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Coupling between arterial pressure, cerebral blood velocity, and cerebral tissue oxygenation with spontaneous and forced oscillations

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Abstract

We tested the hypothesis that transmission of arterial pressure to brain tissue oxygenation is low under conditions of arterial pressure instability. Two experimental models of hemodynamic instability were used in healthy human volunteers; (1) oscillatory lower body negative pressure (OLBNP) ($N = 8$; 5 male, 3 female), and; (2) maximal LBNP to presyncope ($N = 21$; 13 male, 8 female). Mean arterial pressure (MAP), middle cerebral artery velocity (MCAv), and cerebral tissue oxygen saturation (ScO₂) were measured non-invasively. For the OLBNP protocol, between 0 and -60mmHg negative pressure was applied for 20 cycles at 0.05 Hz, then 20 cycles at 0.1 Hz. For the maximal LBNP protocol, progressive 5 min stages of chamber decompression were applied until the onset of presyncope. Spectral power of MAP, mean MCAv, and scO₂ were calculated within the VLF (0.04–0.07 Hz), and LF (0.07–0.2Hz) ranges, and cross-spectral coherence was calculated for MAP-mean MCAv, MAP-ScO₂, and mean MCAv-ScO₂ at baseline, during each OLBNP protocol, and at the level prior to pre-syncope during maximal LBNP (sub-max). The key findings are (1) both 0.11-IZ OLBNP and sub-max LBNP elicited increases in LF power for MAP, mean MCAv, and scO₂ ($p = 0.08$); (2) 0.05 Hz OLBNP increased VLF power in MAP and scO₂ only ($p = 0.06$); (3) coherence between MAP-mean MCAv was consistently higher ($r = 0.71$) compared with MAP-ScO₂, and mean MCAv-ScO₂ ($r = 0.43$) during both OLBNP protocols, and sub-max LBNP ($p = 0.04$). These data indicate high linearity between pressure and cerebral blood flow variations, but reduced linearity between cerebral tissue oxygenation and both arterial pressure and cerebral blood flow. Measuring arterial pressure variability may not always provide adequate information about the downstream effects on cerebral tissue oxygenation, the key end-point of interest for neuronal viability.

Keywords

oscillations; cerebral; tissue oxygenation

1. Introduction

Conventional cardiovascular risk-stratification relies heavily on the assumption that static measurements of brachial blood pressure alone accounts for all blood pressure-related risk of vascular events. However, there is growing recognition that this paradigm is overly simplistic and that blood pressure may have significant limitations for detecting adverse changes in the intra-cranial environment. While blood pressure is commonly monitored on the premise that it informs the state of cerebral it is also well established that cerebral blood flow is affected not only by blood pressure, but also by physiological processes such as cerebral autoregulation (Zhang *et al* 1998a, Panerai *et al* 2002). Consequently, individuals with similar blood pressure can have disparate levels of brain perfusion depending on their individual autoregulation capacity. Similarly, measuring the oxygenation of arterial blood using conventional digit pulse oximetry may not accurately reflect brain tissue oxygenation (Tobias 2008), which is a complex variable that is influenced by local metabolic conditions of oxygen supply and consumption. These are some reasons why direct monitoring of cerebral blood flow, brain tissue oxygenation, and cerebral autoregulation have become conceptually attractive strategies for optimizing outcomes in care settings (Kirkpatrick *et al* 1998, Johnston and Czosnyka 2003, Reinhard *et al* 2005).

Despite decades of research, informed hemodynamic management in many areas of neurocritical care remains enigmatic (Grise and Adeoye 2012). For example, observational studies have shown that blood pressure is frequently elevated during acute stroke and recent data indicate that rapid blood pressure lowering improves functional outcome in hemorrhagic stroke (Anderson *et al* 2013). However, innumerable clinical trials on the effectiveness of blood pressure lowering in acute ischemic have generated divergent results (Hubert *et al* 2013). This has prompted speculation that hemodynamic management based on systemic blood pressure monitoring may be too crude to achieve consistent optimization of local cerebral perfusion and oxygenation (Hadjiev and Mineva 2013).

In light of these practical challenges, the goal of this study is to determine the extent to which blood pressure changes can be used as surrogate indices of cerebral blood flow and brain tissue oxygenation under situations where blood pressure and cerebral perfusion may be threatened. We used static and oscillatory lower body negative pressure (OLBNP) as experimental models of hemodynamic instability and linear function analysis to define the timescale and magnitude of the input–output relations between blood pressure, cerebral blood flow, and brain tissue oxygenation. We hypothesized that the transmission of pressure to brain tissue oxygenation is low across all frequency ranges (0.04–0.40 Hz) under both experimental models of hemodynamic instability.

2. Methods

Data for this study were from two independent protocols; (1) OLBPN at 0.05 and 0.1 Hz, and; (2) maximal LBNP to presyncope. Each protocol is described separately.

2.1. Oscillatory lower body negative pressure

2.1.1. Subjects.—Eight healthy, normotensive, non-smoking subjects (5 male, 3 female; age, 28 ± 1 years; height, 169 ± 3 cm; weight, 75 ± 5 kg; mean $\pm$ SE) volunteered to participate in this study. This protocol is part of an ongoing larger study consisting of additional experiments and interventions that will be published separately at a date, but do not impact the outcome of the data presented herein. The experiments were conducted in the Department of Integrative Physiology & Anatomy at the University of North Texas Health Science Center (UNTHSC), and all experimental protocols and procedures were reviewed and approved by the UNTHSC Institutional Review Board. A complete medical history and physical examination conducted on each potential subject prior to their participation in the study. All female subjects were tested within days 1–4 of the early follicular phase of their menstrual cycle, and were also administered a urine pregnancy test prior to experimentation to ensure they were not pregnant. Due to the potential effects on autonomic function, all subjects were instructed to maintain their normal sleep patterns in addition to abstaining from exercise, alcohol, caffeine and other pharmacological stimulants 24 h before each protocol. After familiarization with the laboratory, subjects were briefed with a description of all procedures and risks associated with the experiments and each gave written informed consent to participate in the study.

2.1.2. Instrumentation.—Subjects were placed in the supine position with their lower body inside a LBNP chamber (VUV Analytics, Austin, TX) and positioned on a bicycle seat to ensure they did not move during chamber decompression. Durable plastic and a neoprene band were wrapped around the subject's waist to create an airtight seal with the LBNP chamber. Subjects were instrumented with a standard lead II ECG (shielded leads, cable and amplifier, AD Instruments, Bella Vista, NSW, Australia), infrared finger photoplethysmography to measure beat-to-beat arterial blood pressure (Finometer®, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands), a 2MHz transcranial Doppler (TCD) ultrasound probe for assessment of blood velocity in the middle cerebral artery (MCAv; ST3, Spencer Technologies, Seattle, WA), a flat near infrared spectroscopy (MRS) sensor over the right or left frontal lobe for assessment of oxy-hemoglobin (HbO₂), deoxy-hemoglobin (dHb), and cerebral oxygen saturation (ScO₂, OxiplexTS, ISS Inc., Champaign-Urbana, IL), and a nasal cannula to capture expired gases for assessment of end-tidal CO₂ (etCO₂) and respiration rate (ML206 Gas Analyzer, AD Instruments, Bella Vista, NSW, Australia). For the majority of subjects, MCAv and ScO₂ were measured on the same side. All signals were recorded at 1000 Hz using commercially available data acquisition hardware and software (PowerLab and LabChart Pro, AD Instruments, Bella Vista, NSW, Australia).

2.1.3. Study design.—Following instrumentation, 5 min of resting baseline data was collected. OLBNP between 0 and –60 mmHg was applied for 20 cycles at 0.05 Hz (very low frequency, VLF), then 20 cycles at 0.1 Hz (low frequency, LF), with a 5 min rest period between each protocol. Subjects remained as relaxed as possible, and breathed spontaneously throughout the OLBNP profiles. Following completion of the OLBNP protocols, subjects remained in the supine posture for an additional 5 min recovery period.

2.1.4. Data analysis.—All waveform data was exported into commercial analysis software (WinCPRS, Absolute Aliens, Turku, Finland). R waves generated from the ECG siB1a1 were detected and marked at their occurrence in time. Heart rate (HR) was derived from the R–R interval (RRI) signal. Diastolic arterial pressure (DAP) and systolic arterial pressure (SAP) were marked from the blood pressure tracings. Mean arterial pressure (MAP) and mean MCAv were automatically calculated from the area under the arterial pressure and MCAv tracings via the WinCPRS software. Stroke volume (SV) was estimated on a beat-to-beat basis by the Finometer® using the established pulse contour method (Jansen *et al* 1990) and recorded directly to the LabChart file. Cardiac output (CO) was calculated as the product of HR and SV, total peripheral resistance (CTPR) was calculated as MAP divided by CO, and cerebrovascular resistance (CVR) was calculated as MAP divided by mean MCAv. All variables were calculated from the 300s baseline period, and from the 20-cycles of 0.05 Hz OLBPN (400s) and 0.1 Hz OLBPN (200s).

Oscillatory patterns of MAP, mean MCAv, and ScO₂ were determined with fast Fourier power spectral analysis. Data were made equidistant by interpolating linearly and re-sampling at 5Hz. Data were then passed through a low-pass filter with a cutoff frequency of 0.5 Hz. Data sets were fast Fourier transformed with a Hanning window to obtain power spectra. Spectral power was expressed as the integrated area within the VLF range (0.04–0.07 Hz), and LF range (0.07–0.2Hz). The coherence between MAP and mean MCAv, MAP and ScO₂, and mean MCAv and ScO₂ was calculated by dividing the squared cross-spectral densities of the two signals by the product of the individual autospectra (60s windows).

2.1.5. Statistics.—One-way repeated measures ANOVAs were used for comparison of all responses (baseline, 0.05 Hz OLBPN, 0.1 Hz OLBPN). For frequency domain variables, comparisons were made only within a frequency band (VLF, LF). Holm-Sidak *post-hoc* tests were used to compare responses to the OLBPN protocols versus baseline only. Paired *t*-tests were used to compare MAP-ScO₂ coherence and mean MCAv-ScO₂ coherence to MAP-mean MCAv coherence within a specific frequency band. Unless otherwise stated, all data are presented as mean $\pm$ SE, and exact *p* values are reported for comparisons.

2.2. Maximal LBNP to presyncope

2.2.1. Subjects.—Twenty-one healthy, normotensive, non-smoking subjects (13 male, 8 female; age, 27 ± 1 years; height, 171 ± 2 cm; weight, 77 ± 3 kg; mean $\pm$ SE) were included in the analysis of this study. Twenty-five subjects completed this protocol, but four did not reach true pre-syncope according to the criteria described below. Six of the final 21 subjects also participated in the OLBPN study. The experiments were conducted in the Department of Integrative Physiology & Anatomy at the University of North Texas Health Science Center (UNTHSC), and all experimental protocols and procedures were reviewed and approved by the UNTHSC Institutional Review Board. A complete medical history and physical examination conducted on each potential subject prior to their participation in the study. All inclusion and exclusion criteria were identical to the OLBPN study. After familiarization with the laboratory, subjects were briefed with a description of all procedures and risks associated with the experiments and each gave written informed consent to participate in the study.

2.2.2. Study design.—Subject instrumentation was to the OLBPN study. The maximal LBNP protocol consisted of a 5 min baseline period followed by progressive 5 min stages of chamber decompression at -15 , -30 , -45 , -60 , -70 , -80 , -90 , and -100 mmHg. The protocol was terminated following completion of 5 min at -100 mmHg LBNP, or with the onset of presyncope, defined as one or a combination of the following criteria: sudden bradycardia, $SAP < 80$ mmHg, and/or voluntary subject termination due to presyncopal symptoms such as gray-out, nausea, sweating, dizziness, or general discomfort. Following presyncope, subjects remained in the LBNP chamber for a 10min recovery period.

2.2.3. Data analysis.—The data processing procedures were identical to the OLBPN study, except that all variables were calculated from the final 240s (4 min) of baseline, and the last completed sub-maximal level of LBNP prior to the onset of presyncope (sub-max). For example, even if a subject reached pre-syncope 4 min into the -70 mmHg LBNP level, the last 4 min of the preceding -60 mmHg level was used for analysis.

2.2.4. Statistics.—Paired t -tests were used to compare responses between baseline and sub-max for all variables. Paired t -tests were also used to compare MAP-ScO₂ coherence and mean MCAv-ScO₂ coherence to MAP-mean MCAv coherence within a specific frequency band. Unless otherwise stated, all data are presented as mean $\pm$ SE, and exact p values are reported for comparisons.

3. Results

3.1. Oscillatory lower body negative pressure

The hemodynamic responses to OLBPN at 0.05 and 0.1 Hz are presented in table 1. The only variable that changed with OLBPN was CVR, increasing compared with baseline at both OLBPN frequencies. The power spectral density (PSD) for MAP, mean MCAv, and ScO₂ at baseline, and during the two OLBPN protocols are shown in figure 1. Compared with baseline, VLF power increased during 0.05 Hz OLBPN for MAP ($p < 0.001$), and ScO₂ ($p = 0.06$). The increase in mean MCAv VLF power was not statistically distinguishable from baseline ($p = 0.49$). LF power increased for MAP ($p < 0.001$), mean MCAv ($p = 0.08$), and ScO₂ ($p = 0.03$) during 0.1 Hz OLBPN compared with baseline. During 0.05 Hz OLBPN, VLF coherence increased for MAP-ScO₂ ($p = 0.04$), and during 0.1 Hz OLBPN LF coherence increased for MAP-ScO₂ ($p < 0.001$) and mean MCAv-ScO₂ ($p = 0.003$) (figure 2). Compared with MAP-mean MCAv coherence within each frequency band, coherence was lower between MAP-ScO₂ and mean MCAv-ScO₂ at baseline and during both OLBPN protocols ($p = 0.004$), except for VLF during 0.1 Hz OLBPN ($p = 0.20$) (figure 2).

3.2. Maximal LBNP presyncope

The LBNP protocol was terminated at -45 mmHg for two subjects, -60 mmHg for six subjects, -70 mmHg for seven subjects, -80 mmHg for subjects, and -90 mmHg for three subjects. The baseline and sub-max hemodynamic data are presented in table 2. As expected, LBNP elicited a $45 \pm 3\%$ reduction in SV, and a decrease in MAP, stimulating baroreflex-mediated increases in HR and TPR. Both mean MCAv and ScO₂ decreased, and CVR

increased with LBNP. Respiration rate remained constant, but etCO_2 was reduced by 8.4 ± 1.3 mmHg.

PSD for MAP, mean MCAv, and ScO_2 at baseline and sub-max are presented in figure 3. LBNP elicited increases in LF power for all three variables compared with baseline ($p = 0.02$), and a decrease in mean MCAv VLF ($p = 0.02$). During LBNP, LF coherence increased between MAP-mean MCAv ($p = 0.04$), and between mean MCAv- ScO_2 ($p = 0.05$), but did not change between MAP- ScO_2 ($p = 0.20$) (figure 4). Compared with MAP-mean MCAv coherence within each frequency band, coherence was lower between MAP- ScO_2 and mean MCAv- ScO_2 at baseline and during LBNP ($p = 0.005$) (figure 4).

4. Discussion

In order to assess blood pressure variability can be used as a surrogate index of cerebral blood flow and brain tissue oxygenation variability, we induced variations in arterial pressure via maximal static LBNP and OLBNP in healthy human subjects, and determined the relationships between arterial pressure, cerebral blood flow, and cerebral tissue oxygenation. Our key findings (1) both 0.1 Hz OLBNP and sub-maximal LBNP elicited increases in LF power for MAP, mean MCAv, and scO_2 ; (2) 0.05 Hz OLBNP increased VLF power in MAP and ScO_2 only; (3) coherence between MAP and mean MCAv was consistently higher compared with coherence between MAP and ScO_2 , and between mean MCAv and ScO_2 . These data indicate high linearity between arterial pressure and cerebral blood flow variations, but reduced linearity between pressure and cerebral tissue oxygenation, and between cerebral blood flow and cerebral oxygenation. These findings suggest that measuring arterial pressure variability may not always provide adequate information about the downstream effects on cerebral tissue oxygenation, the key end-point of interest for neuronal viability in many common neuro-critical care settings. Furthermore, measuring absolute arterial pressure does not provide an accurate representation of absolute cerebral blood flow and oxygenation under hypovolemic conditions either; with a 45% reduction in central blood volume following application of sub-maximal LBNP, cerebral blood flow and oxygenation fell by ~19% and ~6.5%, despite just a ~7% (~7mmHg) decrease in MAP (as a reference, at presyncope MCAv and ScO_2 reduced by up to ~25–30% (Bondar *et al* 1995, Rickards *et al* 2011) and ~10–15% (Glaister and Miller 1990, Madsen *et al* 1995, van Lieshout *et al* 2003)). Collectively, these findings consistent with our hypothesis and support the use of direct measures of cerebral blood flow and/or oxygenation in clinical situations where accurate assessment of the metabolic environment of the brain is desirable (e.g. stroke, traumatic brain injury, myocardial infarction).

4.1. Oscillatory lower body negative pressure

OLBNP has been shown to reliably induce oscillations at specific frequencies of interest, with the amplitude of oscillations proportional to the magnitude of applied pressure (Brown *et al* 2004, Hamner *et al* 2004). In the current study, the frequencies of 0.05 and 0.1 Hz OLBNP were chosen as they fall within the commonly utilized frequency ranges for assessing arterial pressure to cerebral blood flow relationships (VLF: 0.02–0.07 Hz, and LF: 0.07–0.2Hz), often termed ‘dynamic cerebral autoregulation’ (Zhang *et al* 1998a, Claassen

et al 2009). As expected, both 0.1 Hz and 0.05 Hz OLBPN induced large increases in LF and VLF power in arterial pressure, respectively, and induced an increase in cerebral blood flow power (with 0.1 Hz OLBPN), as previously demonstrated (Hamner *et al* 2004, Claassen *et al* 2009) (see Methodological Considerations section for discussion of MCAv VLF response). While cerebral tissue oxygenation variability was also elevated under both OLBPN frequencies (0.05 and 0.1 Hz), the magnitude of oscillations was small compared with pressure and flow (figure 1(c)). To our knowledge, this is one of very few studies (Reinhard *et al* 2006, van Beek *et al* 2012, Oudegeest-Sander *et al* 2014) to assess cerebral oxygen variability with forced oscillations at fixed frequencies (via OLBPN, repeated squat-to-stand maneuvers, or paced breathing). As absolute values of HbO₂, dHb, and ScO₂ did not change from baseline with either 0.1 or 0.05 Hz OLBPN (table 1), it does not appear as though these forced oscillations affect the delivery or utilization of oxygen at the level of the tissue in otherwise healthy individuals.

Many studies utilizing methods to force oscillations in arterial pressure and cerebral blood flow via OLBPN (Brown *et al* 2004, Hamner *et al* 2004, Tzeng *et al* 2011), repeated squat-to-stand (Birch *et al* 1995, Claassen *et al* 2009) or sit-to-stand maneuvers (Oudegeest-Sander *et al* 2014), and paced breathing (Reinhard *et al* 2006, Lucas *et al* 2013) have demonstrated increases in both MAP and mean MCAv and high coherence between MAP and mean MCAv at the specific oscillation frequency. In fact, forced oscillations are frequently used as a simple means to increase coherence between MAP and mean MCAv, and thereby decrease inter-subject variability for subsequent investigation of cerebral autoregulation via transfer function analysis (Reinhard *et al* 2006, Claassen *et al* 2009). In a recent study, Oudegeest-Sander *et al* (2014) also reported an increase in coherence between mean MCAv and HbO₂ during repeated sit-to-stand maneuvers at 0.05 Hz (>0.5) compared with resting baseline (<0.4) in both young and old subjects. In the current study, average baseline coherence between mean MCAv and ScO₂ and between MAP and ScO₂ were consistently below 0.4 at all frequencies, increasing to 0.4 at the specific frequencies of OLBPN, consistent with these findings (Oudegeest-Sander *et al* 2014). Despite these increases in coherence with OLBPN, however, the coherence between MAP and mean MCAv was always higher at each frequency of forced oscillations, suggesting diminished linearity in the coupling of oscillations from mean MCAv to ScO₂ or from MAP to ScO₂. These results, therefore, also indicate that there is not direct linear transmission of oscillations originating in systemic arterial pressure to cerebral blood flow and finally to cerebral oxygenation at the level of the tissue (MAP-MCAv COH > MCAv-ScO₂ COH = MAP-ScO₂ COH). The lower coherence of both pressure and flow to cerebral tissue oxygen, and the small amplitude of ScO₂ oscillations suggest that brain tissue oxygenation may be protected from upstream variability in both pressure and flow. As our subject cohort was young and healthy, we did not assess whether these relationships would be altered in and/or clinical populations.

In a study of older patients with unilateral severe obstructive carotid disease breathing at a paced rate of 6 breaths min⁻¹ (0.1 Hz), Tzeng *et al* (2006) showed a decrease in 0.1 Hz phase between MCAv and HbO₂, while van Beek *et al* (2012) reported increases in both phase and gain between MCAv and HbO₂ in older patients with Alzheimer's disease during repeated sit-to-stand maneuvers at 0.05 Hz. Oudegeest-Sander *et al* (2014) also report a reduced 0.05 Hz phase for MCAv-HbO₂ in elderly subjects compared with young controls during

repeated sit-to-stand maneuvers at 0.05 Hz. When assessing pressure-flow relationships with transfer function analysis, low coherence, high phase, and low gain are traditionally interpreted as a positive response (independence of flow from pressure), while high coherence, low phase and high gain are interpreted as an impaired response (greater dependence of flow on pressure); the same interpretation of transfer function metrics was applied to these studies assessing the relationships between MCAv and HbO₂. While some of the reported relationships are conflicting, reflecting a known lack of convergent validity between transfer function analysis metrics (Tzeng *et al* 2012), it appears as though clinical cerebral pathologies and age may increase the likelihood of high variability in arterial pressure and/or cerebral blood flow negatively impacting cerebral microvascular oxygenation.

4.2. Maximal LBNP

While OLBPN is an ideal method to force hemodynamic variations at specific frequencies, maximal LBNP was also used to induce clinically meaningful reductions in blood volume, and to elicit spontaneous LF variations in arterial It is well established that increases in arterial pressure LF oscillations during hypovolemia are associated with increased LF variability in sympathetic activity. Cooke *et al* (2009) demonstrated a parallel increase in muscle sympathetic activity (MSNA) LF power with increasing MSNA during maximal LBNP, reflected in progressively increasing LF coherence between MSNA and pressure. Similarly, with progressive sympathetic withdrawal in syncopal subjects during head-up Kamiya *et al* (2005) showed concomitant reductions in MSNA and MSNA LF power, and in MAP and MAP LF While some investigations have shown increases in MAP and mean MCAv LF power and high MAP-mean MCAv LF coherence with LBNP (Zhang *et al* 1998b, Rickards *et al* 2011), others have reported increases only in MAP LF power and not MCAv LaF power (Brown *et al* 2003, 2004), citing cerebral autoregulation as the mechanisms responsible for buffering the of variability from pressure to flow, In the current study, transfer of LF variability from pressure to flow is the most plausible explanation for the elevated LF power in both cerebral blood flow and oxygenation at sub-maximal levels of LBNP. As with the OLBPN protocol, however, the magnitude of ScO₂ oscillations was small compared with pressure and flow (figure 3(c)), and the coherence between ScO₂ and both MAP and MCAv was low. While cerebral oxygen variability has not been previously reported with central hypovolemia elicited with LBNP, increased L.F oscillations in cerebral oxygenation have been demonstrated during orthostatic maneuvers (sitting and standing from supine), and were associated with increased LF power in arterial pressure (Tachtsidis *et al* 2004). As the MRS technique assesses tissue sample volumes containing multiple vessel types, including arterioles, capillaries, and venules, measures of dHb, HbO₂, and ScO₂ are generally considered 'post-cellular' (Pollard *et al* 1996, Madsen and Secher 1999). Consequently, based on the HbO₂ and dHb responses, it appears as though oxygen extraction increased with sub-maximal LBNP (decreased HbO₂ and dHb); the role of increased oscillations on oxygen extraction and utilization during cerebral hypoperfusion, however, is unclear as we did not have a control group where oxygen saturation oscillations were suppressed.

The reduced linearity between MAP and ScO₂ is also not surprising considering the large number of physiological steps between MAP and the oxygenation state of a sample of mixed-venous blood (MRS-derived ScO₂). ScO₂ reflects the combined effects of oxygen delivery (affected by cerebral blood flow and arterial oxygen content) and tissue oxygen extraction, which, in turn, is influenced by tissue metabolism. Under normoxic conditions, the low coherence between mean MCAv and ScO₂ may reflect the ability of cerebral blood flow to effectively respond to changing metabolic demand induced by the LBNP stimulus, and functioning metabolic blood flow regulatory mechanisms. On the other hand, increased coherence between flow and ScO₂ may imply impaired regulation in the clinical setting. This is an intriguing hypothesis that requires further investigation, particularly considering variations in oxygen delivery, arterial oxygen content, and tissue metabolism likely differ across patient populations.

4.3. Methodological considerations

Compared with other studies assessing phase and gain between cerebral blood flow and oxygenation (Reinhard *et al* 2006, van Beek *et al* 2012, Oudegeest-Sander *et al* 2014), we were not confident in the reliability of these measures due to low coherence at baseline, and during OLBPN and sub-maximal LBNP (<0.5). As such, a direct comparison with the results of these studies is limited. This low coherence can result not only from non-linearity between two signals, but also due to high extraneous noise (low signal to noise ratio), no relationship between the two signals of interest (Zhang *et al* 1998a), a large time lag between changes in the two signals, or additional factors that may be influencing only one of the variables of interest (e.g. variations in cerebral metabolism, intracranial pressure, the non-linear nature of the oxy-hemoglobin dissociation curve). However, (1) there are clear physiological mechanisms relating all three of these measurements, and; (2) use of OLBPN increases the signal to noise ratio, evidenced by clear increases in in all signals (except MCAv VLF) at the specific oscillating frequency. Therefore, the low coherence was likely a result of reduced linearity between responses of the two pairs of signals (MCAv-ScO₂ and MAP-ScO₂), although the additional potentially confounding factors outlined above cannot be accounted for in this study.

Using broad frequency ranges for assessment of LF and VLF power may have diluted the calculated power for MAP, mean MCAv and ScO₂. For example, despite an average 1.5-fold increase in mean MCAv VLF with 0.05Hz OLBPN, there was no statistically distinguishable difference compared with baseline ($p = 0.49$). Further inspection of this data revealed that MCAv VLF power actually decreased within the range of 0.04–0.07 Hz with 0.05 Hz OLBPN in three of the eight subjects, but there was a distinct peak on the power spectrum at 0.05 Hz for each of these subjects. This entrainment of spontaneous activity to the imposed oscillation frequency may have lead to reduced activity in adjacent frequencies within this band which was not compensated by increased activity at the OLBPN frequency, subsequently leading to an overall reduction in power in this band. The reason for this discrepancy in these three subjects is not clear and warrants further investigation.

Accruing evidence suggests that measurements of cerebral oxygenation with some MRS monitoring devices significantly affected by skin contamination, some by up to 35% (Davie

and Grocott 2012, Sorensen *et al* 2012, Hirasawa *et al* 2014, Sorensen *et al* 2014). In this study, we used a spatially resolved MRS device with emitter distances of 2.0, 2.5, 3.0, and 3.5mm from the detector. Theoretically, the emitters closest to the detector should measure shallow oxygenation (e.g. skin, muscle, fat) which is then mathematically removed from the resultant cerebral HbO₂ and dHb measurements derived from the light emitted and detected furthest from the detector (i.e. cortical tissue). While the influence of skin contamination on this particular MRS device has not been quantified, compared to other systems that have been tested (Davie and Grocott 2012, Sorensen *et al* 2014), this device has four emitters versus only two, increasing the likelihood that superficial tissue contamination is removed from the final measurement of cerebral tissue oxygenation.

As in any investigation utilizing TCD ultrasound, we assume the diameter of the MCA was constant throughout the investigation, so measures of blood velocity reflect blood flow. Recent studies (Coverdale *et al* 2014, Verbree *et al* 2014) using high resolution magnetic resonance imaging (MRI) technology have revealed that increases in arterial CO₂ elicit MCA vasodilation (etCO₂ 9mmHg above baseline), and decreases in arterial CO₂ elicit MCA vasoconstriction (etCO₂ 13mmHg below baseline). As the OLBPN protocols did not alter etCO₂, and sub-maximal LBNP elicited hypocapnia to only 8.4 ± 1.3 mmHg below baseline, it is unlikely that MCA decreased in this study; the effect of profound hypotension and resulting sympathetic activity on MCA diameter, however, has not been assessed.

Finally, in a recent review, we highlighted an emerging debate about the clinical implications of high arterial pressure and blood flow variability, and concluded that the time scale of variability may be of most importance when determining protective versus deleterious effects; short time scale variability appears to be cerebro-protective, while mid-to-longer term fluctuations are associated with primary and secondary end-organ dysfunction (Rickards and Tzeng 2014). In the current study we only assessed very short-term acute variability, on the order of seconds to minutes. Perhaps of more clinical relevance may be assessment of the relationships between arterial pressure, cerebral blood flow, and cerebral tissue oxygenation variability across longer chronic time scales, such as days, weeks, or months. Nevertheless, in many neurocritical care settings, the ability to detect hemodynamic compromise within the order of minutes is paramount and there is data suggesting that even short (5 min) recordings have predictive utility (Dawson *et al* 2000a, 2000b).

5. Conclusions

Preservation of cerebral perfusion and oxygenation with variations in perfusion pressure is essential to the maintenance of consciousness and the survival of cerebral tissue. This study demonstrated that while arterial pressure, cerebral blood flow, and cerebral oxygenation oscillate at the same frequencies with either forced or spontaneous variability, the coupling between flow and oxygenation, and between pressure and oxygenation is consistently lower than the coupling between pressure and flow. The magnitude of oscillations in cerebral oxygen is also diminished compared with pressure and flow. We conclude that measuring variations in arterial pressure should not be regarded as a robust surrogate indicator of cerebral blood flow or brain tissue oxygenation under situations where blood pressure and

cerebral perfusion may be threatened. Instead, we recommend that direct assessment of cerebral blood flow and oxygenation should be assessed whenever feasible.

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Figure 1.

Power spectral density (PSD) for (a) mean arterial pressure (MAP), (b) mean middle cerebral artery velocity (MCAv), and (c) cerebral oxygen saturation (ScO₂) in the very low frequency (VLF) and low frequency (LF) ranges at baseline (BL; white bars) and during oscillatory lower body negative pressure (OLBNP) at 0.05 Hz (gray bars) and 0.1 Hz (black bars). *Denotes $p < 0.08$ compared with BL within the specific frequency band (VLF, LF).

Figure 2.

Cross-spectral coherence (COH) (a) between mean arterial pressure (MAP) and mean middle cerebral artery velocity (MCAv), (b) MAP and cerebral oxygen saturation (ScO₂), and (c) MCAv-ScO₂ in the very low frequency (VLF), and low frequency (LF) ranges at baseline (BL; white bars) and during oscillatory lower body negative pressure (OLBNP) at 0.05Hz (gray bars) and 0.1 Hz (black bars). *Denotes $p < 0.04$ compared with BL within the specific frequency band (VLF, LF); †Denotes $p < 0.04$ compared with MAP-mean MCAv COH within the specific frequency band and OLBPN frequency.

Figure 3.

Power spectral density (PSD) for (a) mean arterial pressure (MAP), (b) mean middle cerebral artery velocity (MCAv), and (c) cerebral oxygen saturation (ScO₂) in the very low frequency (VLF), and low frequency (LF) ranges at baseline (BL; black bars) and during sub-maximal (sub-max; white bars) lower body negative pressure. *Denotes $p < 0.02$ compared with BL within the specific frequency band (VLF, LF).

Figure 4.

Cross-spectral coherence (COH) between (a) mean arterial pressure (MAP) and mean middle cerebral artery velocity (MCAv), (b) MAP and cerebral oxygen saturation (ScO₂), and (c) MCAv-ScO₂ in the very low frequency (VLF), and low frequency (LF) ranges at baseline (BL; black bars) and during sub-maximal (sub-max; white bars) lower body negative pressure. *Denotes $p < 0.05$ compared with BL within the specific frequency band (VLF, LF); †Denotes $p < 0.005$ compared with MAP-mean MCAv COH within the specific frequency band and time point (BL or sub-max).

Table 1.

Time domain cardiovascular responses to OLBNP at 0.05 Hz (VLF) and 0.1 Hz (LF) ($N = 8$).

Physiological parameter	Baseline	0.05 Hz OLBNP	0.1 Hz OLBNP
RRI (ms)	1004 $\pm$ 36	989 $\pm$ 36	986 $\pm$ 40
HR (beats min ⁻¹)	62.0 $\pm$ 2.6	61.8 $\pm$ 2.6	62.1 $\pm$ 2.9
MAP (mmHg)	91.9 $\pm$ 3.1	90.7 $\pm$ 2.6	93.6 $\pm$ 2.9
SV (ml)	98.6 $\pm$ 4.3	99.0 $\pm$ 4.7	99.0 $\pm$ 4.9
CO (l min ⁻¹)	6.1 $\pm$ 0.4	6.1 $\pm$ 0.3	6.1 $\pm$ 0.3
TPR (mmHg l ⁻¹ min ⁻¹)	15.2 $\pm$ 0.5	15.0 $\pm$ 0.4	15.5 $\pm$ 0.5
Mean MCAv (cms ⁻¹)	69.2 $\pm$ 4.2	65.4 $\pm$ 4.3	66.8 $\pm$ 4.7
CVR (mmHg cm ⁻¹ s ⁻¹)	1.3 $\pm$ 0.1	1.4 $\pm$ 0.1 ^a	1.4 $\pm$ 0.1 ^a
ScO ₂ (%)	66.9 $\pm$ 1.7	66.1 $\pm$ 2.1	66.2 $\pm$ 2.1
HbO ₂ (μ M)	33.0 $\pm$ 3.0	32.3 $\pm$ 3.3	32.2 $\pm$ 3.2
dHb (μ M)	16.1 $\pm$ 1.2	16.1 $\pm$ 1.2	16.0 $\pm$ 1.2
etCO ₂ (mmHg)	41.4 $\pm$ 1.1	40.0 $\pm$ 1.3	40.0 $\pm$ 1.3
Respiration rate (breaths min ⁻¹)	12.3 $\pm$ 1.3	13.4 $\pm$ 1.3	11.9 $\pm$ 1.7

^a
p = 0.04 compared to baseline (one-way repeated measures ANOVA).

OLBNP, oscillatory lower body negative pressure; RRI, R-R interval; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MCAv, middle cerebral artery velocity; CVR, cerebrovascular resistance; ScO₂, cerebral oxygen saturation; HbO₂, oxy-hemoglobin; dHb, deoxy-hemoglobin; etCO₂, end-tidal carbon dioxide.

Table 2.Time domain cardiovascular responses to sub-maximal LBNP ($N = 21$).

Physiological parameter	Baseline	Sub-maximal LBNP
RRI (ms)	993 ± 28	631 ± 24^a
HR (beats min^{-1})	62.9 ± 1.8	98.3 ± 3.7^a
MAP (mmHg)	93.6 ± 1.5	86.9 ± 1.3^a
SV (ml)	100.6 ± 3.8	54.5 ± 3.0^a
% SV	0.0	-45.3 ± 2.5^a
CO (l min^{-1})	6.2 ± 0.3	5.2 ± 0.2^a
TPR ($\text{mmHg l}^{-1} \text{min}^{-1}$)	15.6 ± 0.7	17.3 ± 0.9^a
Mean MCAv (cm s^{-1})	62.1 ± 3.1	50.2 ± 2.7^a
CVR ($\text{mmHg cm}^{-1} \text{s}^{-1}$)	1.6 ± 0.1	1.8 ± 0.1^a
ScO ₂ (%)	67.2 ± 1.5	62.9 ± 1.6^a
HbO ₂ (μM)	34.2 ± 2.7	30.8 ± 2.5^a
dHb (μM)	16.2 ± 1.4	17.6 ± 1.4^a
etCO ₂ (mmHg)	41.7 ± 0.7	33.4 ± 1.5^a
Respiration rate (breaths min^{-1})	12.1 ± 0.7	12.3 ± 0.9

^a $p < 0.002$ compared with baseline (paired t -test).

LBNP, lower body negative pressure; RRI, R–R interval; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MCAv, middle cerebral artery CVR, cerebrovascular resistance; ScO₂, cerebral oxygen saturation; HbO₂, oxy-hemoglobin; dHb, doxy-hemoglobin; etCO₂, end-tidal carbon dioxide.