Assessing Inter-subject Variability in Cerebral Blood Flow Control Measurements

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Abstract— **The aim of this study is to assess inter-individual variability and repeatability in measures assessing blood flow control in the brain during spontaneous and enhanced fluctuations in blood pressure. There is clear evidence of inter-individual difference during enhanced blood pressure variability, but not at rest. This difference exceeds the within-individual variability by factor of 2.73.**

Keywords— **cerebral autoregulation, arterial blood pressure, cerebral blood flow control, inter-subject variability.**

I. INTRODUCTION

Cerebral autoregulation (CA) refers to the ability of the brain to maintain blood flow approximately constant in the face of varying blood pressure. Impairment of CA has been linked to a number of serious clinical conditions, including stroke and head-injury. Individual differences in the ability of healthy adults to regulate flow, as well as in other physiological functions [1], might be expected. However, inter-subject variability may be obscured by the inevitable errors in measurements, due to unavoidable noise in data, artefacts or within-subject physiological variability over minutes, hours or days. This problem is compounded by the fact that any parameter extracted from the measurements can only provide a partial representation of complex processes, often based on simplistic models fitted to the data. These resulting errors in estimating parameters will be referred to as measurement errors in this paper.

Inter-individual variability should be taken into account in defining the range of normality, and distinguished from dispersion due to errors in the measurement, since the latter may be under our control, but the former much less so. The objective of this study is to assess inter-individual variability while considering repeatability of measurements and choice of model order in calculating CA measures.

II. METHODS

A. Data Acquisition

The study was performed on 28 healthy normotensive volunteered subjects (age 34±9 years, height 174±8 cm, weight 71±11 kg, SBP 122±12 mmHg, DBP 76±8 mmHg, BMI 23±3, 13 female) at the University of Leicester and approved by the local Research Ethics Committee.

Arterial blood pressure (ABP) was measured with a noninvasive servo-controlled finger cuff device (Finapres 2300, Ohmeda), while the subject was in supine position. 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 (Companion III, Viasys) held in place using an elastic head band. A surface electrocardiogram (ECG) was also recorded (Diascope 1, Simonsen&Weel) and used for detection of heart beats and computing beat average values of the recorded signals.

To observe inter-subject variability during both spontanous and augmented ABP variations, data were analyzed using different system identification models during (i) rest period (baseline) and (ii) period of inflation and deflation of thigh-cuffs controlled by a pressure regulator. For the latter, a pseudo-random binary sequence with step-wise changes of thigh-cuff pressure (TCP) from 10 to 80 mmHg with a duration of 5, 10 and 20 s were applied (see Fig. 1). The recordings were repeated for each subject on two separate occasions, between 1 and 48 days apart (12.1±8.9 days).

All signals were simultaneously recorded over the approximately 5 min duration of the protocol, sampled at 250 Hz and stored for offline analysis. The customized software written in FORTRAN was used to pre-process, visually inspect, mark and interpolate bad data prior to further signal analysis carried out with in-house software written in Matlab®.

B. Data Processing

Isolated spikes that commonly occur in CBFV signals were removed using the median filter and the most prominent remaining ones were 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. The R-peaks were detected from the ECG signal after which the mean (beat average) values of the ABP and left and right CBFV signals (CBFV-L and CBFV-R respectively) were calculated for each cardiac cycle. The mean signals were then interpolated using a third-order polynomial and resampled at 5 Hz to create a time series

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with a uniform time base. A complete set of signals of one recording is shown in Fig. 1. The thigh-cuffs data were taken from the 2nd onset of TCP signal (marked with vertical dotted lines in Fig. 1).

The mean and standard deviation of the recorded signals calculated across all subjects for baseline (BL) and thigh-cuffs (TC) protocols are given in Table 1. The mean values for both CBFV-L and CBFV-R showed significant difference between two protocols (Wilcoxon test, $p<0.005$).

To reduce the serial correlation between samples, the mean ABP and CBFV signals were further decimated to a new sampling rate of 1 Hz after appropriate anti-alias filtering (zero phase) at 0.45 Hz. The signals were then normalized by their mean values and detrended, thus representing relative change of the signals and expressed in %.

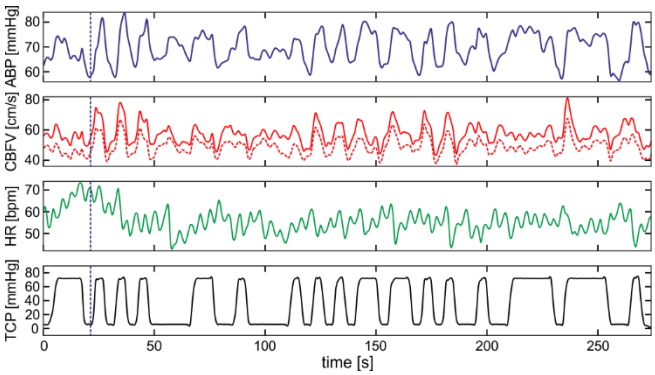

Fig. 1 Sample of the recording with the mean ABP, mean CBFV-L (solid line) and CBFV-R (dashed line), heart rate (HR) and TCP signals.

Table 1 The mean and standard deviation values of mean ABP, CBFV-L and CBFV-R and heart rate calculated across all data segments.

	ABP [mmHg]		CBFV-L [cm/s]		CBFV-R [cm/s]		HR [bpm]	
	mean	Std	mean	std	mean	std	mean	std
BL	88.0	14.5	57.0	11.8	55.9	13.4	68.3	8.6
TC	90.0	13.5	54.6	12.2	52.7	12.5	67.3	7.7

C. Data Analysis

The linear parametric system identification models have been extensively used in assessing CA, which can be quantified through gain and phase in different frequency bands [2]. In the current work this approach has been used based on the following black-box models: (i) the least-square FIR filter denoted as FIR(N_n) where N_n is the filter order (corresponding to the number of zeros in the transfer function) varying from 1 to 20, and (ii) the least-square IIR filter, denoted as IIR(N_n,N_d), where N_n and N_d are the order of numerator and denominator respectively (i.e. the number of zeros and poles in the transfer function), N_n was varied from 0 to 20 and N_d from 1 to 3. The mean values of the gain and phase were then computed from the estimated frequency responses of the filter for the three frequency bands: very low frequency (VLF) [0.02-0.07] Hz, low frequency (LF) [0.07-0.20] Hz and high frequency (HF) [0.20-0.50] Hz. The gain and phase values used in this analysis were averaged between values obtained for CBFV-L and CBFV-R. The consistency of these CA measures for the recordings taken on different days for each individual subject was assessed using the Bland-Altman plots and the intra-class correlation coefficient (ICC). Akaike and Bayesian information criteria (AIC and BIC) were used to estimate the best model fit accounting for the number of estimated parameters and observations included, and the optimal orders identified were compared with those seen to maximize repeatability and ICC between repeated measurements.

III. Results

A. Bland-Altman Plots

A Bland-Altman plot is one of the most extensively used statistical methods for assessing agreement between two measurement methods when a true gold standard is not known [3-5]. It can also be used to assess the repeatability of measurements. In that case, the Bland-Altman plot shows the difference between the two measurements, which represents the amount of disagreement, on the y-axis, against the average of the two measurements, which represents the best estimate of the real value, on the x-axis. The spreads of data across x and y-axes relate to the inter- and intra-subject differences respectively.

An example of the Bland-Altman plots of the phase in the LF range for BL and TC data is given in Fig. 2. Horizontal reference lines are: (i) the mean of differences, denoted as μ, which represents a fixed bias and should be zero since the same method is used, (ii) the lower and upper limits of agreement (LA), denoted as $\mu\pm1.96\sigma$, where σ is the standard deviation of differences between the two measurements (M1 and M2), indicating the magnitude of systematic difference, (iii) the 95% confidence interval (CI) band of the mean of differences and (iv) reference line at y=0 (the zero bias line). In addition, the coefficient of repeatability (CR) can be calculated as CR=1.96σ, where smaller values for CR indicate smaller intra-subject variability and therefore better repeatability of the measurements.

The plots in Fig. 2 show that the LF phase has much smaller CR and slope for TC data (CR=12.69°, $slope$=0.13, μ(95%CI)=2.28° (-0.23, 4.79)) indicating better agreement of the estimated values compared to those for BL data (CR=33.71°, $slope$=-0.50, μ(95%CI)=3.63° (-3.04, 10.30)). Moreover, it can be seen that the variability of estimated phase is not related to its amplitude (i.e. difference between two measurements does not increase with their mean value).