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Optimising the assessment of cerebral autoregulation from black box models

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ABSTRACT

Cerebral autoregulation (CA) mechanisms maintain blood flow approximately stable despite changes in arterial blood pressure. Mathematical models that characterise this system have been used extensively in the quantitative assessment of function/impairment of CA. Using spontaneous fluctuations in arterial blood pressure (ABP) as input and cerebral blood flow velocity (CBFV) as output, the autoregulatory mechanism can be modelled using linear and non-linear approaches, from which indexes can be extracted to provide an overall assessment of CA. Previous studies have considered a single – or at most a couple of measures, making it difficult to compare the performance of different CA parameters. We compare the performance of established autoregulatory parameters and propose novel measures. The key objective is to identify which model and index can best distinguish between normal and impaired CA. To this end 26 recordings of ABP and CBFV from normocapnia and hypercapnia (which temporarily impairs CA) in 13 healthy adults were analysed. In the absence of a 'gold' standard for the study of dynamic CA, lower inter- and intra-subject variability of the parameters in relation to the difference between normo- and hypercapnia were considered as criteria for identifying improved measures of CA. Significantly improved performance compared to some conventional approaches was achieved, with the simplest method emerging as probably the most promising for future studies.

1. Introduction

The active control of the diameter of small cerebral blood vessels protects the brain against injury due to insufficient or excessive blood flow following a temporary drop or surge in arterial blood pressure (ABP). This regulatory mechanism is usually referred to as Cerebral Autoregulation (CA). Autoregulation is of great clinical interest as it can be impaired or lost in a number of conditions, such as stroke [1], subarachnoid haemorrhage [2] or head trauma [3]. In much of the published literature, blood flow velocity is recorded by the safe and non-invasive Doppler ultrasound method in response to transient changes in ABP. Sudden deflation of a thigh cuff, large sinusoidal variations in lower-body negative pressure, periodic breathing or squatting, and the Valsalva manoeuvre have all been used to provoke larger changes in ABP [4]. However, the most desirable experimental protocol for assessing CA is to record data from subjects at rest without performing any specific manoeuvres; this is especially relevant for patients during surgery or in intensive care, those highly vulnerable (e.g. neonates), or otherwise unable or unwilling to cooperate. Many recent studies have thus focused on using only spontaneous fluctuations of ABP for the assessment of CA. Even though this approach increases challenges in terms of analysing the recorded signals, and intra and inter-subject variability is high, its effectiveness has been repeatedly demonstrated [4–6].

Algorithms already described in the literature for estimating CA involve system identification (black-box modelling) to represent the relationship between ABP and cerebral blood flow velocity (CBFV). Most of the studies of CA focus on linear methods [5,7–10] with the more recent inclusion of some non-linear approaches [8,10–13]. Although non-linear techniques can provide improved model fits, their benefit in assessing CA is still unclear with few studies having systematically compared them to linear alternatives.

In the investigation of CA from linear models, parameters extracted from the frequency-, the impulse- or step-response of the models have been used to grade CA. Examples of such autoregulatory parameters include gain, phase and coherence in selected frequency ranges [5,7,8,14], or alternatively features of the step-response – e.g. slopes or amplitudes at selected points [9,14]. An

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alternative method is provided by the autoregulatory index ARI [15]: this varies from 0 (absent CA) to 9 (excellent CA), with each corresponding to a specific linear filter. The filter that best fits the data determines the ARI for the recording, and this can be applied to spontaneous as well as induced blood pressure variations [16,17]. The correlation of the ABP and CBFV time series [18] known as the Mx index has also been very extensively used (e.g. [19]). The majority of published studies have considered one or two measures of CA for the analysis of cerebral blood flow control from spontaneous variations [10,14], and no single parameter has become accepted as a gold standard. To date, it is not clear which combination of model and parameter for the assessment of CA is the most appropriate for future research and clinical practice.

The exploratory work in the current paper aims to compare a range of alternatives and recommend most promising methods. We investigate the performance of both linear and non-linear models, and compare different measures extracted from the models to assess CA. In the continuing absence of a gold standard measure of CA, the autoregulatory parameters are evaluated on a sample of signals recorded from healthy volunteers in whom temporary impairment of CA was induced by hypercapnia [20,21]. Based on the results, we suggest some promising autoregulatory measures for application in future physiological and clinical studies.

2. Methods

2.1. Data collection and pre-processing

The study was performed on 13 healthy volunteer subjects (age 32 ± 8.8 years) and was approved by the local Research Ethics Committee. All recordings were made with subjects in the supine position with the head elevated. Middle cerebral artery velocity was measured using a Transcranial Doppler Ultrasound system (Scimed QVL-120) in conjunction with a 2 MHz transducer held in position by an elastic headband. Simultaneously arterial blood pressure (ABP) was non-invasively monitored using a finger cuff device (Ohmeda 2300 Finapress Bp monitor). End-tidal CO_2 ($EtCO_2$) levels were monitored via an infrared capnograph (Datex Normocap 200). Each recording began with a period of breathing ambient air for approximately 5 min, followed by approximately 2 min of elevated (EtCO2) due to the inhalation of 5% CO_2 in air.

The maximum velocity envelope and the ABP signals were digitised at 200 Hz. After the removal of spikes and other artefacts, the start of each heart cycle was automatically identified (with visual correction) from the ABP signal, and average ABP and CBFVs were calculated for each heartbeat. This time series was then interpolated with a third-order polynomial, and sampled at a constant rate of 5 Hz.

2.2. Modelling and data analysis

For each subject a segment of data was selected from before (normocapnia – NC) and during 5% CO_2 breathing (hypercapnia – HC). The former were approx. 300 s long and the latter 120 s. The initial transients at the onset of HC were removed until the signals were deemed stable, following visual inspection. The signals were decimated to a new sampling rate of 1 Hz, following anti-alias filtering with a cut-off frequency at 0.5 Hz. These segments of the recordings were normalised by their respective mean values (as used in previous works e.g. [8,22,23]), and the relative change (expressed in %) will be denoted by %ABP and %CBFV, respectively – see Fig. 1.

For both linear and non-linear models, %ABP was the input and %CBFV the output. Linear models were estimated according to the usual least-mean-squares approach. A fifth order (6 coefficient) FIR filter [6] was chosen in order to obtain a parsimonious model which includes the main early part of the autoregulatory response [6,24]. The frequency response ('transfer function') was then obtained by applying the Fourier Transform to the impulse response. A 2nd order Volterra–Wiener model, as previously proposed [8,12,25], was also estimated using the Wiener–Laguerre (W–L) estimation procedure (for more details see for example [8]). The number of lags used for both the linear and non-linear kernels was 12 samples (i.e. 12 s in duration) and 6 filters were used for the Laguerre expansion.

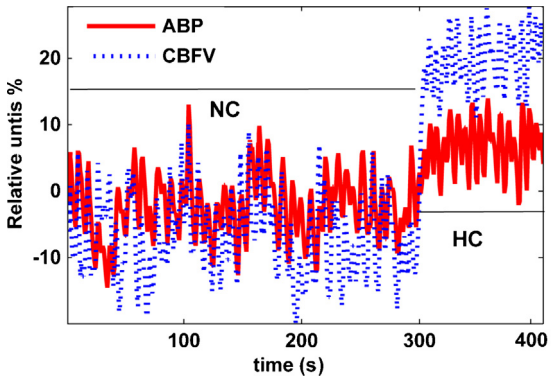

Fig. 1. Representative recording of ABP (arterial blood pressure) and CBFV (cerebral blood flow velocity) changes following inhalation of 5% CO_2 in air. The first 300 s correspond to normocapnia (NC), and the last segment (120 s) to hypercapnia (HC).

3. Assessment of cerebral autoregulation

3.1. Selection of autoregulatory parameters

The final value of the models response (both linear and non linear) after applying an idealised step (see Fig. 2A) is a commonly used approach [6,8,26] to assess CA, and will be denoted as FVS (Final Value from the Step); in absent CA, FVS remains elevated [15]. Also, the amplitude at 3 s was calculated and expressed as a percentage change from the initial segment of the response (amplitude at 1 second) – denoted PCS (Percentage Change from the Step), as this was shown to be more robust than FVS [6].

In [27] a broadband filtered impulse (generated by applying a Gaussian window to a cosine wave at 0.08 Hz – Figs. 2B and 3A) was proposed as an alternative test input. This is visually similar to spontaneous fluctuations observed in recorded ABP signals (Fig. 3B), and has a centre frequency in the range previously used in the assessment of CA from gain or phase [5,8,19]. The response to this input will be denominated as the pressure-pulse-response (PPR).

Figs. 2B and 3A show the expected left-shift (phase lead) in the PPR [7] resulting from the high-pass characteristics of the autoregulatory response [5,14]. Results from preliminary work [13] based on simulations using Tiecks model [15] and recorded data showed that the PPR at 1.5 s (A1.5) and the amplitude at 7 s (A7) (as shown in Fig. 3A) provide good separation of different levels of CA and are thus selected for inclusion in the current study.

From transfer function analysis the average phase (Pha) and coherence (Coh) were estimated in the frequency range from 0.07 Hz to 0.2 Hz [5,24]. Using the correlation method [18], Mx was estimated as the average Pearson's correlation coefficient of four equal segments of the %ABP and %CBFV time series. The Autoregulatory Index ARI was calculated by evaluating the set of models proposed in [15] using the parameter values given by the authors. In each recording, the model was applied to the %ABP signal and the model leading to the highest correlation coefficient between the model generated velocity and the measured %CBFV determined the