Medical Engineering and Physics 000 (2017) 1–8

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

Increased blood pressure variability upon standing up improves reproducibility of cerebral autoregulation indices

Adam Mahdi[a,*], Dragana Nikolic[b], Anthony A. Birch[c], Mette S. Olufsen[d], Ronney B. Panerai[e], David M. Simpson[f], Stephen J. Payne[a]

[a] Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford, UK
[b] Institute of Sound and Vibration Research, University of Southampton, Southampton, UK
[c] Department of Medical Physics and Bioengineering, Southampton General Hospital, Southampton SO16 6YD, UK
[d] Department of Mathematics, North Carolina State University, Raleigh, USA
[e] Department of Cardiovascular Sciences and NIHR Cardiovascular Biomedical Research Unit, University of Leicester, Leicester, UK
[f] Institute of Sound and Vibration Research, University of Southampton, Southampton, UK

ARTICLE INFO

Article history:
Received 22 September 2016
Revised 19 April 2017
Accepted 1 June 2017
Available online xxx

Keywords:
Cerebral autoregulation
Cerebral blood flow
Reproducibility
Variability

ABSTRACT

Dynamic cerebral autoregulation, that is the transient response of cerebral blood flow to changes in arterial blood pressure, is currently assessed using a variety of different time series methods and data collection protocols. In the continuing absence of a gold standard for the study of cerebral autoregulation it is unclear to what extent does the assessment depend on the choice of a computational method and protocol. We use continuous measurements of blood pressure and cerebral blood flow velocity in the middle cerebral artery from the cohorts of 18 normotensive subjects performing sit-to-stand manoeuvre. We estimate cerebral autoregulation using a wide variety of black-box approaches (including the following six autoregulation indices ARI, Mx, Sx, Dx, FIR and ARX) and compare them in the context of reproducibility and variability. For all autoregulation indices, considered here, the intra-class correlation was greater during the standing protocol, however, it was significantly greater (Fisher's *Z*-test) for Mx ($p < 0.03$), Sx ($p < 0.003$) and Dx ($p < 0.03$). In the specific case of the sit-to-stand manoeuvre, measurements taken immediately after standing up greatly improve the reproducibility of the autoregulation coefficients. This is generally coupled with an increase of the within-group spread of the estimates.

1. Introduction

Cerebral autoregulation (CA) refers to the brain's control mechanisms responsible for maintaining cerebral blood flow at an appropriate, approximately constant, level despite changes in arterial blood pressure (ABP) [1]. Lassen [2] was the first to show this phenomenon, by plotting the so-called autoregulation curve combining the measurements from different human studies [3]. Other authors have obtained similar results both in animals [4–7] and more recently in humans [8,9].

The application of Doppler ultrasound in obtaining continuous measurements of cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA) has allowed the study of cerebral blood flow noninvasively (under the assumption that the vessel diameter remains constant). This has stimulated the development of quantitative methods for CA assessment. In particular, it has allowed the study of dynamic aspects of CA by considering the adaptation of CBFV in response to ABP change.

Having fast, reliable and noninvasive autoregulation assessment techniques is of great importance because of the link between CA impairment and many clinical disorders. For example, poor CA assessment has been demonstrated in stroke [10], subarachnoid hemorrhage [11] and head injury [12]. Other studies have also pointed to a potential link between impaired autoregulation and syncope or cerebral microvascular disease [13].

Over the years many different mathematical methods have been developed in order to quantify autoregulation. Common approaches include transfer function analysis (TFA) [14], autoregulation index (ARI) [15], parametric time series models such as finite impulse response (FIR) [16] and autoregressive with exogenous input (ARX) [17,18] and the three correlation coefficient indices between the mean CBFV and the mean pressure (Mx), systolic pressure (Sx) and diastolic pressure (Dx) [19,20], neural networks [21]; wavelet synchronization analysis [22,23] and other

* Corresponding author.
E-mail addresses: adam.mahdi@gmail.com, adam.mahdi@eng.ox.ac.uk (A. Mahdi).

http://dx.doi.org/10.1016/j.medengphy.2017.06.006
1350-4533/

modelling techniques [24–27]. Experimental protocols have been designed that focus on spontaneously occurring variability in ABP–CBFV signals and those that induce changes in ABP using different manoeuvres. The latter include lower body negative pressure [28], thigh-cuffs [29], controlled breathing [30], cyclic leg raising [31], and sit-to-stand [32] manoeuvres. One aspect that has been noted is that increased variability of blood pressure leads to more robust estimates of autoregulation (see [33,34]).

The vast majority of studies use only one or a few measures of autoregulation for a given data collection protocol. In the continuing absence of a gold standard the choice of a computational method to assess dynamic CA is not obvious. In practice, the choice is often ad-hoc or based on the authors' preference in using a specific technique. Despite the fast growing body of literature on CA it remains unclear what the difference is between various quantitative methods and their dependence on the data collection protocols.

In Angarita-Jaimes et al. [35] the authors explored a number of different autoregulation parameters and compared them in normocapnia and hypercapnia (which is known to impair autoregulation) using Monte-Carlo simulations to assess within-subject measurement errors. Lower between- and within-subject variability of the parameters were considered as criteria for identifying an improved metric of CA. In another recent study Nikolic et al. [36] compared the reproducibility of CA measures based on the phase and gain of FIR and IIR filters of many different orders (0–20) for the baseline and thigh-cuff manoeuvres.

The current paper extends the previous works by considering the short-term repeatability of autoregulation measures considering repeatability within the same recording session, and comparing rest with standing-up, as a manoeuvre that increases blood pressure variations. We use six types of black-box approaches (ARI, Mx, Sx, Dx, FIR and ARX) for estimating autoregulaton in the context of reproducibility and variability for two different protocols: baseline (sitting) and orthostatic stress (sit-to-stand manoeuvre). Although some authors have studied various aspects of autoregulation during sit-to-stand, the assessment was based primarily on a few specific CA coefficients such as ARI or TFA [32,37]. As far as we know, this is one of the first studies that compares such a wide range of different autoregulation coefficients on the same dataset with repeated measurements.

2. Methods

In this section we describe the data collection protocol, data preprocessing and computational methods for CA assessment.

2.1. Data collection protocol

2.1.1. Data collection

The eighteen ABP and CBFV time series, used in this study, are taken from cohorts of normotensive young (24 ± 1 years) and normotensive elderly (72 ± 3 years) subjects, see Table 1 for the main characteristic of the signal. The data collection project has previously been discussed in Lipsitz et al. [32]. ABP was measured noninvasively using a photoplethysmographic Finapres monitor (Ohmeda Monitoring Systems, Englewood, CO). In order to eliminate hydrostatic pressure effects, the subject's nondominant hand was supported by a sling at the level of the right atrium. The individuals were asked to breathe at the rate of 15 breaths per minute to standarise the effects of respiration. Doppler ultrasonography was used to measure the changes in CBFV within the MCA. The 2 MHz probe of a portable Doppler system (MultiDop X4, DWL-Transcranial Doppler Systems Inc., Sterling, VA) was strapped over the temporal bone and locked in position with a Mueller–Moll probe fixation device. Flow velocity was recorded at a depth of approximately 50–65 mm, digitized and stored for analysis. After instrumentation, subjects sat in a straight-backed chair with their legs elevated at 90° in front of them. First subjects rested in the sitting position for 5 min, then stood upright for one minute. The data were recorded during the final one minute of sitting and first minute of standing and the initiation of standing was timed from the moment both feet touched the floor. The active stand protocol was repeated in each subject. For a more detailed description of the data collection procedure, the reader is referred to the work of Lipsitz et al. [32].

2.1.2. Data preprocessing

Artefacts including spikes that commonly occur in CBFV signals were removed as the first step of data preprocessing using a median filter. The pulsatile ABP and CBFV were low-pass filtered using a 4th-order Butterworth filter, in both the forward and reverse directions, with a cutoff frequency of 20 Hz (see [16]). Subsequently, the beginning and end of each cardiac cycle were marked by the onset of the systole using the ABP signal. The onsets were detected using a windowed and weighted slope sum function and adaptive thresholding [38]. The beat-to-beat average of ABP and CBFV were calculated for each detected cardiac cycle. A first-order polynomial was used to interpolate the resulting time series, which was followed by downsampling at 10 Hz to produce signals with a uniform time base. Preprocessed ABP and CBFV time series are denoted by $P[k]$ and $V[k]$, respectively, as used in each of the modelling approaches described below.

2.1.3. Data segments for sitting and standing

To study autoregulation during the standing protocol approximately 55 s data segments have been selected starting from the moment subjects stood up (see Fig. 1). The characteristic 'dip', the overshoot and adaptation of the ABP–CBFV signals lasted approximately 20–30 s, depending on the individual's cardiovascular properties. From the available 1 min recording of the signals during the sitting protocol we removed the last 5 s of data in order to separate the baseline from the transient part of ABP–CBFV.

2.2. Cerebral autoregulation estimates

2.2.1. ARI

Tiecks et al. [15] proposed by of difference equations for CBFV response to a change in ABP, from which an autoregulation index (ARI) can be calculated. The method itself and its variations have been used extensively to provide a quantitative assessment of CA [35,39,40]. The index ranges from 0, representing the absence of autoregulation, to 9, indicating the best autoregulation. For more details on the computational aspects of ARI, see Appendix A.1.

2.2.2. FIR and ARX

FIR [41] and ARX models have been applied to CA by several authors [17,18,30,36]. First, the raw signals are normalized and detrended. Then, they are fitted using either FIR or ARX (FIR being a special case of ARX) models of different orders and cerebral autoregulation is estimated by analysing the phase shift and gain of the corresponding transfer function calculated as the average of the values taken around [0.07–0.20] Hz. For more details on the computational aspects of FIR and ARX, see Appendix A.2.

2.2.3. Mx, Sx and Dx

The Mx (Sx and Dx) autoregulatory index is a correlation coefficient between the mean (systolic and diastolic) ABP and mean CBFV over a certain interval. If a moving window is applied the values are averaged for each investigation and each patient. Several authors [19,42] have suggested that the values less than 0.3

Please cite this article as: A. Mahdi et al., Increased blood pressure variability upon standing up improves reproducibility of cerebral autoregulation indices, Medical Engineering and Physics (2017), http://dx.doi.org/10.1016/j.medengphy.2017.06.006