Medical Engineering & Physics 36 (2014) 628–637

Contents lists available at ScienceDirect

Medical Engineering & Physics

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

Model-based physiomarkers of cerebral hemodynamics in patients with mild cognitive impairment

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ARTICLE INFO

Article history:
Received 14 February 2013
Received in revised form 17 February 2014
Accepted 26 February 2014

Keywords:
Modeling of cerebral autoregulation
Cerebral hemodynamics
Nonlinear modeling
Principal dynamic modes
Closed-loop PDM-based model
Mild cognitive impairment
Model-based physiomarkers
Alzheimer's disease

ABSTRACT

In our previous studies, we have introduced model-based "functional biomarkers" or "physiomarkers" of cerebral hemodynamics that hold promise for improved diagnosis of early-stage Alzheimer's disease (AD). The advocated methodology utilizes subject-specific data-based dynamic nonlinear models of cerebral hemodynamics to compute indices (serving as possible diagnostic physiomarkers) that quantify the state of cerebral blood flow autoregulation to pressure-changes (CFAP) and cerebral CO2 vasomotor reactivity (CVMR) in each subject. The model is estimated from beat-to-beat measurements of mean arterial blood pressure, mean cerebral blood flow velocity and end-tidal CO2, which can be made reliably and non-invasively under resting conditions. In a previous study, it was found that a CVMR index quantifying the impairment in CO2 vasomotor reactivity correlates with clinical indications of early AD, offering the prospect of a potentially useful diagnostic tool. In this paper, we explore the use of the same model-based indices for patients with amnestic Mild Cognitive Impairment (MCI), a preclinical stage of AD, relative to a control subjects and clinical cognitive assessments. It was found that the model-based CVMR values were lower for MCI patients relative to the control subjects.

1. Introduction

Cognitive impairment in patients with early-stage Alzheimer disease (AD) has been associated with cerebrovascular dysfunction [1–9] and cerebrovascular lesions [10–12]. Thus, quantitative and objective measures of cerebral hemodynamic function may offer useful means for early diagnosis of AD. Patients with amnestic mild cognitive impairment (MCI) have high risk of developing AD and may represent a transitional stage between normal aging and AD [13]. Thus, measures of cerebrovascular function may be useful in monitoring disease progression and the effects of interventions for prevention and treatments.

The physiological process of cerebral blood flow autoregulation in response to pressure-changes (CFAP) and CO2 vasomotor reactivity (CVMR) have been viewed as two fundamental aspects of cerebral hemodynamic autoregulation [14–33]. To advance the study of these processes, a modeling methodology has been introduced and tested with beat-to-beat hemodynamic data using open-loop analysis [34] and closed-loop analysis [35]. These modeling studies of cerebral hemodynamics explored the potential of model-based "physiomarkers" for improved diagnosis of early-stage AD and discovered that a subject-specific CVMR index attained significantly lower values in AD patients (relative to the normative population of control subjects), suggesting potential diagnostic utility for such indices [36]. Whether such model-based indices can be sensitive and specific "physiomarkers" for improved clinical diagnosis will have to be ascertained through analysis of appropriate and large size clinical data. This paper is part of such a continued effort and presents results from an initial set of MCI patients and normal control subjects. Since this is only a pilot study, definitive conclusions cannot be drawn regarding potential clinical utility before more extensive clinical data are analyzed in the future.

2. Methods

2.1. Experimental methods

We analyzed time-series data of beat-to-beat averages over each R-R interval of mean arterial blood pressure (MABP), end-tidal CO2 (ETCO2) and mean cerebral blood flow velocity (MCBFV) from 17 control subjects (67.3 ± 7.7 age, 7 men and 10 women) and

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http://dx.doi.org/10.1016/j.medengphy.2014.02.025
1350-4533/

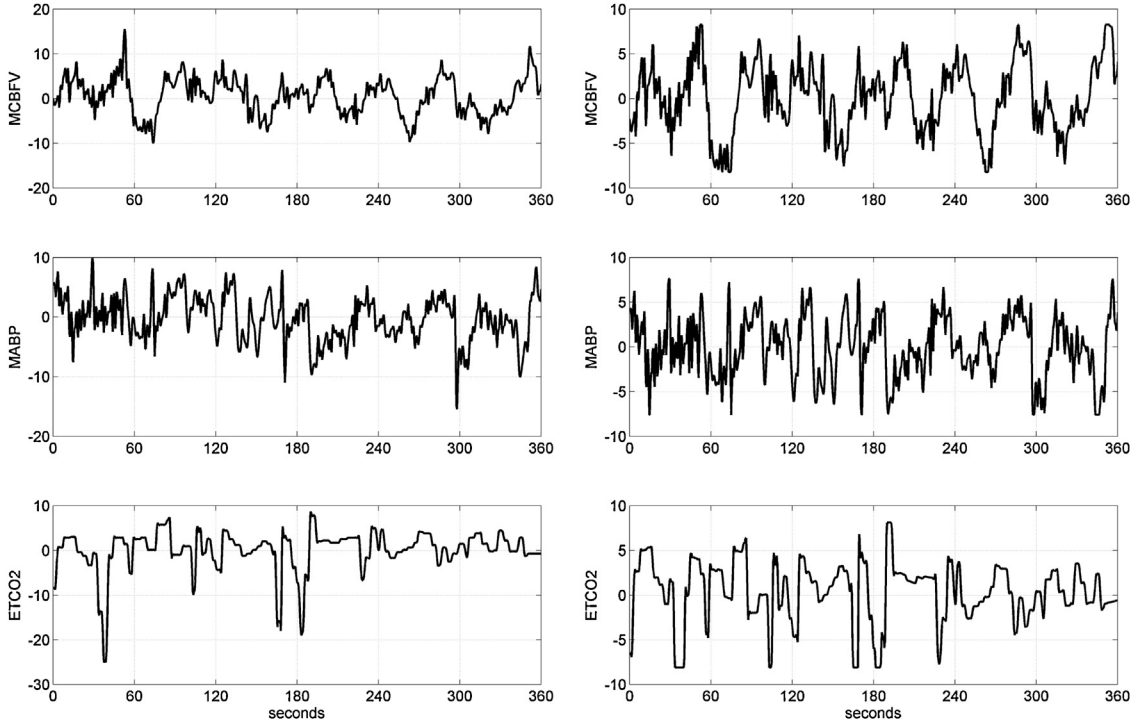

Fig. 1. Illustrative time-series data over 6 min of a typical MCI patient, representing beat-to-beat spontaneous variations of MCBFV (top), MABP (middle) and ETCO2 (bottom). The raw data are on the left column and the pre-processed data are on the right column. The units of the ordinate axis are: cm/s for MCBFV and mmHg for MABP and ETCO2.

22 MCI patients (65.8 ± 6.6 ages, 11 men and 11 women) who participated voluntarily in this study and signed the Informed Consent Form that has been approved by the IRB of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas, where the data were collected at the Institute for Exercise and Environmental Medicine. The diagnosis of amnestic MCI was based on modified Petersen criteria [13]. Subjects were screened to exclude clinical histories of stroke, major medical and psychiatric disorders, unstable heart diseases, uncontrolled hypertension and diabetes mellitus.

Arterial blood pressure was measured continuously and non-invasively with finger photoplethysmography (Finapres) and cerebral blood flow velocity was measured in the middle cerebral artery using a 2 MHz transcranial Doppler (TCD) probe (Multiflow, DWL) placed over the temporal window and fixed at constant angle with a custom-made holder. Heart rate was monitored by electrocardiogram (ECG) and end-tidal CO2 tension was obtained via a nasal cannula using capnography (Criticare Systems). All experiments were performed in a quiet, environmentally controlled laboratory under resting conditions. After at least 20 min of supine rest, 6–8 min of recordings were made in the supine position for 17 control subjects (CS) and 22 MCI patients (MP). These non-invasive measurements are reliable, safe and comfortable for older subjects.

2.2. Data preprocessing

Occasional measurement artifacts in the beat-to-beat time-series data of MABP, ETCO2 and MCBFV were removed by applying a threshold criterion on the maximum change that is physiologically possible from beat to beat in these variables. These beat-to-beat values were re-sampled every 0.5 s via cubic-spline interpolation and were high-pass filtered (via subtraction of a 2-min moving-average with Hanning window) to remove the constant baseline and very low frequency trends below ~0.01 Hz. The resulting time-series data were clipped at ±2 standard deviations to mitigate the effects of occasional outliers. The ETCO2 data were shifted by 3.4 s to compensate for the latency of the measurement apparatus. Fig. 1 shows illustrative time-series data (both raw and pre-processed) for one of the MCI patients over 6 min.

2.3. Modeling methods

In this study, we employ the concept of Principal Dynamic Modes (PDMs) to obtain compact dynamic nonlinear models of the relationship between two beat-to-beat input signals: MABP and ETCO2, and one output signal: MCBFV. The use of PDMs makes the obtained dynamic nonlinear models compact and allows their accurate estimation from short data-records (6–8 min). The PDMs also facilitate the physiological interpretation of the obtained model [34–38]. We briefly outline below the proposed PDM-based modeling approach, which is also summarized in Appendix I. For the many mathematical and technical details of Volterra-type modeling and related issues, the reader is referred to the monograph [38] and to our recent publications presenting its application to cerebral hemodynamics in the input-output open-loop context [34] and in the closed-loop context [35]. In short, the output of the PDM-based *open-loop* model is formed by additive signal components that are generated by cascaded operations of convolutions of the input signal with each PDM and nonlinear transformations by the respective Associated Nonlinear Function (ANFs). The resulting signals are summed to form the model output with the addition of cross-terms that represent the multiplicative interactions between PDM outputs (see Fig. 2). The mathematical operations involved in this process are summarized in Appendix I, along with the procedure by which the PDMs and the ANFs are obtained from the data.

In the closed-loop analysis, we consider two input–output models, $\boldsymbol{A}$ and $\boldsymbol{B}$, which describe how MCBFV and MABP (viewed as outputs, respectively) are influenced by the other two variables (viewed as the two inputs). A block-diagram for the closed-loop model is shown in Fig. 3 and indicates the presence of two putative external (systemic) "disturbances" which are the residuals for each