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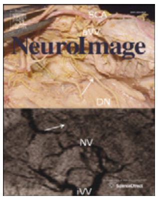

The human brain pacemaker: Synchronized infra-slow neurovascular coupling in patients undergoing non-pulsatile cardiopulmonary bypass☆

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ABSTRACT

In non-pulsatile cardiopulmonary bypass surgery, middle cerebral artery blood flow velocity (BFV) is characterized by infra-slow oscillations of approximately 0.06 Hz, which are paralleled by changes in total EEG power variability (EEG-PV), measured in 2 s intervals. Since the origin of these BFV oscillations is not known, we explored their possible causative relationships with oscillations in EEG-PV at around 0.06 Hz. We monitored 28 patients undergoing non-pulsatile cardiopulmonary bypass using transcranial Doppler sonography and scalp electroencephalography at two levels of anesthesia, deep (prevalence of burst suppression rhythm) and moderate (prevalence of theta rhythm).

Under deep anesthesia, the EEG bursts suppression pattern was highly correlative with BFV oscillations. Hence, a detailed quantitative picture of the coupling between electrical brain activity and BFV was derived, both in deep and moderate anesthesia, via linear and non linear processing of EEG-PV and BFV signals, resorting to widely used measures of signal coupling such as frequency of oscillations, coherence, Granger causality and cross-approximate entropy. Results strongly suggest the existence of coupling between EEG-PV and BFV. In moderate anesthesia EEG-PV mean dominant frequency is similar to frequency of BFV oscillations (0.065 ± 0.010 Hz vs 0.045 ± 0.019 Hz); coherence between the two signals was significant in about 55% of subjects, and the Granger causality suggested an EEG-PV → BFV causal effect direction. The strength of the coupling increased with deepening anesthesia, as EEG-PV oscillations mean dominant frequency virtually coincided with the BFV peak frequency (0.062 ± 0.017 Hz vs 0.060 ± 0.024 Hz), and coherence became significant in a larger number (65%) of subjects. Cross-approximate entropy decreased significantly from moderate to deep anesthesia, indicating a higher level of synchrony between the two signals.

Presence of a subcortical brain pacemaker that drives vascular infra-slow oscillations in the brain is proposed. These findings allow to suggest an original hypothesis explaining the mechanism underlying infra-slow neurovascular coupling.

Introduction

Infra-slow oscillations (ISO) of around 0.1 Hz in brain circulation have long been detected in animals and in humans (Diehl et al., 1998; Fujii et al., 1990; Giller et al., 1999; Golanov et al., 1994; Haubrich et al., 2004; Jones et al., 1995; Kleinfeld et al., 1998; Mayhew et al., 1996; Nicolet et al., 2005; Rosenblum et al., 1987). ISO of cerebral circulation reflects arterial vasomotion, which has been defined as the rhythmic contractions of the arteriolar smooth vessel, varying vessel caliber and blood flow of the entire cerebral-vascular tree synchronous and in phase (Fujii et al., 1990; Giller et al., 1999; Rosenblum et al., 1987). In peripheral circulation, ISO also have been identified (Akselrod et al., 1981; Bernardi et al., 1997; Malliani et al., 1991; Podgoreanu et al.,

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Abbreviations: BFV, blood flow velocity; EEG-PV, EEG power variability; ISO, infra-slow oscillations; CBF, cerebral blood flow; NP-CPB, non-pulsatile cardiopulmonary bypass; TCD, transcranial Doppler; BOLD, blood oxygen level dependent; tr-NIRS, time resolved near-infrared spectroscopy; AR, autoregressive; MVAR, multivariate autoregressive; C-ApEn, cross-approximate entropy.

☆ This work was conducted at the Department of Cardiovascular Diseases and of Anesthesia and Intensive Care of Treviso Regional Hospital, Italy.

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2002). Arterial vasomotion might originate from oscillators in cytosolic compartment of smooth muscle cells of arteries, in which Ca^{2+} waves released from sarcoplasmic reticulum synchronously with oscillations of membrane potential (Aalkjaer and Nilsson, 2005; Gustafsson, 1993). There is an ongoing debate whether the oscillatory pattern in the cardiovascular system might reflect some interactions between the sympathetic and parasympathetic tone activated by the baroreceptor reflex or a central respiratory gate (deBoer et al., 1987; Eckberg, 2003; Grasso et al., 1995; Malliani et al., 1991; Podgoreanu et al., 2002; Preiss and Polosa, 1974). However, the exact origin of ISO in cerebral circulation is still unknown.

Brain electrical activity also shows ISO (Aladjalova, 1954; Leistner et al., 2007; Monto et al., 2008; Vanhatalo et al., 2004), including oscillations in EEG frequency bands and EEG power (Mantini et al., 2007; Palva and Palva, 2012; Steriade et al., 1993). The brain electrical ISO, reflexive of variability in cortical excitability (Steriade et al., 1993), seem to be of importance for neocortical function regarding memory consolidation, performance, and sleep (Achermann and Borbely, 1997, 1998; Buzsaki, 2006; Csercsa et al., 2010; Destexhe et al., 2007; Dijk et al., 1990; Molle et al., 2002; Monto et al., 2008; Sirota and Buzsaki, 2005).

The available data suggest that thalamocortical relations may have a leading role in setting the cortical excitability (Steriade and Contreras, 1995, 1998). Non-invasive imaging techniques such as the resting state functional magnetic resonance imaging (rs-fMRI) and time resolved near-infrared spectroscopy (trNIRS), have demonstrated that the blood oxygen level dependent (BOLD) signal and the oxygenated–deoxygenated hemoglobin concentrations oscillates slowly in the human brain (Biswal et al., 1995; Lu et al., 2010; Zhang et al., 2010; Zuo et al., 2010). trNIRS is a complementary brain imaging technique to rs-fMRI since the BOLD signal is determined by regional change of blood flow, blood volume and cerebral blood oxygenation; indeed recent studies demonstrated that tr-NIRS and rs-fMRI reflect spontaneous hemodynamic fluctuations that characterize the resting state anatomical network (Cooper et al., 2012; Sasai et al., 2012; Tong et al., 2011). Moreover simultaneous recordings from direct current magnetoencephalography (DC-MEG) and trNIRS, has shown that neural activation precedes the brain vascular response by 1–4 s (Mackert et al., 2004, 2008).

While the exact origin and significance of ISO in brain electrical activity has yet to be established (Hughes et al., 2011), the interconnection between cerebral blood flow (CBF) and EEG is supported by observations that EEG bursts suppression rhythm (Golanov et al., 1994) and bursts of seizure activity (Roche-Labarbe et al., 2010) are accompanied by increase in CBF.

To further explore this correlation, the present work examines the coupling between electrical brain activity and blood flow velocity in human subjects undergoing non-pulsatile cardiopulmonary bypass (NP-CPB) — absence of physiological cardiac and respiratory activity in hypothermia and general anesthesia — at two levels of anesthesia, moderate and deep. First, we explored a linear relation between EEG bursts and BFV oscillations in deep anesthesia. Second, we performed linear and nonlinear multivariate analysis of BFV and a variability of EEG power, to extend the analysis to a moderate anesthesia experiment, where EEG bursts suppression are not present.

Material and methods

The present study was approved by local Institutional Ethical Committee and is in accord with the Declaration of Helsinki.

Participants

We retrospectively analyzed brain BFV and EEG data obtained from 28 anaesthetized patients who showed clear oscillations in brain BFV during NP-CPB. These patients belong to a group of 166 patients who underwent intraoperative neurophysiological monitoring during cardiac surgery with NP-CPB from July 2007 to July 2010 (Zanatta et al., 2011). Written informed consent for multimodal brain monitoring was obtained from all patients.

Procedures

All patients were divided in two groups according to the level of anesthesia defined as moderate and deep. Moderate anesthesia was defined as state when EEG theta rhythm became dominant. Level of anesthesia with prevalence of burst suppression pattern, characterized by alternative periods of waves of high amplitude (the burst) and periods of flat EEG (the suppression), was defined as deep. The prevalence of the burst suppression pattern was defined by a burst suppression ratio (percentage of time that the EEG is in the suppressed phase) above the 50%. During on-pump cardiac surgery, the proximal ascending aorta was clamped and the spontaneous cardiac activity was substituted by a continuous non-pulsatile perfusion aimed to maintain constant blood pressure. The rhythmic physiological pulmonary activity was substituted by supra-optimal continuous delivery of oxygen and removal of carbon dioxide through an extracorporeal oxygenator. A moderate hypothermia around 33–30 °C was also established to achieve a better organ protection during CPB.

Patients were premedicated in the ward with an intramuscular injection of fentanyl 100 mcg and midazolam 5 mg. Anaesthetic induction was established with fentanyl 5 mcg/kg, midazolam 0.2 mg/kg, propofol 1 mg/kg, and cisatracurium 0.1 mg/kg before tracheal intubation was performed. Anesthesia was maintained with propofol 2–4 mg/kg/min, remifentanil 0.2–0.4 mcg/kg/min or isoflurane 0.5–1.5 end tidal concentration. All patients were anesthetized by the same physician, who also performed the neurophysiological monitoring.

After anesthesia induction, electrical brain activity and BFV were monitored in a multimodality manner described in recent literature (Zanatta et al., 2011) using the following methods:

1. Bipolar EEG recordings from bilateral fronto-central channels (F3–C3′/F4–C4′) using the international 10–20 system. EEG parameters included sampling rate 250 Hz and pass-band filter at 1–30 Hz. The ground electrode was placed on the left shoulder. The electrode impedance was kept below 1 kΩ.
2. EEG power spectral density, computed via FFT on 2 s-segments of EEG recordings.
   EEG and EEG power density were recorded using Eclipse Neurological Workstation-Axon System (Hauppauge, NY, US). The variability of EEG power (EEG-PV) signal was derived from the time series of absolute power estimates obtained from the area under the curve of the power density spectrum of successive segments, as indicated in Fig. 1. We chose the term EEG-PV in analogy with Heart Rate Variability, which defines the cardiac cycle length variability.
3. Bilateral transcranial Doppler (TCD) recordings of blood flow velocity (BFV) from middle cerebral arteries. A multifrequency probe (2.5–2 MHz) was fixed on the bilateral trans-temporal windows using the Lam rack helmet (Doppler box-DWL/Compumedics Germany GmbH, Singen, Germany).

Data analysis

The relation between EEG activity and BFV in deep anesthesia was calculated using linear regression between the numbers of BFV fluctuations and EEG bursts in 5 min recordings, counted off-line by visual inspection of the recordings, in a blind manner, by the neurophysiologist and the technician who performed the neuromonitoring. Burst onset was defined as appearance of high amplitude EEG oscillations following the period of isoelectricity. Onset of BFV fluctuation was defined as a moment of the base line crossing of wave-like increase in BFV significantly exceeding (over 10%) random short-lasting increases of BFV.