Assessing Cerebral Blood Flow Control from Variability in Blood Pressure and Arterial CO_2 Levels

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Abstract—**Blood flow to the brain is controlled by a number of physiological mechanisms that respond to changes in arterial blood pressure, arterial CO_2 levels and many other factors. Assessing the integrity of this control system is a major challenge. We report on repeatability of measures based on single and multiple input models during spontaneous and enhanced fluctuations in blood pressure.**

I. Introduction

The brain, more than any other organ in the body, requires a constant supply of blood in order to maintain its function. When blood pressure drops, small arteries dilate to restore flow levels, and when pressure rises, they constrict to protect the most delicate blood vessels and avoid bleeding in the brain. This control system can however become impaired, for example following stroke, head trauma, in dementia or following premature birth, and this has been associated with worse outcomes for the patient. Failure of the control system also has important implications for the management of patient's blood pressure: changes in blood pressure could be dangerous without the protection of this autoregulatory system. The current work is part of a larger project to improve methods for measuring cerebral autoregulation and to gain a deeper understanding of the complex relationship between blood pressure and blood flow, focusing on the diversity of ways in which brain blood flow may operate in different healthy individuals. An understanding of these individual differences is required for example for a personalized approach to managing blood pressure control after stroke to protect patients' brains from further damage.

The robust assessment of cerebral autoregulation (CA) presents major challenges, with no gold-standard having become established yet. There is considerable variability over time [1] and sometimes poor agreement between different approaches [2]. The assessment of autoregulation is typically based on modelling the dynamic relationship between arterial blood pressure (ABP) and cerebral blood flow (CBF) [3] using linear or non-linear approaches [4] and models may be augmented with additional inputs, most commonly arterial CO_2 levels [5]. Parameters are then extracted from these models to assess autoregulation; typically these include phase and gains in different frequency bands, or features extracted from the step-response [3]. Data recorded from subjects at rest are most commonly used, as this is also the protocol most easily applied to patients who are unable to undergo more challenging protocols, for example subjects in intensive care. The relatively low spontaneous variability of ABP during rest has been, not surprisingly, associated with reduced reliability [6]. A wide range of techniques have been used to increase ABP variations and thus the challenge to the autoregulatory system, including the inflation and release of thigh-cuffs, the Valsalva maneuver, sit-to-stand, squat-to-stand, cold pressors or sinusoidal lower-body negative pressure (LBNP). These may require subjects' collaboration and can be uncomfortable. In order to assess if rather less aggressive challenges can improve the assessment of autoregulation, we applied pseudorandom step-wise changes in lower-body negative pressure (LBNP). The objective of the current work is to assess the impact of this, coupled with multivariate analysis, on measures of autoregulation.

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II. Methods

A. Data Acquisition.

The study was performed on 15 healthy volunteered subjects (age 32±10 years, height 171±8 cm, weight 73±15 kg, 7 female) at the Southampton General Hospital and approved by the local Research Ethics Committee.

Cerebral blood flow velocity (CBFV) was recorded from the left and right middle cerebral arteries with a transcranial Doppler ultrasound instrument and a 2 MHz transducer (Multidop-t, DWL), while the subject was in supine position with the head elevated. Arterial blood pressure (ABP) was measured with a noninvasive servo-controlled finger cuff device (Finapres 2300, Ohmeda) which has been considered as a reliable alternative to invasive recording for beat-by-beat ABP variation. Respiratory pCO_2 was recorded with an infrared capnograph (Capnocheck, BCI). A surface electrocardiogram (ECG) was also measured (Diascope 1, Simonsen&Weel) and used for heartbeat detection and computing beat average values of the recorded signals.

To observe CA during both spontaneous and augmented ABP variations, data were analyzed (i) during rest (5 minutes) and (ii) during pseudo-random LBNP step-wise changes. For the latter, 20 step-wise changes of low-body negative pressure (LBNP) (from approximately −15 to −100 mmHg) with a duration of 5, 10 and 20 s were applied over 5 minute (see Fig. 1). The recordings were repeated on two separate occasions, between 2 and 25 days apart (9.9±6.2 days).

All signals were simultaneously recorded over the approximately 5 minute duration of the protocol (MP150, BIOPAC), sampled at a rate of 250 Hz (with an exception of

the ECG signal which was sampled at 500 Hz) and stored for offline analysis. The customized software written in Matlab was developed and employed to pre-process, visually inspect, mark bad data sections and extract the signals for further analysis.

B. Data Processing.

Isolated spike-like artefacts that commonly occur in CBFV signals were removed using the median filter of order 9 and the most prominent remaining ones were manually edited and removed by linear interpolation. All signals were then low-pass filtered using a fourth-order Butterworth filter with a cut-off frequency of 20 Hz applied in the forward and backward direction to compensate for phase shifts, and then manually edited to mark evident artefacts not removed in prevous stages. These segments were marked as missing data (in Matlab marked as not-a-number), i.e. they were neither interpolated nor removed by concatenation but left as gaps in the signals. This procedure ensures that most of the recorded data could be exploited, even when the original data quality was not consistently high. The length of gaps varied from 1 s to 47 s and the total amount of gapped data is 1.3% for ABP and 0.5% for CBFV. The end-tidal CO_2 ($etCO_2$) signal was derived from the individual breaths in the CO_2 signal combining automatic detection of the breathing cycles with manual adjustment of the detected breaths performed based on visual inspection. The $etCO_2$ is deemed to provide a good (non-invasive) approximation to arterial CO_2 in healthy subjects, breathing spontaneously at rest. The beginning and end of each cardiac cycle were detected from the ECG signal after which the beat average values of the ABP and CBFV signals were calculated. The signals ($etCO_2$, mean ABP and CBFV) were then linearly interpolated and resampled at 10 Hz. A complete set of one such recording is shown in Fig. 1. In the case of application of LBNP, the data were taken from the second onset of LBNP (marked with dotted lines in Fig. 1).

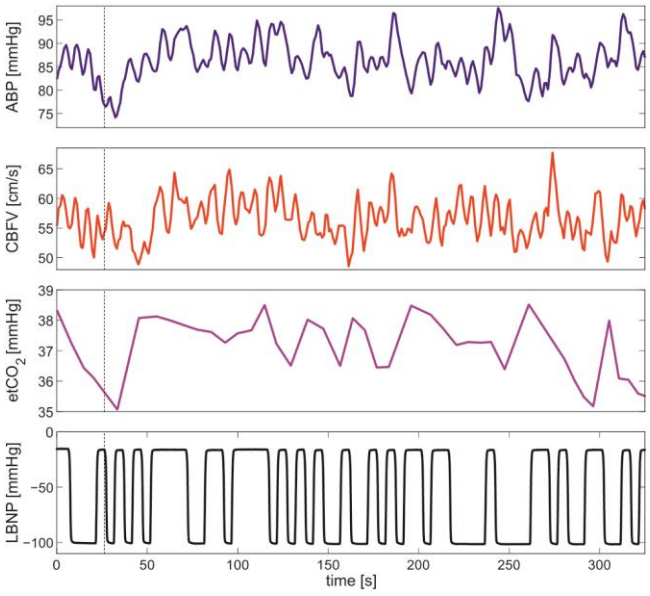

Figure 1. A sample recording with the mean ABP, mean CBFV, $etCO_2$, and LBNP signals sampled at 10 Hz.

In preparation for parametric system identification and in order to reduce the serial correlation between samples, the signals were decimated to a new sampling rate of 1 Hz after appropriate anti-alias filtering (zero phase) at 0.45 Hz. The mean ABP and CBFV signals were normalized by their mean values and detrended, such that both represent relative change of the signal expressed in %. The $etCO_2$ signal was calibrated in mmHg.

C. Data Analysis.

The relationship between mean ABP, $etCO_2$ and CBFV, denoted as $p(n)$, $c(n)$ and $v(n)$ respectively, can be modeled by multivariate parametric model (see Fig. 2) as:

$$\hat{v}(n) = \hat{v}_p(n) + \hat{v}_c(n) = \sum_{i=0}^{N_p-1} h_{pv}^{(i)} p(n-i) + \sum_{j=0}^{N_c-1} h_{cv}^{(j)} c(n-j) \quad (1)$$

where $h_{pv}^{(i)}$ and $h_{cv}^{(j)}$ ($0 \le i \le N_p-1$, $0 \le j \le N_c-1$) represent the causal FIR filter coefficients of the impulse responses $\mathbf{h}_{pv} = \left[h_{pv}^{(0)} \ \cdots \ h_{pv}^{(N_p-1)} \right]^T$ and $\mathbf{h}_{cv} = \left[h_{cv}^{(0)} \ \cdots \ h_{cv}^{(N_c-1)} \right]^T$, that can be derived by minimizing the mean square error function:

$$\sigma_e^2 = \frac{1}{N} \sum_{n=0}^{N-1} \left(v(n) - \hat{v}(n) \right)^2 , \quad (2)$$

where N is the length of available samples in the time series, taking into account that $\hat{v}(n)$ cannot be calculated for the first samples of the recording and that there are gaps in the signals resulting from the editing process. N_p and N_c are the lengths of the impulse responses $\mathbf{h}_{pv}$ and $\mathbf{h}_{cv}$ respectively (in this study N_p=10 and N_c=25, at the sampling rate of 1 Hz).

The optimal Wiener-Hopf solution for the input signals $p(n)$ and $c(n)$ is given as:

$$\mathbf{H} = \mathbf{R}_{xx}^{-1} \cdot \mathbf{R}_{xy} , \quad (3)$$

where the optimal multivariate (two-input) FIR causal filter vector $\mathbf{H}$ is represented as:

$$\mathbf{H} = \left[\mathbf{h}_{pv}^T \quad \mathbf{h}_{cv}^T \right]^T = \left[h_{pv}^{(0)} \ \cdots \ h_{pv}^{(N_p-1)} \ h_{cv}^{(0)} \ \cdots \ h_{cv}^{(N_c-1)} \right]^T , \quad (4)$$

and

$$\mathbf{R}_{xx} = \begin{bmatrix} \mathbf{R}_{pp} & \mathbf{R}_{cp} \\ \mathbf{R}_{pc} & \mathbf{R}_{cc} \end{bmatrix}, \ \mathbf{R}_{xy} = \begin{bmatrix} \mathbf{R}_{pv} \\ \mathbf{R}_{cv} \end{bmatrix} . \quad (5)$$

where $\mathbf{R}_{xx}$ is the $(N_p+N_c)\times(N_p+N_c)$ auto-correlation matrix formed of the auto-correlation and cross-correlation matrices of the input signals $p(n)$ and $c(n)$ and $\mathbf{R}_{xy}$ is the $(N_p+N_c)\times 1$ cross-correlation matrix of the input signals and the output $v(n)$.

Due to the strongly low-frequency nature of $etCO_2$, the matrix $\mathbf{R}_{xx}$ can become ill-conditioned thus increasing errors in determining its inverse. To overcome this, the $etCO_2$ signal was further downsampled by a factor of 5 to 0.2 Hz, after applying suitable anti-aliasing filter, as suggested in [5]. This was carried out by decimating the correlation matrixes rather than the signals themselves, which is equivalent to rewriting equation (1) as:

$$\hat{v}(n) = \sum_{i=0}^{N_p-1} h_{pv}^{(i)} p(n-i) + \sum_{j=0}^{N_c/m-1} h_{cv}^{(mj)} c(n-mj) , \quad (6)$$

where now m=5 (i.e. the filter $\mathbf{h}_{cv}$ only uses every fifth sample), and the filter length reduces to N_c/m. This approach was taken as the input signals of different sampling rate cannot be employed in (3), without discarding much data. It should be noted that here we estimate only the filter coefficients for the decimated $c(n)$ signal. This impulse response can be applied to the non-decimated (but anti-alias filtered) $c(n)$ signal by placing $m-1$ zeros in between each sample. As a result, the filter $\mathbf{h}_{cv}$ now has a non-zero response above the Nyquist frequency of the decimated $etCO_2$ signal (0.1 Hz), but this is not a problem since the anti-alias filter has removed any signal power above that frequency in $c(n)$.

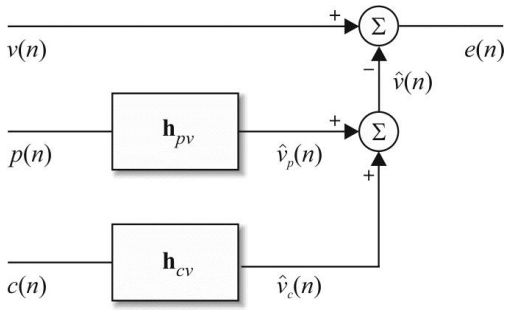

Figure 2. Multivariate model estimation.

For the univariate model [7], where only $p(n)$ is used as an input signal, the optimal FIR causal filter $\mathbf{H}$ was estimated employing equations (3)-(5) with $\mathbf{H} = \left[h_{pv}^{(0)} \ \cdots \ h_{pv}^{(N_p-1)} \right]^T$, $\mathbf{R}_{xx} = \mathbf{R}_{pp}$, and $\mathbf{R}_{xy} = \mathbf{R}_{pv}$.

In order to assess cerebral autoregulation, the mean values of the gain and phase were computed from the frequency responses of the estimated impulse responses $\mathbf{h}_{pv}$ for both the uni- and multivariate model for the two frequency bands: very low frequency (VLF) [0.02-0.07] Hz and low frequency (LF) [0.07-0.20] Hz. The normalized root mean square error is also reported for the estimated models. The repeatability of autocorrelation measures from the recordings taken on different days is assessed using the intra-class correlation coefficient (ICC).

III. Results

Table I shows the mean and standard deviation (calculated across the 30 files) of the key variables, demonstrating a significant change in ABP, CBFV, $etCO_2$ and HR (p<0.05, Wilcoxon) between protocols. Autoregulation measures (gain and phase in the LF band) did not change significantly (p>0.1). Repeatability of these basic measures of cardiovascular function, as quantified by the ICC (2,1), calculated between the repeated sessions, is high. Repeatability of autoregulation measures, comparing the measurements of autoregulation parameters from the first recording with those from the second recording are shown in Table II. The values are low and only in some instances reach statistical significance, indicating that repeatability across the group of healthy volunteers is very poor. There is a consistent increase in ICC values with the use of LBNP, compared to baseline-rest, except for phase in VLF. The use of the multivariate model did not notably improve the ICC, though it did (as expected) improve the model fit. At baseline the normalized rms error was 62%±12% and 48%±13% for the uni- and multivariate models respectively, decreasing to 44%±16% and 37%±14% for LBNP. The model fit was significantly improved for LBNP, compared to baseline (p<0.005, Wilcoxon).

Given the low ICC observed between sessions, the gain and phase from two consecutive segments of signal (the first 150 s and the second 150 s from the same recording session) were also compared with each other. ICCs are generally much higher, as indicated in Table III. Again, multivariate modeling did not notably improve repeatability.

TABLE I. The mean and standard deviation values of gain and phase in LF range, ABP, CBFV, $ETCO_2$ and HR calculated for the whole dataset.

	BASELINE		LBNP		BASELINE vs LBNP	
	mean	std	mean	std	ICC	PCC
$Gain^{UV}$ [%/%]	1.35	0.34	1.41	0.52	0.47[b]	0.51[b]
$Phase^{UV}$ [°]	35.16	11.57	36.67	13.15	0.56[b]	0.56[b]
$Gain^{MV}$ [%/%]	1.31	0.31	1.40	0.52	0.50[b]	0.57[b]
$Phase^{MV}$ [°]	35.83	11.70	37.06	13.29	0.67[a]	0.67[b]
ABP [mmHg]	87.15	11.31	83.95	12.71	0.68[a]	0.70[a]
CBFV [cm/s]	67.44	11.58	63.47	10.74	0.89[a]	0.94[a]
$ETCO_2$ [mmHg]	37.98	3.68	35.53	3.44	0.67[a]	0.83[a]
HR [b/min]	67.95	11.04	66.37	10.72	0.95[a]	0.96[a]

[a] $p<5\cdot10^{-5}$, [b] $p<5\cdot10^{-3}$, [c] $p<5\cdot10^{-2}$, [UV] univariate model, [MV] multivariate model

TABLE II. Intra-class correlation coefficients of the gain and phase calculated between two recording sessions

		Univariate model				Multivariate model			
		BASELINE		LBNP		BASELINE		LBNP	
		ICC	p	ICC	p	ICC	p	ICC	p
Gain	VLF	0.07	0.4014	0.74	0.0006	0.06	0.4041	0.61	0.0074
[%/%]	LF	0.05	0.4085	0.35	0.0962	0.12	0.2640	0.37	0.0866
Phase	VLF	0.38	0.0767	0.14	0.3190	0.26	0.1484	0.39	0.0758
[°]	LF	−0.10	0.6424	0.47	0.0383	−0.10	0.6329	0.54	0.0197

TABLE III. Intra-class correlation coefficients of the gain and phase calculated between two consecutive segments in the same recording. Pearson Correlation Coefficients (PCC) are also given.

		Univariate model				Multivariate model			
		BASELINE		LBNP		BASELINE		LBNP	
		ICC	PCC	ICC	PCC	ICC	PCC	ICC	PCC
Gain	VLF	0.60[b]	0.63[b]	0.73[a]	0.74[a]	0.53[b]	0.54[b]	0.62[b]	0.62[b]
[%/%]	LF	0.62[b]	0.61[b]	0.92[a]	0.92[a]	0.56[b]	0.55[b]	0.93[a]	0.93[a]
Phase	VLF	−0.17	−0.18	0.36[c]	0.36[c]	0.18	0.20	0.15	0.16
[°]	LF	0.73[a]	0.76[a]	0.79[a]	0.81[a]	0.64[b]	0.68[a]	0.75[a]	0.76[a]

[a] $p<5\cdot10^{-5}$, [b] $p<5\cdot10^{-3}$, [c] $p<5\cdot10^{-2}$

IV. Discussion and Conclusion

The assessment of autoregulation from spontaneous variability in blood pressure has been often reported, and impairment of autoregulation has been consistently observed when comparing different groups of patients with healthy subjects. However, a gold-standard method for assessing autoregulation has not yet become established and robustness of measures currently used has remained a concern [2]. The current work underlines that problem.

Poor repeatability of autoregulation measures between sessions is noted here. The results in the LF range are of most interest, since it is gain and phase in this frequency range that

is usually considered of most relevance to autoregulation. ICC (similar to the Pearson correlation coefficient (PCC)) is strongly affected by the amplitude range of the variables. Given that the sample here only included healthy volunteers, this range is relatively limited, reducing the ICC one might expect. A sample that includes both patients and healthy subjects is likely to provide higher ICC values. However, the use of LBNP improved consistency of the estimated phase in LF range between sessions.

The application of LBNP does not only affect the variability of ABP, it is also seen (perhaps surprisingly) to reduce heart-rate and $etCO_2$. The latter in particular is of concern, as hypocapnia is known to affect (enhance) autoregulation. In the current dataset, this does not appear to have occurred to any notable extent.

It is interesting to note that while the multivariate model clearly improved model fit, it did not lead to more robust estimates of cerebral autoregulation. This is perhaps not surprising, since $etCO_2$ predominantly affects the lowest frequencies [8], below the range that is of primary concern for the assessment of cerebral autoregulaton.

The comparison of ICC values from recordings within the same session with those taken on different days suggests marked changes occurring within subjects over time, rather than predominantly individual differences between subjects that may reflect distinct and stable phenotypes in autoregulatory function.

The results however need to be treated with some caution. The sample size is small and results may be quite strongly affected by the data segments selected. It is also still unclear if the dispersion (and hence low ICC) is due to noise or remaining artefacts in the signals, a poor choice of model or input variables included, poor choice of parameter extracted from the model to quantify CA, or reflects genuine changes in physiological function. Addressing these questions is a priority in the continuation of this work.

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