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Low-frequency oscillations in cerebrovascular and cardiovascular hemodynamics: Their interrelationships and the effect of age

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ABSTRACT

The aim of this study was to investigate how the interrelationships between low-frequency oscillations (LFOs) in the cerebral and systemic cardiovascular hemodynamic systems change with aging and systemic hemodynamic perturbation. Seventeen young adult (28.4 ± 3.5 years) and seventeen elderly subjects (69.4 ± 8.7 years) underwent continuous measurements of arterial blood pressure (ABP), heart rate (HR), and cerebral oxygenation (oxy-hemoglobin, deoxy-hemoglobin, and total hemoglobin) using near-infrared spectroscopy. The LFOs were subdivided into three frequency intervals (FI-1: 0.01–0.02 Hz, FI-2: 0.02–0.06 Hz, and FI-3: 0.06–0.15 Hz) via spectral analysis based on continuous wavelet transform. The amplitudes of the LFOs at these FIs were calculated to examine the effects of aging and head-up tilt (HUT) on cerebral and cardiovascular hemodynamics. Granger causality (GC) was used for analyzing the causal relationships between the LFOs observed in ABP, oxy-hemoglobin, and HR. The amplitudes of the LFOs were generally higher in young adults than in the elderly and increased significantly only in the younger subjects after HUT. GCs in FI-3 oscillations were significantly higher in young subjects compared to older participants in the HUT state. These results indicate that aging dampens systemic and cerebral hemodynamic regulatory mechanisms, and the interrelationships between systemic and cerebral hemodynamics become weaker with age.

Introduction

Spontaneous low-frequency oscillations (LFOs) occur in the cerebrovascular and systemic cardiovascular systems and have distinct characteristics, such as spontaneity, slowness, and modulability, that differentiate them from other physiologic oscillations (Obrig et al., 2000). These oscillations have been studied in various ways, but their origins have yet to be clearly elucidated (Obrig et al., 2000). LFOs are strongly associated with oscillations in vascular tone known as vasomotion, and theoretically the oscillations within the blood vessels result in positive physiologic effects (i.e., an improvement of tissue oxygenation with high conductance) (Nisson and Aalkjer, 2003; Sassaroli et al., 2012).

In several studies undertaken to determine the biological significance of these oscillations, specific frequency intervals (FIs) were analyzed by subdividing frequency bands of spontaneous oscillations using spectral analysis (Bernjak et al., 2008; Li et al., 2010, 2012, 2013; Obrig et al., 2000; Peng et al., 2008; Rowley et al., 2007; Schroeter et al., 2004; Shiogai et al., 2010; Stefanovska et al., 1999; Zhang et al., 2000). Tachtsidis et al. (2004) examined oscillation amplitudes in three frequency bands (very low frequency: 0.02–0.04 Hz, low frequency: 0.04–0.15 Hz, and high frequency: 0.15–0.4 Hz). Stefanovska et al. (1999) separated frequency bands from 0.0095 Hz to 1.6 Hz into five FIs through a continuous wavelet transform based on the peak positions of frequency and a priori knowledge of physiological hemodynamics. Oscillations at lower frequency intervals at a range of 0.01 Hz to 0.15 Hz are thought to reflect endothelial-related metabolic activity, neurogenic activity in the vessel walls, and myogenic activity of the smooth muscle in the vasculature. Higher FIs from 0.15 Hz to 2 Hz reflect hemodynamic changes due to respiration and the cardiac cycle (Li et al., 2013; Shiogai et al., 2010; Stefanovska et al., 1999).

The LFO components have been known to change according to the characteristics of the signals, pathological conditions, and aging (Li et al., 2010, 2012, 2013; Obrig et al., 2000; Peng et al., 2008; Sassaroli et al., 2012; Schroeter et al., 2004). Orthostatic challenges (e.g. head-up tilt (HUT) test) are used for the examination of vasovagal reaction, HR variability, and blood pressure adaptation (Benditt et al., 1996; Forleo et al., 2012). Li et al. demonstrated that the amplitude of LFOs observed in arterial blood pressure (ABP) and cerebral oxygenation (COx) measurements changes in accordance with age, which may reflect a natural degenerative process of the blood vessels (Li et al.,

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2013), as aging is known to influence the decline in cerebrovascular and systemic cardiovascular hemodynamic activities (Marin, 1995; Mehagnoul-Schipper et al., 2000; Peng et al., 2008; Schroeter et al., 2004; Toth et al., 2013). Blood vessel stiffening due to aging also reduces the metabolic rate of oxygen consumption by decreasing vasoregulatory activity (Schroeter et al., 2004).

The analyses of cerebrovascular and systemic cardiovascular LFO hemodynamic signals have been applied to study cerebral autoregulation, a physiological mechanism by which cerebral perfusion is maintained despite fluctuations in system blood pressure: The transfer function and phase relationships were analyzed in the low-frequency bands between cerebral blood flow velocity and ABP (Panerai et al., 1999, 2001; Zhang et al., 1998). The effect of ABP and heart rate (HR) on LFOs of around 0.1 Hz of COx signals was studied by near-infrared spectroscopy (NIRS) using information transfer analysis (Katura et al., 2006).

In the present study we analyzed the interrelationships between LFOs in ABP, COx, and HR and explored how their relationships change with aging. In addition, we sought to determine whether the interrelationships among the LFO variables change with systemic hemodynamic perturbation, such as the HUT test. The objectives of this study also included investigating the influences of orthostatic challenge and the effect of aging on the LFO components and their relationships, by spectral and causal connectivity analyses of the signals.

Materials and methods

Subjects

Seventeen young (age, 28.4 ± 3.5 years; range, 25 to 34 years; 10 males; systolic blood pressure, 116.7 ± 12.8 mm Hg; diastolic blood pressure, 74.5 ± 9.8 mm Hg) and 17 elderly (age, 69.4 ± 8.7 years; range, 52 to 83 years; 6 males; systolic blood pressure, 125.2 ± 10.9 mm Hg; diastolic blood pressure, 80.4 ± 7.9 mm Hg) adults who visited a tertiary medical center in South Korea were recruited for the study. Written informed consent was obtained from all subjects before the session. Brief information including age, height, weight, body mass index, blood pressure, and medical history was recorded. None of the subjects had hypertension, hypotension, and a history of cardiovascular or cerebrovascular diseases. Institutional review board approval was obtained from the ethics committee of Seoul National University Hospital and all experiments were conducted in accordance with the Declaration of Helsinki (Table 1).

Measurements

Arterial blood pressure (ABP), near-infrared spectroscopy (NIRS), and electrocardiogram (ECG) measurements were acquired simultaneously. The NIRS signal was measured to analyze cerebral oxygenation (Oxymon MK-III, Artinis Medical System, Zetten, the Netherlands). Tissue absorbance measurements of two different near-infrared light sources (760 nm and 850 nm) were obtained to calculate changes in oxy-hemoglobin (O_2Hb) and de-oxy-hemoglobin (Hb) concentrations applying the modified Beer–Lambert law. Total hemoglobin concentration changes were calculated as the sum of O_2Hb and Hb. The NIRS probe consisted of a light emitter and detector pair (35 mm apart from one another) that was embedded in a black probe holder. The probe holder was placed on the left side of subject's forehead 3 cm apart to the central line to avoid the sagittal sinus, and securely fastened by an adjustable strap.

Table 1
Subject characteristics.

Characteristic	Young	Elderly	P-value
N	17	17	
Age (years)	28.4 ± 3.5	69.4 ± 8.7	<0.001
Body mass index (kg/m^2)	22.4 ± 3.5	24.6 ± 2.2	0.032
Male sex (%)	58.8	35.3	0.303
Systolic blood pressure (mm Hg)	116.6 ± 12.8	125.2 ± 10.9	0.044
Diastolic blood pressure (mm Hg)	74.5 ± 9.8	80.4 ± 7.9	0.060

All information is for the supine resting state. Values are presented as the mean ± s.d. and percentages. P-values were calculated using the independent t-test (mean ± s.d.) and chi-square test (percentages).

Continuous non-invasive BP data were measured by finger cuffs using a continuous BP monitoring system (CNAP® monitor 500, CNSystems, Graz, Austria). Oscillometric BP was measured by an upper arm cuff to calibrate the continuous finger pressure waveform at the beginning of the session. All measurements were performed in the right arm. The right arm was placed on an armrest installed beside the tilting bed at a right angle. A three-lead ECG signal was used to calculate the heart rate by real-time detection of R peaks from the QRS complex (Pan and Tompkins, 1985).

All data were recorded on a personal computer through a data acquisition card (NI PCI-6255, National Instruments, Austin, Texas, USA) at a 400 Hz sampling rate. Data processing was performed by analysis programs custom-built using Matlab 7.14 (Mathworks Inc., Natick, Massachusetts, USA).

Measurements were performed in two postural states. Continuous data was recorded for 5 min in the supine position (0°) and for 5 min in the HUT position (45° from horizontal) on the tilt table. Subjects were cautioned against posture changes, moving their head and sleeping to minimize motion artifacts during the measurements.

Spectral analysis

A continuous wavelet transform was used for spectral analysis. The wavelet transform of a signal $g(u)$ is defined as

$$\tilde{g}(s,t) = \int_{-\infty}^{+\infty} \Psi_{(s,t)}(u) g(u) du$$

where $\tilde{g}(s,t)$ is the mapping of the signal $g(u)$ onto the time-scale plane as a wavelet transform. $\Psi_{(s,t)}(u)$ is a wavelet function, which is defined as

$$\Psi_{s,t} = |s|^{-p} \psi\left(\frac{u-t}{s}\right)$$

where ψ is the mother wavelet, t is time, and s is a scale factor. The frequency resolution can be determined by adjusting the parameter p, which is an arbitrary positive number. In this study, we chose the parameter p to be 1/2, then frequency f would be expressed as $1/s$. The Morlet wavelet was selected for the most proper localization in time and frequency within the uncertainty principle (Stefanovska et al., 1999).

The frequency interval of the wavelet transforms from 0.01 Hz to 2 Hz was included for analysis. This interval can be divided into five frequency intervals (FIs) based on specific physiological phenomena (Stefanovska et al., 1999). FI-1 (0.01 Hz to 0.02 Hz) reflects endothelial-related metabolic activity, FI-2 (0.02 Hz to 0.06 Hz) reflects the neurogenic activity in the vessel walls, and FI-3 (0.06 Hz to 0.15 Hz) reflects the myogenic activity of the smooth muscle. FI-4 (0.15 Hz to 0.4 Hz) and FI-5 (0.4 Hz to 2 Hz) reflect respiration and heart beats, respectively (Li et al., 2013; Stefanovska et al., 1999; Shiogai et al., 2010). The average amplitude of the wavelet transform within a given frequency interval $Amp_i(f_{i1}, f_{i2})$ was defined as

$$Amp_i(f_{i1}, f_{i2}) = \frac{1}{t}\int_0^t \int_{1/f_{i2}}^{1/f_{i1}} \frac{1}{s^2} |\tilde{g}(s,t)|^2 ds\, dt$$

where f_{i1} and f_{i2} are the upper and lower limits of each frequency interval, respectively (Li et al., 2013; Stefanovska et al., 1999; Shiogai et al., 2010). In this study, FI-4 and FI-5 were excluded in the analysis, because