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Implementing transfer function analysis method and autoregulation index to assess cerebral autoregulation: a preliminary study

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Background, Motivation and Objective. The brain cannot tolerate significant volume increases due to the rigid enclosure represented by the skull. Moreover, the brain's ability to store energy is very limited, making it uniquely dependent on a continuous, and adequate, supply of substrate. An important mechanism that regulates the homeostatic circulatory balance in the human brain is called cerebral autoregulation (CA). CA is the mechanism that maintains cerebral blood flow (CBF) relatively constant over a wide range of blood pressure (BP). Changes in BP trigger vasomotor adjustments in cerebral vascular resistance, by changing arteriolar diameter, in an attempt to maintain CBF constant. In the case of a reduction in BP, dilatation of the arteriolar bed occurs and cerebral perfusion is maintained. In addition to providing protection against cerebral ischemia due to arterial hypotension, the autoregulatory mechanism also protects cerebral vessels against excessive flow during transient or chronic arterial hypertension, which could damage capillaries or lead to intracranial hypertension because of the corresponding increase in cerebral blood volume. Different methodologies have been proposed in the literature to quantitatively evaluate CA. The methods most commonly used describe the relationship between BP and CBF as a linear dynamic system in the frequency domain or time domain, are called Transfer Function Analysis (TFA) and auto regulatory index (ARI) methods, respectively. Recently, the Cerebral Hemodynamic Regulation Network (CARNet) has set up guidelines for standardization of parameters and settings adopted for application of TFA in CA studies. Therefore, this study aimed to implement both TFA and ARI methods by using the CARNet guideline.

Methods. Bilateral CBF velocity (CBFv) and BP were acquired during 5 min with Transcranial Doppler (Doppler-Box) and Finometer (PRO-Finapress) (sampling frequency, Fs= 100 Hz) from 4 participants of each group: Control, Stroke and Sepsis. All analysis was done in Matlab (R2014a). Preprocessing: the time of the start and the end of each cardiac cycle was segmented on both CBFv and BP signals, allowing beat-to-beat detection (refractory period threshold of 350 ms). Then, each beat cycle average was calculated and placed at the centre beat time position in surrogate signals (Fs_{mean} around 1.9 Hz). It follows by signals interpolation at 4 Hz using spline interpolation and calculation of the power spectrum by the Welch method (segments of 100 s, 50% overlap and Hanning window, F_{res} 0.01 Hz). The BP auto-spectrum (P_{BP}) and the cross-spectrum between BP and CBFv ($P_{CBFv\text{-}BP}$) were calculated to obtain the CA transfer function ($TFA=P_{BP}/P_{CBFv\text{-}BP}$). With the TFA signal, gain, phase, and coherence were obtained in three frequencies band: very low frequency (VLF, 0.02-0.07Hz), low frequency (LF, 0.07-0.2 Hz) and high frequency (HF, 0.2-0.5Hz). CA has been previously described as "high-pass filter" phenomenon. This indicates that, in a relatively high frequency range (>0.02 Hz), autoregulation may be less effective, and changes in BP may transfer simply to changes in CBFv. In the TFA, gain quantifies the damping effect of CA on the magnitude of the BP oscillations. A low gain indicates an efficient autoregulation, whereas an increase in gain represents a diminished efficiency of CA. In terms of

phase, a positive shift difference indicates an intact CA, whereas complete loss of CA is represented by phase shift close to zero. The coherence function, tests the linear relation between BP and CBFv, where values close to zero suggests no linear relationship between the signals, indicating effective CA. TFA proceeds with the participants ARI determination, where firstly the inverse Fourier Transform (IFFT) is applied to the TF signal and then low-pass filtered at 0.5 Hz with a forward-backward Butterworth filter of order 10. The resulting signal is compared with the 10 ARI curves (0 until 9) from the Tiecks model where the root mean square error (RMSE) with the smallest error is used to determine participant ARI value (ARI<4 suggests impaired CA, otherwise effective CA).

Results. CBFv data from 5 participants was discarded due noise (left side from 1 control and stroke patient, 2 left and 1 right sides from the sepsis group). The results are summarized in Table 1. Cells with no values (--) show that their respective confidence magnitude squared values were lower than 0.34 and excluded from the analysis. Controversially, controls presented the highest gain in the three frequencies bands. This was also seen in previous studies with higher population, highlighting the inherent physiological variability among individuals. From our phase results, no systematic pattern of response could be seen among groups, and analysis limited to the LF band. All three subjects groups presented lower coherence values (ranging from 0.19 to 0.50), with exception of LF in controls, indicating CA impairment. Stroke and sepsis participants showed lower values compared to controls, indicating poor CA. ARI estimation seems to change according to the impulse response segment duration. When much longer segment durations were considered (> 5 s), control subjects also showed to have their minimum RMSE proximally to low ARI values.

Discussion and Conclusions. We have successfully implemented both TFA and ARI methods to assess CA. Although no further clinical conclusions could be drawn due to the small group of participants, this preliminary analysis showed that the TFA parameters for the controls highlights an inherent physiological variability with outcomes close to the remaining groups. Determination of the patient ARI showed sensitive to the impulse response segment duration choice for RMSE estimation. Analysis using a higher number of participants is ongoing as well as the development of a graphic user interface for future research monitoring of CA at bedside by clinicians.

Table 1. Mean TFA and ARI results

		Gain			Phase (rad)			Coherence			ARI
		VLF	LF	HF	VLF	LF	HF	VLF	LF	HF	
Control	Right	1.45(0.48)	1.83(0.70)	1.90(0.88)	1.02(0.01)	-1.79(0.48)	-1.52(0.86)	0.19(0.05)	0.63(0.29)	0.32(0.09)	5(1)
	Left	1.48(0.39)	2.07(0.55)	2.32(0.18)	1.04(0.01)	-2.12(0.53)	-2.17(0.63)	0.28(0.04)	0.81(0.08)	0.26(0.07)	4(1)
Stroke	Right	0.75(0.08)	0.60(0.06)	0.46(0.14)	--	-1.87(2.30)	1.09(1.37)	0.30(0.09)	0.34(0.16)	0.27(0.22)	1(1)
	Left	0.44(0.33)	0.44(0.07)	0.56(0.14)	--	-1.28(0.23)	-0.71(1.15)	0.20(0.14)	0.47(0.31)	0.50(0.25)	3(1)
Sepsis	Right	1.38(0.01)	1.52(0.17)	1.40(0.05)	0.17(0.01)	-0.04(0.03)	0.02(0.04)	0.33(0.24)	0.33(0.18)	0.20(0.08)	0
	Left	1.30(0.40)	1.17(0.01)	2.10(0.01)	--	0.90(0.01)	-0.17(0.01)	0.33(0.03)	0.18(0.12)	0.20(0.15)	0

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Keywords. Cerebral autoregulation; transfer function analysis; autoregulation index; signal processing and modelling; neurological patients.