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Nonstationarity of dynamic cerebral autoregulation

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ABSTRACT

Dynamic cerebral autoregulation (dCA), the transient response of cerebral blood flow (CBF) to rapid changes in arterial blood pressure (BP), is usually quantified by parameters extracted from time- or frequency-domain analysis. Reproducibility studies of dCA parameters and consideration of the physiological determinants of the dynamic BP-CBF relationship provide strong indications that dCA is a nonstationary process. As a consequence, new analytical approaches are needed to estimate dCA parameters with greater temporal resolution thus allowing its longitudinal patterns of variability to be assessed in health and disease states. Techniques proposed for this task include ARMA models with moving windows, recursive least-squares, Laguerre–Volterra networks, wavelet phase synchronisation, and multimodal pressure-flow analysis. Initial results with these techniques have revealed the influence of some key determinants of dCA nonstationarity, such as $PaCO_2$, as well as their ability to reflect dCA impairment in different clinical conditions. One key priority for future work is the development and validation of multivariate time-varying techniques to minimise the influence to the many co-variates which contribute to dCA nonstationarity.

1. Introduction

The vital supply of oxygen to the brain is thighly controlled by several regulatory mechanisms, including cerebral blood flow pressure-autoregulation that maintains blood supply to the brain approximately constant, despite changes in mean arterial blood pressure (BP) within the range 60–150 mmHg [94]. Within these limits, cerebral autoregulation (CA) protects the brain from ischaemia due to hypotension and also prevents capillary damage due to surges in BP. Early studies of CA in humans relied on indicator-dillution methods for measurement of cerebral blood flow (CBF) which could not provide information about the response time of CBF recovery following sudden changes in BP [50]. This limitation was overcome with the introduction of transcranial Doppler ultrasound (TCD), which could then reflect the transient response of CBF velocity (CBFV) to sudden changes in mean BP. This new approach to study CA was termed *dynamic cerebral autoregulation* in contrast to methods based on measurements of CBF and BP averaged over several minutes which are now referred to as *static* CA [2,75,109].

In addition to the sudden release of inflated thigh cuffs introduced by Aaslid et al. [2], the Valsalva manouever [108], changes in posture [4,17,41,103], synchronised breathing [22,26], rhythmic hand grip [49], and lower body negative pressure [5,25,118], were some of the manoeuvres used to provoke changes in mean BP and a corresponding transient response in CBFV to allow assessment of dynamic CA. A major advantage of dynamic CA is the possibility of obtaining estimates of its efficiency, based on beat-to-beat spontaneous fluctuations in BP which induce corresponding fluctuations in CBF [75,86]. This possibility offers the best approach to assess dynamic CA in volunteers and patients at rest whilst maintaining stable physiological conditions, thus reducing the influence of any other intervening variables, such as changes in autonomic nervous system activity [114,120].

Despite considerable progress achieved in the last two decades, there are still concerns about the reliability of different indices or parameters used for assessment of CA. One of the tenets of measurement science is that measurements should be reproducible, but this is only possible if the quantity to be measured remains constant, at least between the two separate measurements. Is this the case with dynamic CA? The main objective of this review is to address this question, by examining the evidence available in the literature and by discussing the different modelling and analytical techniques that might help to shed light on the temporal variability of dynamic CA. More broadly, the problem can be framed around the concept of *stationarity*. A random process is defined as stationary if all its statistical moments remain constant over time. In most practical situations this rigorous definition cannot be met and the more pragmatic definition of *weak stationarity* is usually adopted, requiring that only the first (mean) and second

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(variance) moments remain constant over time [3]. In the literature there is often confusion about the statistical concept of stationarity and the lay use of the term to reflect physiological stability or homeostasis. Both uses of the term are relevant, but the review will give greater importance to the latter. Moreover, emphasis will also be given to identifying and understanding the nonstationarity of CA under the most stable physiological conditions possible, thus implying greater focus on measurements performed at rest, based on spontaneous fluctuations of mean BP and CBF, rather than during physiological manoeuvres that are more likely to lead to changes in CA.

2. Classical analysis of dynamic CA

The literature on assessment of dynamic CA based on spontaneous fluctuations of BP and CBF is dominated by the use of transfer function analysis (TFA) using beat-to-beat values of mean BP as input and corresponding values of CBFV as output [6,31,75,76,87,90,119]. The most common implementation of TFA is via cross-spectral analysis, using the Welch method to obtain spectral estimates with the Fast Fourier Transform (FFT) algorithm [116]. The main parameters of interest derived from TFA are the coherence function, the amplitude ('gain') frequency response and the phase frequency response [3,76]. A representative set of results is given in Fig. 1. Of note, under steady-state conditions the phase between BP and CBFV is positive when CA is preserved [4,22,41]. In addition to the frequency-domain parameters, TFA can also provide time-domain estimates of the CBFV step response using the inverse FFT of gain and phase (Fig. 1D). The CBFV step response gives a very useful visual indication of the efficiency of CA, and it can also be quantified by estimation of the ARI index, with the least-squares fitting of the step response templates proposed by Tiecks et al. [109]. Physiological and clinical studies based on TFA of spontaneous fluctuations provide indications that impairment of CA leads to increases in coherence for frequencies below 0.05 Hz [31], increases in gain [52,74,111,121], a reduction in phase [4,22,36,90], and a slower rate of decay of the CBFV step response, with a corresponding reduction in the values of ARI [88,93,109]. Of these, the phase and the ARI index have shown the greatest promise in clinical studies [77,78].

In addition to TFA, dynamic CA during spontaneous fluctuations in mean BP and CBF have been studied with other linear and non-linear modelling techniques. The main approaches have been the coherent averaging of spontaneous BP transients [81,86], moving average (or finite impulse response, FIR) filters [66,82,92,104,105], autoregressive moving average models (ARMA) [29,32,43,54,56,57,122], the multimodal pressure-flow method [70], cross-correlation analysis [15,16,107], and neural networks [14,80].

3. Reproducibility of dynamic CA

Reproducibility studies of parameters used to assess dynamic CA have been performed with a number of different protocols to induce changes in BP, such as lower body negative pressure [5], sit-to-stand manoeuvre [112], carotid artery compression [106] and the thigh-cuff technique [62]. However, to keep the focus on estimates derived from spontaneous fluctuations of BP and CBF,

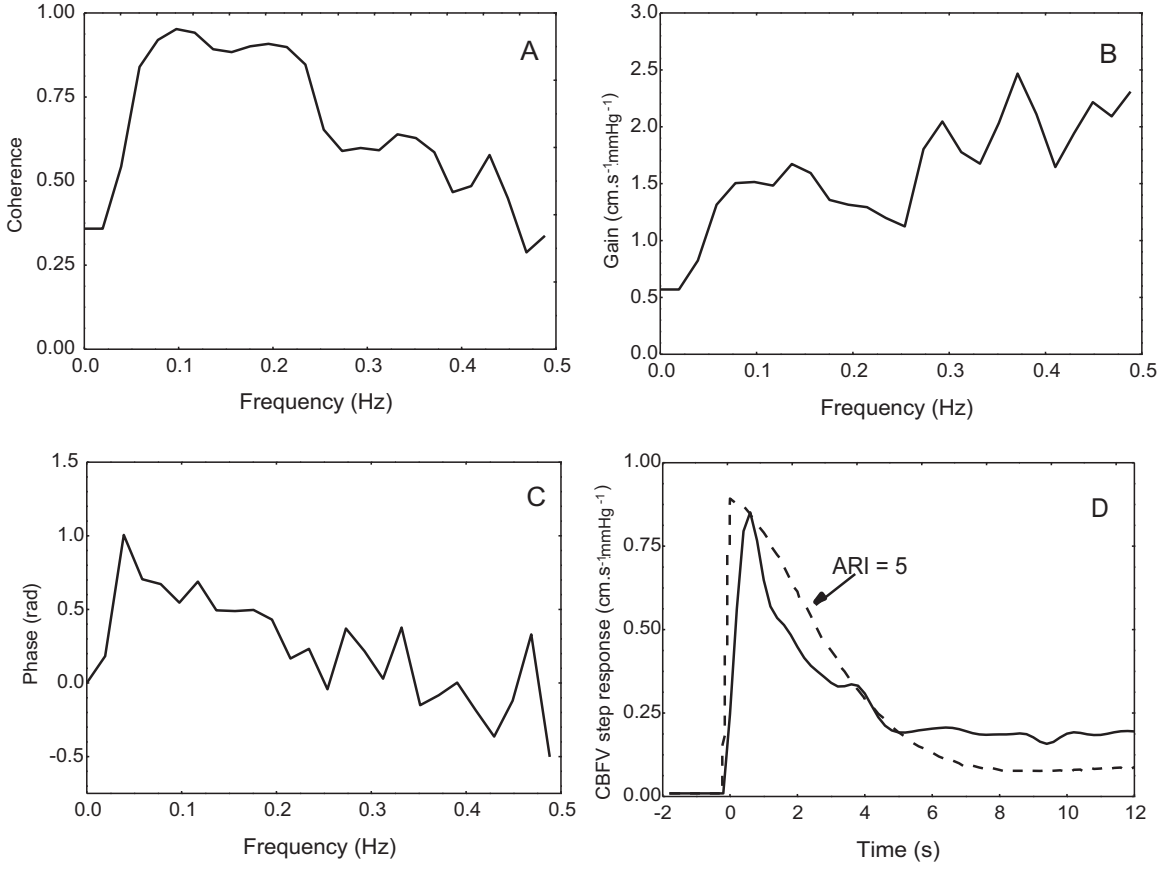

Fig. 1. Transfer function analysis between beat-to-beat mean BP (input) and CBFV (output) in a healthy 28 year old male subject. Spectral estimates were obtained with the Welch method using 8 segments with 102.4 s and 40% superposition. (A) Coherence function, (B) amplitude (gain) frequency response, (C) phase frequency response. The CBFV step response (D, solid line) was derived using the inverse Fourier transform of gain and phase. The best fit curve for the Tiecks model [109] is also shown (D, dashed line), corresponding to an ARI = 5.