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Rapid pressure-to-flow dynamics of cerebral autoregulation induced by instantaneous changes of arterial CO_2

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A B S T R A C T

Continuous assessment of CA is desirable in a number of clinical conditions, where cerebral hemodynamics may change within relatively short periods. In this work, we propose a novel method that can improve temporal resolution when assessing the pressure-to-flow dynamics in the presence of rapid changes in arterial CO_2. A time-varying multivariate model is proposed to adaptively suppress the instantaneous effect of CO_2 on CBFV by the recursive least square (RLS) method. Autoregulation is then quantified from the phase difference (PD) between arterial blood pressure (ABP) and CBFV by calculating the instantaneous PD between the signals using the Hilbert transform (HT). A Gaussian filter is used prior to HT in order to optimize the temporal and frequency resolution and show the rapid dynamics of cerebral autoregulation. In 13 healthy adult volunteers, rapid changes of arterial CO_2 were induced by rebreathing expired air, while simultaneously and continuously recording ABP, CBFV and end-tidal CO_2 ($ETCO_2$). Both simulation and physiological studies show that the proposed method can reduce the transient distortion of the instantaneous phase dynamics caused by the effect of CO_2 and is faster than our previous method in tracking time-varying autoregulation. The normalized mean square error (NMSE) of the predicted CBFV can be reduced significantly by 38.7% and 37.7% ($p < 0.001$) without and with the Gaussian filter applied, respectively, when compared with the previous univariate model. These findings suggest that the proposed method is suitable to track rapid dynamics of cerebral autoregulation despite the influence of confounding covariates.

1. Introduction

Patient specific continuous assessment of CA can help in determining the optimal blood pressure to achieve favorable outcomes in a number of clinical conditions, where cerebral hemodynamics may change within relatively short periods. This may occur for example in patients in a neurosurgical intensive care unit, for example following subarachnoid hemorrhage or head injury, or during cardiovascular surgery [4,10,35,39]. Univariate linear models of dynamic CA, such as the moving window based autoregulation index, transfer function analysis, and linear regression, using beat-to-beat data of CBFV and ABP (or cerebral perfusion pressure—CPP) have been proposed to track this vital physiological function continuously [6,10,26]. However, the sensitivity and specificity of these methods might be constrained by a number of physiological confounding covariates as well as the limitations of modeling techniques that are applied [6,26,28].

Arterial CO_2, usually measured as the partial pressure of end-tidal CO_2 ($ETCO_2$), is known as a powerful cerebral vasodilator that can change blood flow greatly within seconds [33]. In

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addition, hyper- or hypocapnia induced by increased or decreased $ETCO_2$ can result in significant changes in the effectiveness of autoregulation [1,3,23], and a number of studies have used modeling to understand the underlying variations in pressure-to-flow dynamics [2,9,14,17,18,20,21,24,31,34,37].

Panerai et al. showed that a multivariate model with $ETCO_2$ as an additional input can improve the prediction of CBFV [24]. Peng et al. [31] also reported that the linearity of the system can be significantly increased when using a multiple input model, especially in the frequencies below 0.1 Hz. In a recent study of phase dynamics, they also found that the low synchronization of phase difference (PD) between ABP and CBFV can be attributed to CO_2, which can be corrected by a CO_2 term derived from a multivariate model [32]. There thus appears to be a growing consensus that a multiple-input-and-single-output (MISO) system is more suitable to model the cerebral hemodynamics than a single-input-and-single-output (SISO) system [14,17,18,32].

In addition to the multivariate characteristics, time-varying assessments are also of growing interest [8,14,18,25,29,30]. Dineen et al. proposed a continuous autoregulation index and showed that the response of dynamic autoregulation to a change of $ETCO_2$ is delayed with respect to the change in CBFV [8]. This finding agrees with the results reported by Liu et al. using adaptive filtering techniques to track time-varying dynamics of autoregulation in response to step-wise changes of CO_2 [16]. These studies indicate that the pressure-to-flow dynamics might not be changing at the same pace as the dilation of arterioles. However, univariate models were employed by these studies and the tracking speed might be relatively slow, as the updating rate of the continuous estimate is either constrained by the relatively long length of the moving window or the slow forgetting factor for the adaptive filter. We thus aim now to elucidate if the reported delay in autoregulatory response is due to physiological phenomena or reflects the limitations of the signal processing methods.

Autoregulation can be quantified by many parameters. Instantaneous phase dynamics has been reported as a standalone autoregulatory parameter in a number of recent papers, using Hilbert transform (HT) and wavelet transform techniques [11,12,15,22,32]. The instantaneous phase estimated by these techniques is intrinsically a continuous parameter, as it is calculated sample by sample from the recordings. This approach therefore readily lends itself to the investigation of the time-varying property of autoregulation.

Previous publications have shown that dynamics of autoregulation can be assessed within a relatively narrow band around 0.1 Hz [1,3,7,15,16,22]. The choice of bandwidth (and thus the band-pass filter that needs to be applied to the signals prior to using the Hilbert transforms [5]) requires a compromise between temporal and frequency resolution.

In the present study, we thus combine multivariate modeling and instantaneous signal processing methods to shed further light on the continuous evolution of CA with improved temporal resolution in the presence of rapid changes in arterial CO_2. The objective is to provide a method that may track rapid changes of dynamic CA despite the influence of confounding covariates.

2. Methods

2.1. Outline

The approach may be summarized as follows: we model the cerebral hemodynamics as a multivariate system. The recursive least square (RLS) method is applied to adaptively remove the contribution of changes in $ETCO_2$ to CBFV. Gaussian filters with minimal spread in the time-frequency domain are used prior to applying the RLS filter to limit fluctuations to the frequency band where autoregulation is usually considered as most evident. The instantaneous PD is then estimated from the HT of the filtered residual CBFV and ABP. In the following section a simulation is described to validate our method, which was then applied to the recorded data to show the underlying time-varying pressure-to-flow dynamics during changes of $ETCO_2$ induced by rebreathing.

2.2. Mathematical methods

Cerebral autoregulation is modeled as a multivariate system [24], where ABP ($p[n]$), and $ETCO_2$ ($c[n]$) are the inputs and CBFV ($v[n]$) is the output,

$$v[n] = v_p[n] + v_c[n] + e[n] = \sum_{i=0}^{L_{pv}-1} h_{pv}[i]p[n-i] + \sum_{j=0}^{L_{cv}-1} h_{cv}[i]c[n-j] + e[n], \quad (1)$$

and n denotes sample number at 1 Hz sampling rate. $e[n]$ is the residual CBFV unexplained by the model. $v_p[n]$ and $v_c[n]$ are parts of CBFV that can be attributed to ABP and $ETCO_2$, respectively; $h_{pv}[i]$ and $h_{cv}[i]$ are their respective causal FIR filter impulse responses; L_{pv} and L_{cv} denote the orders of the filters. Based on a compromise between the known time for a physiological response to occur, the number of free parameters, and the length of data available, these orders are chosen to be equal 10 for both filters.

Based on (1), we extended our previous time-varying univariate model identified by a SISO RLS adaptive filter to a time-varying multivariate model identified by a MISO RLS adaptive filter. We rearrange (1) by vectors, where the vector of the filter impulse responses can be written as:

$$\boldsymbol{H}[n] = \begin{bmatrix} \boldsymbol{H_{pv}}[n] \\ \boldsymbol{H_{cv}}[n] \end{bmatrix}, \quad (2)$$

$$\boldsymbol{H_{pv}}[n] = \left[h_{pv}[0] \ldots h_{pv}\left[L_{pv}-1\right]\right]^t, \quad (3)$$

$$\boldsymbol{H_{cv}}[n] = \left[h_{cv}[0] \ldots h_{cv}[L_{cv}-1]\right]^t. \quad (4)$$

The inputs can be defined as:

$$\boldsymbol{x}[n] = \begin{bmatrix} \boldsymbol{x_p}[n] \\ \boldsymbol{x_c}[n] \end{bmatrix}, \quad (5)$$

$$\boldsymbol{x_p}[n] = \left[p[n], p[n-1], \ldots, p\left[n-L_{pv}+1\right]\right]^t, \quad (6)$$

$$\boldsymbol{x_c}[n] = \left[c[n], c[n-1], \ldots, c[n-L_{cv}+1]\right]^t. \quad (7)$$

According to (1), the error can be expressed as:

$$e[n] = v[n] - \boldsymbol{H}[n]^t \boldsymbol{x}[n]. \quad (8)$$

We can then follow the algorithm of the RLS adaptive filter to update $\boldsymbol{H}[n]$. We first estimate the Kalman gain vector, $\boldsymbol{k}[n]$, as:

$$\boldsymbol{k}[n] = \frac{\lambda^{-1}\boldsymbol{P}[n-1]\boldsymbol{x}[n]}{1+\lambda^{-1}\boldsymbol{x}^t[n]\boldsymbol{P}[n-1]\boldsymbol{x}[n]} \quad (0 \le \lambda \le 1), \quad (9)$$

where $\boldsymbol{P}[n]$ is the inverse autocorrelation matrix of the input signals. This is updated by:

$$\boldsymbol{P}[n] = \lambda^{-1}\boldsymbol{P}[n-1] - \lambda^{-1}\boldsymbol{k}[n]\boldsymbol{x}[n]^t\boldsymbol{P}[n-1]. \quad (10)$$

The vector of the filter impulse responses, $\boldsymbol{H}[n]$, is then updated by:

$$\boldsymbol{H}[n] = \boldsymbol{H}[n-1] + e_n[n]\boldsymbol{k}[n]. \quad (11)$$