.

Finally, we showed that the repeatability of the MMPF measure is significantly higher than the standard autoregulation index. This is not surprising because, unlike traditional approaches, the MMPF makes no assumptions of stationary signals and linear BP–BFV relationships and, thus, can more reliably quantify nonlinear relationship between nonstationary signals such as blood pressure and blood flow velocity. This result along with other findings indicate that inherent nonlinearities of cerebral autoregulation can be better described by nonlinear methods such as MMPF and multivariate coherence—an approach that takes into account contributions of other inputs, e.g., pressure and cerebrovascular resistances (Panerai et al. 2006). Note that, for a demonstration that MMPF can be used for the assessment of autoregulation during baseline conditions, we applied the method to one selected cycle of spontaneous BP and BFV oscillations during baseline each time. To improve the statistical reliability, average BP–BFV phase shifts for all identified cycles of BP and BFV oscillations during the whole baseline recordings should be used (Hu et al. 2007b). In such cases, MMPF measures are comparable to the traditional Fourier based measures such as coherence, gain, phase of transfer function analysis that performs cross-power spectrum between BP and BFV signals during baseline (Diehl et al. 1995; Zhang et al. 1998). Therefore, it will be important to compare reliability of the MMPF method and that of the transfer function analysis.

To conclude, our results indicate that cerebral autoregulation dynamics can be reliably assessed from ambulatory blood pressure and cerebral blood flow measurements during supine rest conditions, and that the improved MMPF method, based on phase relationship of blood flow and blood pressure, has better performance than traditional standard methods for autoregulation assessment.

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Abbreviations

BP Blood pressure

ABP Intra-arterial blood pressure

CPP Cerebral perfusion pressure

ICP Intracranial pressure

BFV Blood flow velocity

BI Brain injury

ARI Autoregulation index

MMPF Multimodal pressure-flow

EMD Empirical mode decomposition

EEMD Ensemble empirical mode decomposition

VM Valsalva maneuver

HTN Hypertensive

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Appendix

Signal Decomposition

The main concept of the MMPF method is to probe nonlinear BP–BFV relationship by concentrating on intrinsic components of BP and BFV signals that have simplified temporal structures but still can reflect nonlinear interactions between two physiological variables. The first step of the MMPF is to decompose each signal into multiple intrinsic mode functions (IMFs), each mode representing the frequency-amplitude modulation at a specific time scale corresponding to different physiologic influences. To achieve this, the original MMPF used the empirical mode decomposition (EMD) method (Huang et al. 1998a). For a time series $x(t)$ with at least 2 extremes, the EMD applies a sifting procedure to extract IMFs one by one from a smallest time scale to the largest time scale

$$\begin{aligned} x(t) &= s_1(t) + r_1(t) \\ &= s_1(t) + s_2(t) + r_2(t) \\ &\vdots \\ &= s_1(t) + s_2(t) + \cdots + s_n(t) \end{aligned} \tag{1}$$

where $s_k(t)$ is the kth IMF and $r_k(t) = x(t) - \sum_{i=1}^{k} s_i(t)$ is the residual after extracting the first k IMF. There are six steps in the extraction of the kth IMF:

- **i.** Initialize $h_0(t) = h_{i-1}(t) = r_{k-1}(t)$ (if $k = 1$, $h_0(t) = x(t)$), where $i = 1$;
- **ii.** Extract local minima/maxima of $h_{i-1}(t)$ (if the total number of minima and maxima is less than 2, $s_k(t) = h_{i-1}(t)$ and stop the whole EMD process);
- **iii.** Obtain upper envelope (from maxima) and lower envelope (from minima) functions $p(t)$ and $v(t)$ using cubic spline fittings to interpolate local minima and maxima of $h_{i-1}(t)$, respectively;
- **iv.** Calculate the $h_i(t) = h_{i-1}(t) - (p(t) + v(t))/2$;
- **v.** Calculate the standard deviation (SD) of $(p(t) + v(t))/2$;

vi. If SD is small enough (less than a chosen threshold SD_{max}, typically between 0.2 and 0.3) (Huang et al. 1998b), the *k*th IMF is assigned as $s_k(t) = h_i(t)$ and $r_k(t) = r_{k-1}(t) - s_k(t)$; Otherwise repeat steps (ii) to (v) for $i + 1$ until $SD < SD_{max}$

The above procedure is repeated to for $k + 1$ to obtain different IMFs at different scales until there are less than 2 minima or maxima in a residual $r_k(t)$ which will be assigned as the last IMF (see the step ii above).

The EMD can extract the true oscillation components embedded in the original signal without presuming oscillation frequency. However, for nonstationary signals with intermittent oscillations, a limitation of EMD can be caused by the "mode mixing" problem, i.e., a mode obtained from EMD could comprise of oscillations with different wavelengths (corresponding to different physiological functions) at various temporal locations or oscillations corresponding to a physiological function appear in different modes at different temporal locations (Huang et al. 1998a). In order to reliably extract the spontaneous oscillations in BP and BFV during baseline conditions, the improved MMPF method uses a noise-assisted EMD algorithm, namely the Ensemble Empirical Mode Decomposition (EEMD) (Wu and Huang 2005). The EEMD consists of an ensemble of the EMD decompositions of data with added white noise and treats the resultant means of the corresponding intrinsic mode functions from different decompositions as the final result. Shortly, for a time series $x(t)$, the EEMD includes the following steps:

i. Generate a new signal $y(t)$ from the original time series $x(t)$ by superposing to $x(t)$ a white noise with amplitude equal to 10% of the standard deviation of $x(t)$ (applying noise with larger amplitude requires more realizations of decompositions);

ii. Perform the EMD on $y(t)$ to obtain intrinsic mode functions;

iii. Repeat steps (i)–(ii) m times with different white noise to obtain an ensemble of intrinsic mode functions (IMFs) $\{ s_k^1(t), k = 1,2\ldots,n\},\{ s_k^2(t), k = 1,2\ldots,n\},\ldots, \{ s_k^m(t), k = 1,2\ldots,n\}$;

iv. Calculate the average of intrinsic mode functions $\{s_k(t), k = 1,2\ldots,n\}$, where

$$s_k(t)=\frac{1}{m}\sum_{i=1}^{m} s_k^i(t).$$

The last two steps are applied to reduce noise level and to ensure that the obtained IMFs reflect the true oscillations in the original time series $x(t)$. In this study, we repeated decomposition $m = 100$ times so that the final noise level is approximately less than $1\%\ (=\text{amplitude of white noise}/\sqrt{m})$.

The EEMD approach overcomes the mode-mixing problem and ensures the decompositions to compass the range of possible solutions in the sifting process and to collate the signals of different scale in the proper IMF naturally.

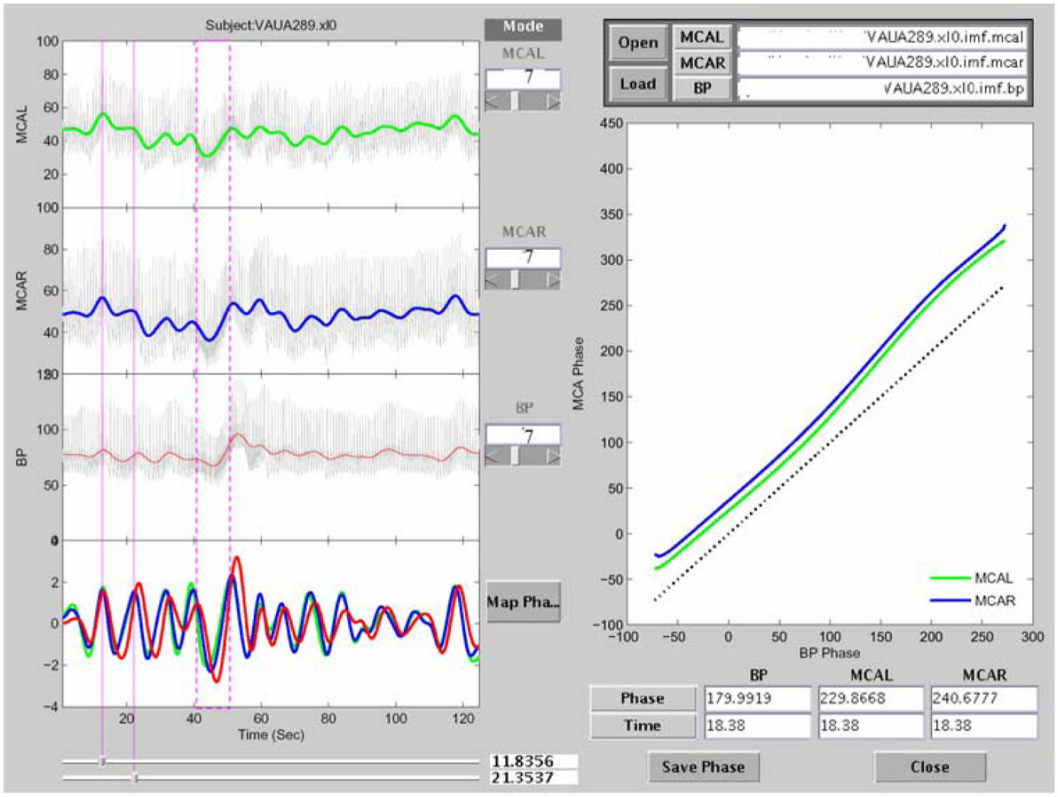

Fig. 1.

Screen copy of our MMPF analysis software. The data shown in this plot are from a healthy subject. The top three panels on the left show BFV (left side and right side) and BP signals, respectively. The colored curves in these panels show the results after removing faster fluctuations from the original signals. The bottom left panel shows the corresponding intrinsic modes for these three signals (red: BP; blue: BFV on right side; green: BFV on left side). The vertical red dashed box (around 40–50 s) identifies the Valsalva maneuver. The spontaneous oscillations in these signals during resting conditions prior to the Valsalva maneuver can also be visualized. One of these oscillations (around 14–22 s) is identified by two vertical red lines. The result of the BP–BFV phase shift analysis of this period is plotted in the right panel. A reference line (dotted black line), indicating synchronization between BP and BFV, is shown in this panel for easy comparison. The result is representative of normal autoregulation where BFV leads BP (by about 50 degrees in phase)

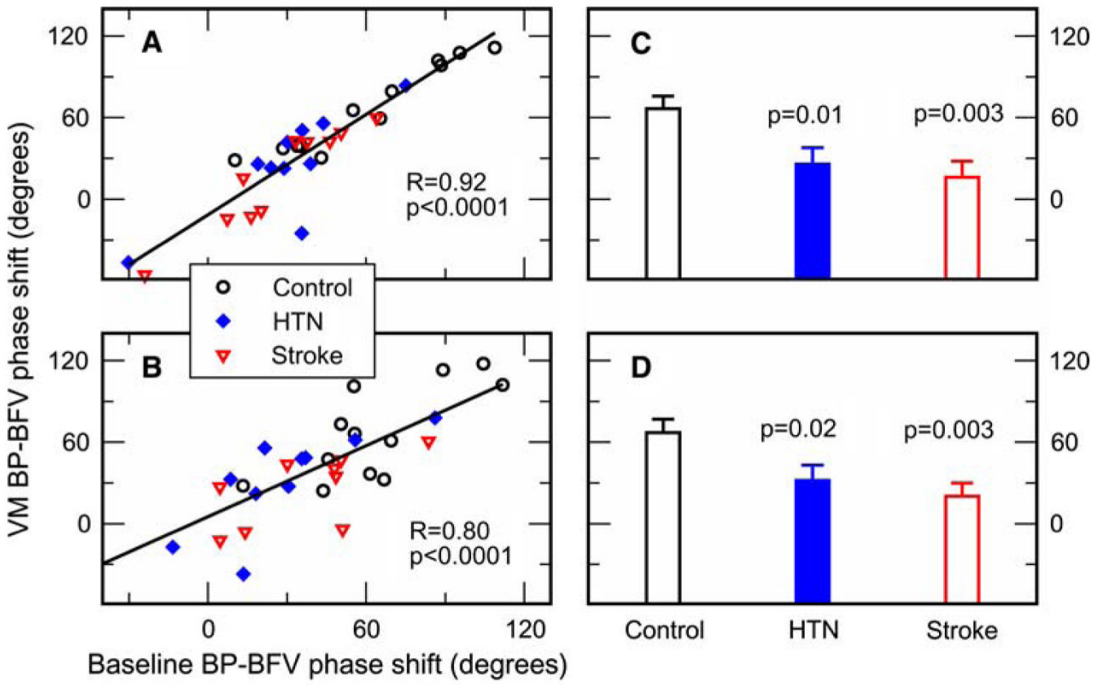

Fig. 2.

Comparison of the BP–BFV phase shift during two different conditions and between control, hypertensive (HTN), and stroke groups. (**a**, **b**) For each subject in this study, BP–BFV phase shifts for left (**a**) and right (**b**) side middle cerebral arteries (MCA) were measured during Valsalva maneuver (VM) and spontaneous BP oscillation under supine rest. The straight line is the linear regression fit of the data. The phase shifts during the Valsalva maneuver and baseline showed a strong correlation (left $R = 0.92$, $P < 0.0001$; right $R = 0.8$, $P < 0.0001$). (**c**, **d**) BP–BFV phase shifts during the Valsalva maneuver were smaller in hypertensive and stroke groups than in control group in both left and right MCAs (HTN: left p = 0.01, right $P = 0.02$; Stroke: left $P = 0.003$, right $P = 0.003$)

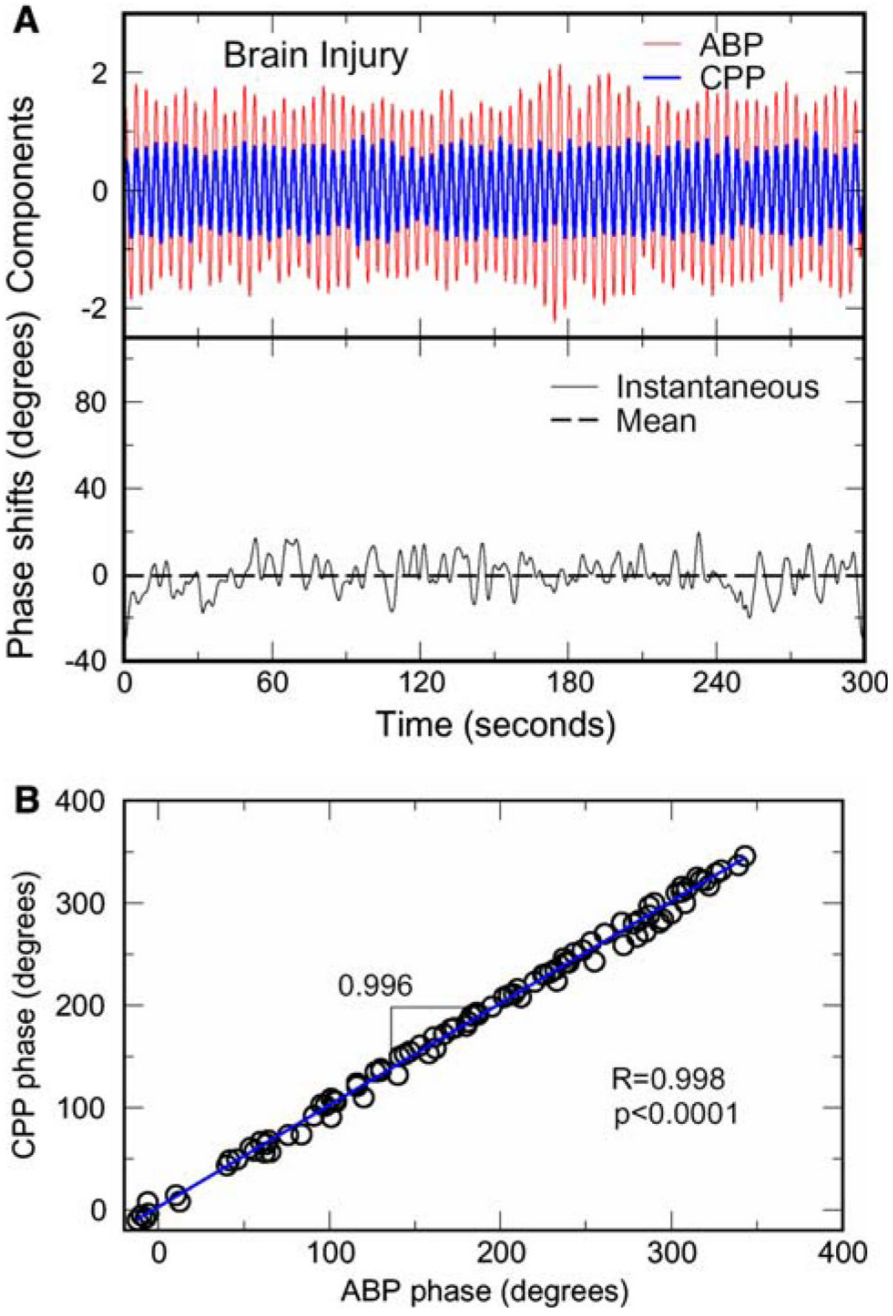

Fig. 3.

Comparison of BP phases obtained from the peripheral intra-arterial pressure (ABP) and the cerebral perfusion pressure (CPP). Results of a typical individual are shown. (**a**). The components corresponding to dominant oscillations at frequency from ~0.1 to 0.4 Hz were extracted using EEMD. Instantaneous phases of ABP were similar to the phases of CPP. (**b**) ABP phases and CPP phases show a strong linear relationship ($P < 0.0001$) with the slope close to 1. The group average of the phase differences between ABP and CPP were 2.4 ± 8.2 degrees

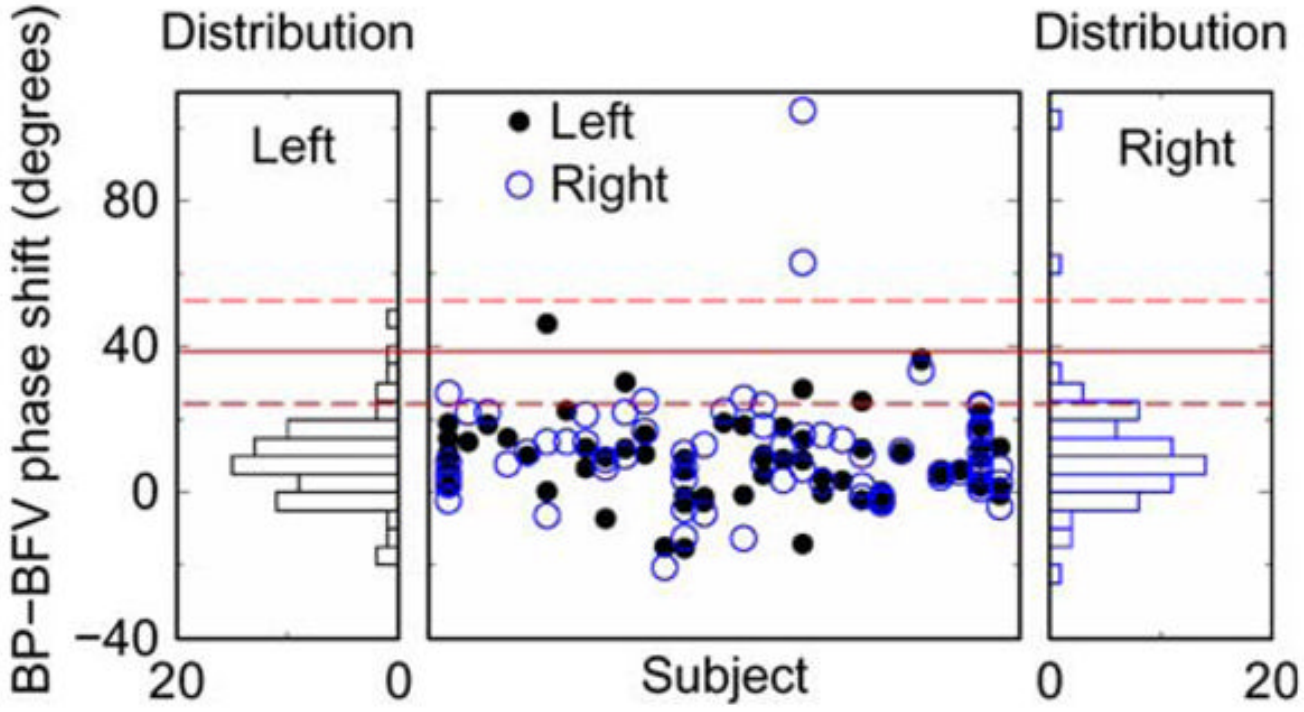

Fig. 4.

Phase shifts between the CPP minimum and the BFV minimum for 30 patients with brain injuries. For each patient four spontaneous intracranial pressure oscillations were randomly chosen to estimate the CPP–BFV phase shifts. The phase shifts obey a normal distribution with the center close to 0. Most of the phase shift values are much smaller than those for control subjects as indicated by the horizontal solid red line (mean) and by the two dashed red lines (standard deviation), manifesting impaired cerebral autoregulation in the patients with brain injuries.

Table 1

Demographic characteristics for control, hypertensive, stroke and brain injury groups

	Control	**Hypertensive**	**Stroke**	**Brain Injury**
Age	**43.7 ± 11.9**	**46.8 ± 7.6**	**50 ± 9.1**	**38 ± 16**
Sex (F, M)	4, 8	4, 6	8, 2	7, 23
Mean ABP (mmHg)	86.2 ± 7.5	102.5 ± 14.3	95.3 ± 10.9	96.7 ± 10.4
Mean ICP (mmHg)				18.5 ± 6.8
Mean BFV (left) (cm/s)	56.5 ± 19.8	54.6 ± 12.8	59.1 ± 14.3	65.7 ± 33.9
Mean BFV (right) (cm/s)	57.4 ± 16.1	53.8 ± 13.9	60.1 ± 14.6	62.5 ± 28.2

Data are presented as mean ± SD

Table 2

Phase shifts between BP and BFV oscillations during the Valsalva maneuver and baseline conditions

	Control	Hypertensive	Stroke	*P*
VM oscillation period (s)	15.8 ± 6.9	19.0 ± 10.0	18.7 ± 6.8	0.58
VM BP–BFV phase shift (left)	66.6 ± 32.0	25.8 ± 38.0	16.1 ± 37.5	0.005
VM BP–BFV phase shift (right)	67.0 ± 34.4	31.9 ± 35.6	20.3 ± 30.4	0.007
Baseline oscillation period (s)	15.0 ± 10.1	16.5 ± 9.9	15.7 ± 8.2	0.94
Baseline BP–BFV phase shift (left)	60.1 ± 30.7	30.1 ± 26.1	26.5 ± 25.3	0.013
Baseline BP–BFV phase shift (right)	63.9 ± 27.4	29.4 ± 27.3	27.3 ± 40.1	0.017

Data are presented as mean ± SD

P values indicate between group comparisons

Table 3

Repeatability of BP–BFV phase shifts and autoregulation indices

	Oscillation period (s)	CPP–BFV phase shift (degrees)	ARI
Trial 1	4.7 ± 1.4	7.4 ± 20.3	4.4 ± 3.8
Trial 2	4.6 ± 1.3	8.8 ± 14.8	3.4 ± 3.8
Trial 3	4.5 ± 1.3	5.8 ± 17.4	4.8 ± 3.9
Trial 4	4.5 ± 1.3	7.7 ± 20.2	3.3 ± 4.0
Variance within subjects		123.6	14.0
Variance between subjects		768.7	18.8
Coefficient		0.58	0.08

Data are presented as mean ± SD

Coefficients (intraclass correlation coefficient) were obtained from the values of 4 trials and represented the repeatability