Investigation of the correlation between low frequency oscillations of cerebral haemodynamics and systemic blood pressure

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1 Introduction

Diastolic blood pressure (DBP) and cerebral oxyhaemoglobin concentration (cHbO2) oscillate spontaneously at a range of frequencies [1]. Of particular interest is the low-frequency (LF) oscillation (LFO), which occurs in the range of 0.04-0.15 Hz. DBP LFO can be formed by long-period instabilities in the autonomic nervous system; however, other contributors to LFO, particularly those concerning the vasomotion thought to elicit cHbO2 LFO, are still under investigation [2].

DBP LFO tends to increase in amplitude following head-upright tilt table testing [3]. Recently, it has been shown that cerebral cHbO2 LFO exhibits a similar trend [4]. The question which the present study addresses is whether these two types of LFO act independently. If a causal link could be excluded, this might suggest that patients with cerebral autoregulatory failure (an inability to properly control blood flow to the brain in the face of systemic challenges) should be identifiable by a transmission of LFO from DBP to cHbO2. To test this hypothesis, the correlation between the two types of LFO was computed for patients with primary autonomic failure – pure autonomic failure (PAF) or multiple system atrophy (MSA) – as well as for healthy controls.

2 Patient Protocol

Nine patients with PAF (mean age 67±8), 7 patients with MSA (mean age 55±9), and 10 healthy controls (mean age 62±7) took part in this study. After an initial 10-minute resting period in the supine position, the subject was tilted upright to an angle of 60° for another 10 minutes and then returned to the supine position for an additional 10 minutes. Head-upright testing was interrupted if severe symptoms of orthostatic intolerance occurred, whereupon the patient was immediately returned to the supine position.

A continuous-wave near-infrared spectrometer with a sampling rate of 6 Hz (NIRO 300, Hamamatsu Photonics KK) was used to measure changes in cHbO2 using the modified Beer-Lambert law. The probe was placed on the forehead (taking care to avoid the midline sinuses) and was shielded from ambient light by using an elastic bandage and a black cloth; the studies took place in a darkened room. In addition, a Portapres system (TNO Institute of Applied Physics) was used to measure non-invasively on a beat-to-beat basis the blood pressure (BP) in the finger.

3 Data Analysis

3.1 Preprocessing

Following automated artefact removal, DBP was extracted from the continuous BP trace using a trough-detection algorithm. The cHbO2 and DBP time series were re-sampled to 1 Hz, using cubic-splines interpolation, and bandpass-filtered to eliminate frequencies lower than 0.04 Hz or higher than 0.15 Hz. For each patient, three periods were selected for analysis: 3 minutes in the supine position (P1), the last 3 minutes of the first 5 minutes in the upright position (P2), and the final 3 minutes in the upright position (P3).

3.2 Correlational Analysis

For each of the three periods, correlations were examined in two ways. First, Pearson's product-moment correlation coefficient was calculated:

$$r = \frac{\mathrm{cov}(O_2Hb, DBP)}{s_{O_2Hb} s_{DBP}} \quad (1)$$

where *cov()* represents covariance, and *s* standard deviation. This was repeated five times for time lags of 0, 1, 2, 3, and 4 seconds, to recognise the possibility that DBP may affect cHbO2 after a time delay. Second, the two time series were divided into 10-second segments, and the energy of each segment was calculated. The correlation of these energies was calculated in a similar manner as in (1), with the result r_{energy}.

3.3 Statistical Analysis

Simple hypothesis testing was used to confirm whether *r* was statistically different from zero, with a one-tailed 99% confidence level (the use of $z_{critical} = 2.88$ reflected a Bonferroni correction for the 5 time lags). A two-

tailed test was unnecessary since it was inconceivable that cHbO2 and DBP could be negatively correlated. Correlation coefficients higher than $\frac{z_{critical}}{\sqrt{N-2}}$ were considered significantly nonzero, where N represented one of two possibilities: N was simply the sample size (180) in cases of insignificant first-order autocorrelations in either cHbO2 or DBP, whereas N was the "effective sample size" [5] in cases of significant ($p<0.05$) autocorrelation:

$$N = 180\frac{1-r_{1,O_2Hb}r_{1,DBP}}{1+r_{1,O_2Hb}r_{1,DBP}} \quad (2)$$

where $r_{1,x}$ represents the first-order autocorrelation coefficient of time series x. In addition, r_{energy} was tested similarly using $z_{critical} = 2.326$, with no Bonferroni correction. The importance of this test is made apparent by the following example. Whereas two independent 10-s oscillators could be expected to exhibit a strong correlation provided an appropriate time lag is introduced to align their phase, r_{energy} offers evidence that the amplitude modulation of the oscillators occurs simultaneously.

4 Results

Four PAF patients, two MSA patients, and no controls, experienced syncope or presyncope during the upright portion of the test. As expected, no significant negative correlations were found between cHbO2 and DBP in any subject. Table 1 demonstrates the positive correlations which were found in some cases.

		No correlation			***r correlation***			***r_{energy} correlation***			***r and r_{energy} correlations***		
	n	***P1***	***P2***	***P3***	***P1***	***P2***	***P3***	***P1***	***P2***	***P3***	***P1***	***P2***	***P3***
PAF patients	9	89	56	56	0	22	44	11	0	0	0	22	0
MSA patients	7	71	57	29	14	43	71	14	0	0	0	0	0
Controls	10	60	70	80	20	20	20	0	0	0	20	10	0

Table 1. Percentage distribution (%) of significant ($p<0.01$) correlations. n represents the number of patients.

5 Discussion

Several theories concerning the cause of cHbO2 LFO rely on the existence of a cerebral oscillator [2]. The current work supports the existence of an independent oscillator in the brain, since many controls and patients failed to exhibit correlations between cHbO2 and DBP LFO. However, it is notable that several controls and patients did show such correlation. Since the controls did not suffer from cerebral autoregulatory failure, the hypothesis stated in the introduction was refuted: autoregulatory failure cannot be diagnosed by the conduction of LFO from DBP to cHbO2. Rather, the entrainment of two oscillators – one systemic, one cerebral – appears to be possible within the bounds of normal cerebral autoregulation. Such entrainment was likely to occur only for 2 PAF patients and 2 controls, who appear in the rightmost section of Table 1.

The main findings of this work are that (a) cHbO2 LFO can occur independently of any perceivable influence from the systemic vasculature, presumably by a separate cerebral mechanism; and (b) more interestingly, cerebral autoregulation need not be impaired for LFO conduction to occur from the systemic to the cerebral blood vessels. The latter finding may offer an important contribution to researchers modelling cHbO2 LFO.

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