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

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Abbreviations: BFV: blood flow velocity; EEG-PV: EEG power; ISO: infra-slow oscillations; CBF: cerebral blood flow; NP-CPB: non-pulsatile cardiopulmonary bypass; CSA: compressed spectral analysis; TCD: transcranial Doppler; AR: autoregressive; MVAR: multivariate autoregressive; C-ApEn: cross-approximate entropy.

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 (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 anaesthesia – deep (prevalence of burst suppression rhythm) and moderate (prevalence of theta rhythm).

Under deep anaesthesia, 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 anaesthesia, 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 anaesthesia 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 anaesthesia, 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 anaesthesia, indicating a higher level of synchrony between the two signals.

Presence of a subcortical brain pacemaker that triggers 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.

Keywords: infra-slow oscillations, non-pulsatile cardiopulmonary bypass, multimodality neuromonitoring, brain blood flow velocity, EEG power

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1 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., 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). 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 (Monto et al., 2008; Leistner et al., 2007; Vanhatalo et al., 2004; Aladjalova, 1954), including oscillations in EEG frequency bands and

EEG power (Mantini et al., 2007; 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; Dijk et al., 1990; Buzsaki, 2006; Csercsa et al., 2010; Destexhe et al., 2007; 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), have demonstrated that the blood oxygen level dependent (BOLD) signal oscillates slowly in the human brain (Zuo et al., 2010). BOLD signal is determined by regional change of blood flow, blood volume and cerebral blood oxygenation and is considered a marker of neural activation. Simultaneous recordings from direct current magnetoencephalography (DC-MEG) and time resolved near-infrared spectroscopy (trNIRS), has shown that neural activation precedes the brain vascular response by 1-4 s (Mackert et al., 2004 and 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 anaesthesia – at two levels of anaesthesia, moderate and deep. First, we explored a linear relation between EEG bursts and BFV fluctuations in deep anaesthesia. Second,

we performed linear and nonlinear multivariate analysis of BFV and a variability of EEG power, to extend the analysis to a moderate anaesthesia experiment, where EEG bursts suppression are not present.

2 Material and Methods

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

2.1 Participants

We retrospectively analyzed brain BFV and EEG data obtained from 28 anaesthetised 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.

2.2 Procedures

All patients were divided in two groups according to the level of anaesthesia defined as moderate and deep. Moderate anaesthesia was defined as state when EEG theta rhythm became dominant. Level of anaesthesia with prevalence of burst suppression pattern was defined as deep. 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. Anaesthesia 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 anesthetised by the same physician, who also performed the neurophysiological monitoring.

After anaesthesia 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. Compressed spectral analysis (CSA) of 2 s segments of EEG with absolute power and a “spectral edge frequency” of 95% (frequency below which 95% of the total power is contained). EEG and CSA 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.

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).

2.3 Data analysis

The relation between EEG activity and BFV in deep anaesthesia was calculated using linear regression and comparing the numbers of BFV fluctuations to the numbers of EEG bursts in 5 min recordings.

To derive a more detailed quantitative picture of the coupling between the two signals – also applicable to moderate anaesthesia when EEG bursts are not present – linear and nonlinear processing methods were applied to EEG-PV and BFV signals to calculate widely used measures of signal coupling, as follows:

1. Frequency of BFV and EEG-PV oscillations were identified after transforming the signals in the frequency domain. To this purpose, univariate spectral analysis of each signal was performed by using a parametric approach (Muthuswamy and Thakor, 1998) based on preliminary identification of an AutoRegressive (AR). Single-peak spectra were characterised by the peak frequency, multipeak spectra by the mean dominant frequency.
2. Coherence function between EEG-PV and BFV, which is a widely used measure of linear coupling at any given frequency, was evaluated as the ratio between the absolute value of the cross-spectrum between the two signals, which was normalised by their auto-spectra. Auto- and cross-spectra were estimated via MultiVariate AutoRegressive (MVAR) models, identified by simultaneous analysis of EEG-PV

and BFV data (Hytti et al., 2006). By definition coherence values range in the 0–1 interval, with values close to 0 at a given frequency being associated with independent signals at that frequency, while values close to 1 are reached by linearly related signals. Values above 0.5 were indicative of a reliable coherence (Bendat and Piersol, 2010).

3. Granger causality, based on the idea that time series *x* causes series *y* if the prediction of *y* can be improved – in the mean square sense – by adding the past of *x* to the set of predictor variables (Granger, 1969), computed as follows:

$$GC_{x\to y} = \ln \frac{\mathrm{var}(y)}{\mathrm{var}(y|x)}$$

where *ln* is the natural logarithm, *var(y)* is the residual variance of the univariate AR model, which measures the reliability of *y* predictions based on the past of *y*, while *var(y|x)* is the residual variance of the multivariate model, which measures the reliability of *y* predictions based not only on the past of *y* but also on the values of *x*. A significant positive difference in Granger causality between EEG-PV→BFV and BFV→ EEG-PV indicates a causal effect direction between the two signals, namely of EEG-PV on BFV.

4. Cross-approximate entropy (C-ApEn) provides a statistic measure of nonlinear interactions: A stronger coupling between two time series results in a lower value of C-ApEn, while more discordant signals are associated with higher values of the index. (Pincus et al., 1996).

2.4 Calculations

Data are expressed as mean ± standard deviation. A non-parametric Mann-Whitney test was used to determine the significance of differences between moderate and deep anaesthesia. A non-parametric Wilcoxon test was used to determine the significance of differences between paired data. $P < 0.05$ was considered to statistically significant. All signal processing methods were implemented in MATLAB. AR and MVAR model identifications were performed by least squares, and model orders were selected by minimising the Akaike Information Criteria (Akaike, 1992). Cross-approximate entropy was calculated according to the formulas in Kreuzer et al. (2010), setting the pattern length equal to 1 and the noise threshold equal to 0.20.

3. Results

3.1 BFV and EEG activity

In our 28 patients, during moderate anesthesia, BFV showed regular oscillation with a periodicity of approximately 14 s and a mean value ranging from 30 to 40 cm/s (Fig. 2a), (supplementary videos 1 and 2). In states of gradually increasing depth of anaesthesia (increasing the dose of isoflurane, propofol, or remifentanil), an EEG bursts suppression pattern appeared associated with a gradual reduction in average BFV amplitude (Fig. 3a), (supplementary videos 3 and 4). Subsequently, increase in BFV followed bursts of EEG with a latency of 1.95 ± 0.6 s, (supplementary video 5).

3.2 Relationship between bursts of EEG activity and BFV in deep anaesthesia

The number of BFV oscillations and EEG bursts in a 5 min time period strongly correlated ($R = 0.849$, $p < 0.01$) (Fig. 4) in our patients during deep anaesthesia (supplementary video 5).

3.3 Frequency of BFV and EEG-PV oscillations

Frequency domain representation of BFV signal in a representative patient , indicates a similar frequency of BFV oscillations in both moderate (Fig 2b) and deep anaesthesia (Fig 3b) since BFV spectrum had a sharp peak at frequency 0.065 ± 0.010 and 0.060 ± 0.024 Hz respectively. However, the intensity of BFV oscillations significantly decreased in transition from moderate to deep anaesthesia (from 141 ± 118 to 85 ± 78 $(cm/s)^2/Hz$ – $p < 0.05$). The frequency domain representation of EEG-PV indicates that EEG-PV oscillations occurred over a wide band, with upper limit increasing from moderate (Fig 2d) to deep anaesthesia (Fig 3d) (0.159 ± 0.075 vs 0.197 ± 0.060 Hz) and a significant increase in the mean dominant frequency (from 0.045 ± 0.019 to 0.062 ± 0.017 Hz – $p < 0.05$). These results suggest an alignment of EEG-PV with BFV during deep anaesthesia, since the mean dominant frequency of EEG-PV was not significantly different from the BFV peak frequency. No significant difference in BFV and EEG-PV spectral parameters was observed between the two hemispheres; therefore, all values reported above were calculated by pooling together results from the two hemispheres.

3.4 Coherence function between EEG-PV and BFV

Coherence function, peaked at frequency 0.063 ± 0.016 Hz and 0.068 ± 0.026 Hz for moderate and deep anaesthesia, respectively, not significantly different in the two conditions and both close to the mean dominant frequency of the EEG-PV and BFV spectrum (Fig. 5). As regards the peak amplitude, its value indicates a significant (i.e., greater than a value of 0.5) linear interaction between BFV and EEG-PV in 6 of 11 subjects under moderate anaesthesia and 11 of 17 subjects under deep anaesthesia. Coherence phase, evaluated at peak frequency, which is an indicator of the lag between the two signals, was not significantly different from zero (

0.364 ± 1.241 rad in moderate and -0.045 ± 0.307 rad in deep anaesthesia), suggesting no significant time delay between EEG-PV and BFV.

3.5 Granger causality

When Granger causality was analysed, a significant positive difference emerged between EEG-PV→BFV and BFV→ EEG-PV both in moderate (0.348 ± 0.464 – $p < 0.05$) and in deep (0.183 ± 0.473 – $p < 0.05$) anaesthesia, indicating a causal effect of EEG-PV on BFV.

3.6 Cross Approximate Entropy

A significant decrease was detected on C-ApEn calculated on EEG-PV and BFV time series during moderate versus deep anaesthesia (1.838 ± 0.173 vs 1.572 ± 0.126 – $p < 0.5$), indicating that the reduction of cerebral metabolic activity caused by anesthetics promotes the level of synchrony between EEG-PV and BFV signals.

4 Discussion

In our study we observed slow oscillations of EEG-PV and BFV in middle cerebral artery in deeply anesthetized patients in the absence of pulsatile blood flow and respiration. Analysis of observed oscillations strongly suggests that slow fluctuations of middle cerebral artery BFV in anesthetized humans is being driven by brain activity. These findings expand earlier observation of close coupling of spontaneous EEG activity and cerebral blood flow in deeply anesthetized rats suggested by Golanov et al. (1994). The only human study by Roche-Labarbe and collegues (2007) demonstrated comparable coupling of burst of EEG activity at 0.05-0.1 Hz and spontaneous fluctuations of the concentration of oxy- and deoxy-hemoglobin as recorded by Near Infrared Spectroscopy (NIRS) over the scalp during quiet sleep in premature babies.

We used quantitative analysis and advanced modeling approach to evaluate the presence of EEG and BFV oscillations and the extent of coupling between these parameters under deep (prevalent burst suppression rhythm) and moderate (prevalent theta rhythm) anaesthesia. Univariate and multivariate spectral analysis of EEG-PV revealed symmetrical bilateral ISO of mean dominant EEG frequency of lower than 0.1 Hz in all subjects. Analysis of BFV showed presence of similar slow oscillations with a peak frequency of about 0.06 Hz. In addition, coherence analysis demonstrated tight coupling between the two signals, which increased with the depth of anaesthesia. Moreover, the mean dominant frequency of EEG-PV, which was lower than BFV frequency peak in moderate anaesthesia, increased in deep anaesthesia and reached a value close to 0.07 Hz. Similarity of fluctuations of EEG-PV and BFV suggested both linear and nonlinear coupling between the two signals. Further coherence analysis demonstrated significant linear relation between two parameters in most subjects. This conclusion was confirmed by approximated entropy (C-ApEn) analysis, which in addition revealed nonlinear coupling component and increase in coupling with the depth of anaesthesia. Use of Granger causality index established deterministic role of EEG-PV in EEG-PV - BFV coupling.

Together these results suggest the existence of a brain generator that leads electrical synchronisation that, subsequently, determines oscillations in local vasomotion.

The experimental condition of extracorporeal circulation, non-pulsatile cardiopulmonary bypass (NP-CPB), allowed us to exclude any cardiac-respiratory influence on brain vasculature, which can introduce slow oscillation BFV (Newell et al., 1992). Moreover, the moderate hypothermia delivered during CPB enhanced the effects of anaesthesia on EEG (Kochs 1995). Observed causative relations between EEG and BFV strongly suggest an association between brain activity and cerebral blood flow known as neurovascular coupling (Attwell et al., 2010). General

anaesthesia effectively suppresses brain activity related to higher brain functions, sensory information processing, and generation of efferent signaling (Brown et al., 2010). Thus, moderate and deep anaesthesia, in particular deep anaesthesia accompanied by burst suppression pattern, facilitates observation and analysis of neurovascular coupling.

What is the nature of ISO in the brain?

It is well-established that arterial vasomotion is the basis for maintaining tissue perfusion, especially at the lower limit of cerebral vessel auto-regulation (Diehl et al., 1998; Giller et al., 1999). Arterial vasomotion is determined by a series of oscillatory waves that decrease vascular resistance in an inverse relationship with arterial blood pressure (Jones et al., 1995). Moreover, Diehl et al. (1998) found an oscillatory relationship between vascular resistance and brain blood flow velocity to be most efficacious with respect to a simple linear one. The amplitude of these ISO differs in different parts of the brain. In fact, the amplitude of these ISO is significantly larger in the posterior with respect to anterior brain circulation (Haubrich et al., 2004). These differences are mainly due to the need to maintain the cardio-respiratory drive during syncope because of a low perfusion pressure in the posterior circulation.

There is also evidence that brain vascular vasomotion oscillations are synchronous with intracranial pressure oscillations – called “B wave” or “Mayer waves” – especially in conditions of reduced intracranial compliance (Newell et al., 1992). It is interesting to note, however, that these blood flow oscillations are independent of variations in metabolic parameters – such as arterial partial pressure of CO_2, arterial blood pressure, and regional cerebral glucose utilization – and that this vasoregulatory mechanism exists in the cerebral microvasculature independent of

local metabolic changes (Fox and Raichle 1986; Giller et al., 1999; Golanov et al., 1994; Newell et al., 1992).

The UP and DOWN states – biphasic depolarisation and hyperpolarization, respectively – characterising ISO in EEG recordings of human and animal experimental models of deep sleep have been suggested to form the fundamental basis of neuronal network dynamics (Kerr et al., 2005; Lampl et al., 1999; Petersen et al., 2003). During the positive slow-wave UP state, neuronal firing increases and intense synaptic activity seizes the brain. This depolarizing phase is then followed by a longer DOWN state, during which all synaptic activity ceases.

With regard to brain activity, ISO in resting human and rat brains detected by rs-fMRI (Biswal et al., 1995; Pawela et al., 2008), are likely a manifestation of functional cortical connectivity and represent an epiphenomenon of specific resting state anatomical networks (Damoiseaux et al., 2006).

Interesting researches by Mackert et al. show that non invasive neuroimaging method like trNIRS combined with DC-MEG could be helpful in studying evoked and resting slow neurovascular coupling (Mackert et al., 2004 and 2008).

There is substantial evidence that the electrical oscillatory phenomenon promotes a spatio-temporal synchronization among different neural structures: fast oscillations seem to facilitate activation of small volume of neurons while ISO promotes temporal organization of neural activity in a larger and distant neural population (Sirota and Buzsaki, 2005). This temporal organization of distant neural structures provides a possible mechanism for storage, readout, and transfer of information, thereby providing a basis for the consolidation of memories (Buzsaki, 2006; Sirota and Buzsaki, 2005). Interestingly, long-term memory formation can be disrupted by blocking the lactate transfer into astrocytes (Suzuki et al., 2011), suggesting not only a

fundamental role of astrocytes in the maintenance of the functional coupling between neurons and vessels and vasomotion (Hamel, 2006, Attwell et al. 2010) but also a probable glial origin of ISO (Lörincz et al., 2009). Literature suggests the presence of ISO ingamma band oscillations power (Logothetis et al.,2001; Nir et al., 2008; Magri et al., 2012).However, since gamma rhythm is suppressed under anesthesia in human subjects (e.g. Uchida et al., 2000; Sleigh et al.., 2001), as shown in our experimental conditions (i.e. moderate and deep anesthesia), we did not includ analysis of higher EEG frequencies.

Hence, while slow electrical fluctuations maintain the synchronization between neural structures, the neurovascular coupling allows slow fluctuations in blood flow to maintain and provide an adequate tissue perfusion.

Where is the origin of ISO in the brain?

The origin of coupled EEG-PV – BFV fluctuations is still largely debated. Pioneer work by Mircea Steriade identified the origin of the brain's electrical slow oscillations in the intrinsic networks of the cerebral cortex (Amzica and Steriade, 1995). Moreover, an analysis of EEG signals placed a possible origin of slow wave oscillations in the anterior cerebral cortical areas (Massimini et al., 2004). EEG slows down under deepening anesthesia (Brown E.N. et al., 2010) comparable to slow-wave sleep, when thalamocortical neurons switch from tonic to bursting mode inhibiting transmission of somatosensory information (Steriade et al 2003). Further deepening of anesthesia leads to development of burst-suppression rhythm driven by periodic activity of thalamocortical neurons (Steriade et al., 1994), which together with astrocytes form the system capable of generation of intrinsic ATP-dependent slow oscillations (Lornicz et al., 2009). Burst-suppression is spatially homogenous and synchronously occurs over the whole

cortex. It is thus conceivable that observed coupling of EEG-PV and BFV is determined, as our data suggest, by simultaneous excitation of number of cortical neurons followed by increase in cerebral blood flow reflected in the increase in BFV in middle cerebral artery. The phenomenon is comparable to coupled increase in cortical DC-magnetoencephalographic activity and time-resolved NIRS signal observed in awakening subjects (Mackert et al.., 2004, 2008). Importantly, the delay between the changes in cortical activity and changes in blood flow, while measured by different methods, is very close, 1-4 sec, suggesting the common coupling mechanism. Similar delay between EEG burst and local cerebral flow increase was observed in rats (Golanov et. al., 1994). Taking into account the innate inertia of circulatory response, it is surprising that latency of BFV response in middle cerebral artery is comparable to that observed in local cortical vasculature using laser Doppler flowmetry (Golanov et al., 1994) or time resolved NIRS (Mackert et al., 2008). Recently significant progress has been achieved in our understanding of the end-effector mechanisms of neurovascular coupling (Attwell et al., 2010). However, the initiation of the cascade of events leading to vasodilation remains unclear. Relatively short latency between neuronal activation evidences in favor of devoted vasodilator pathways that may originate in thalamus and be spatially organized (Golanov et al., 2001)(Drew et al., 2008). Spatial organization of the vasodilator pathways is supported by the correlation of slow oscillations of cerebral blood flow in functionally correlated sites revealed by fMRI (Fox et al., 2005, 2007; Damoiseaux et al., 2006). At the same time, distribution of spatially specific changes in fMRI signal in awake subjects differs from globally occurring EEG-PV – BFV coupled fluctuations in our observations, which are frequency stable and does not seem to follow 1/f -like temporal dynamics. In literature, there is also evidence that ISOs may have other subcortical drivers. Neurophysiologic studies demonstrate a firing rate of 0.1 Hz in the

medullary, pontine and raphe neurons of vagotomised cats (Montano et al., 1996; Morris et al., 2010). In addition, others studies have shown the existence of neural projections from basal forebrain nuclei (nucleus basalis, locus coeruleus, and raphe nucleus) to cortical microvessels and associated astrocytes (Edvinsson et al., 1983; Hamel, 2006; Reinhard et al., 1979). There is also evidence that the 0.1 Hz activity is coupled both with medullary central respiratory drive areas and with slow oscillations of arterial pressure (Mayer waves) (Morris et al., 2010).

The work of Golanov et al. (1994) revealed a complex pathway from the cerebellum brainstem and thalamus to the cortex that causes spontaneous oscillations in the cerebral blood flow associated with synchronized slow wave oscillations in the cortex (Golanov et al., 1994; Golanov and Reis, 1995; Golanov et al., 2000; Golanov et al., 2001). These findings are in agreement with the hypothesis that brain ISO are accompanied by neurogenic changes in cerebral blood flow driven by thalamic neurons (Hughes et al., 2011; Magor et al., 2009). As suggested by Golanov and colleagues (2001), the thalamic area involved in cerebral blood flow regulation might also receive input from medullary neurons connected to sympathetic preganglionic neurons (Pyner and Coote, 1998). Cervical sympathetic preganglionic neurons play a major role in the extrinsic innervation of extracerebral blood vessels (Hamel, 2006). The subcortical origin of ISO is also supported by a recent study of simultaneous EEG recording and functional magnetic resonance imaging acquisition during deep sleep in which a positive correlation between ISO and blood dependent–oxygen dependent activity in subcortical regions was demonstrated (Picchioni et al., 2011).

Interestingly, the level of anaesthesia seems to have a role in modulating the strength of ISO without any interference with the frequency of EEG rhythm, similar to studies by Golanov et al. (1994). Moreover, our study confirms a reassessment of the significance of EEG burst

suppression pattern in condition of deep anaesthesia. The EEG burst suppression pattern might be the expression of brain autonomic function detected on the scalp, the ultimate cortical electric activity to remain before isoelectric EEG.

In light of our results, it is possible that specific neurons in the human thalamus constitute a deep brain pacemaker that synchronizes the brain slow wave rhythm both in blood flow and electrical activity with a frequency close to 0.06 Hz. The significance of this pacemaker might be crucial not only in explaining the phenomenon of ISO during deep sleep, vasomotion, and resting state fMRI but also in its essential role of a ISO neurovascular unit in the vital brain cognitive functions, such as consolidation of memories, determination of the default network, and protection of the human brain.

It is also possible to speculate that thalamic vasodilator area and medullar nuclei might have bidirectional connections. That allows explanation of the arterial vasomotion in the peripheral vasculature. In fact, ISOs of 0.07 Hz were detected in the peripheral capillary bed of patients undergoing NP-CPB using finger laser Doppler flow meter (Podgoreanu et al., 2002). To this extent, in the 1970s, microneurography studies showed that bursts of multi-unit sympathetic activity with interposed periods of more or less total neural silence (Hagbarth and Vallbo, 1968) recorded in the peroneal nerves are subjected to a homogenous central drive, and their occurrence shows an inverse correlation to variation in diastolic blood pressure (Wallin, 2006). They suggested a possible systemic neurovascular coupling that preserves basal tissue perfusion. It has been proposed that sympathetic nerve activity might have a role in the maintenance of haemodynamic homeostasis interacting with cardiac output and blood pressure (Charkoudian et al., 2006).

Some limitations affect our data interpretation. Although the main target of this work is to explore the infraslow neurovascular coupling in absence of cardiac and respiratory confounding factors, future studies will clarify BFV and EEG-PV coupling in awake subjects. Moreover to show whether infra slow neurovascular coupling are globally present in all subjects, the correlation of BFV and EEG-PV might be investigated in all patients submitted to intraoperative neuromonitoring. Further research should include a neuropsychological evaluation in order to investigate the strength of the correlation between BFV and EEG-PV and the amplitude of BFV oscillations with cognitive performance.

We were not able to replicate the work of Podgoreanu (2002) with laser Doppler flowmetry during CPB to investigate simultaneous oscillations in brain and peripheral vascular bed. Nevertheless visualization of heart rate and blood pressure in next works could give additional information on ISO generator and patient neurovegetative regulation.

5 Conclusions

Based on our results and literature data, we suggest that specific neurons in human thalamus constitute a deep pacemaker that controls electrical broad-band synchronization globally, observed through the temporal variability of EEG power. Moreover, the alignment of EEG-PV and BFV oscillations to the same frequency close to 0.07 Hz in the condition of deep anaesthesia clearly demonstrate the existence of an ISO and vascular coupling. This pacemaker might be important not only for explaining temporal evolution of EEG power during deep sleep, local vasomotion, and resting state fMRI but also in terms of neurovascular unit for the regulation of

brain cognitive functions, such as consolidation of memories, determination of the default network, and protection of the human brain.

Figure Legends

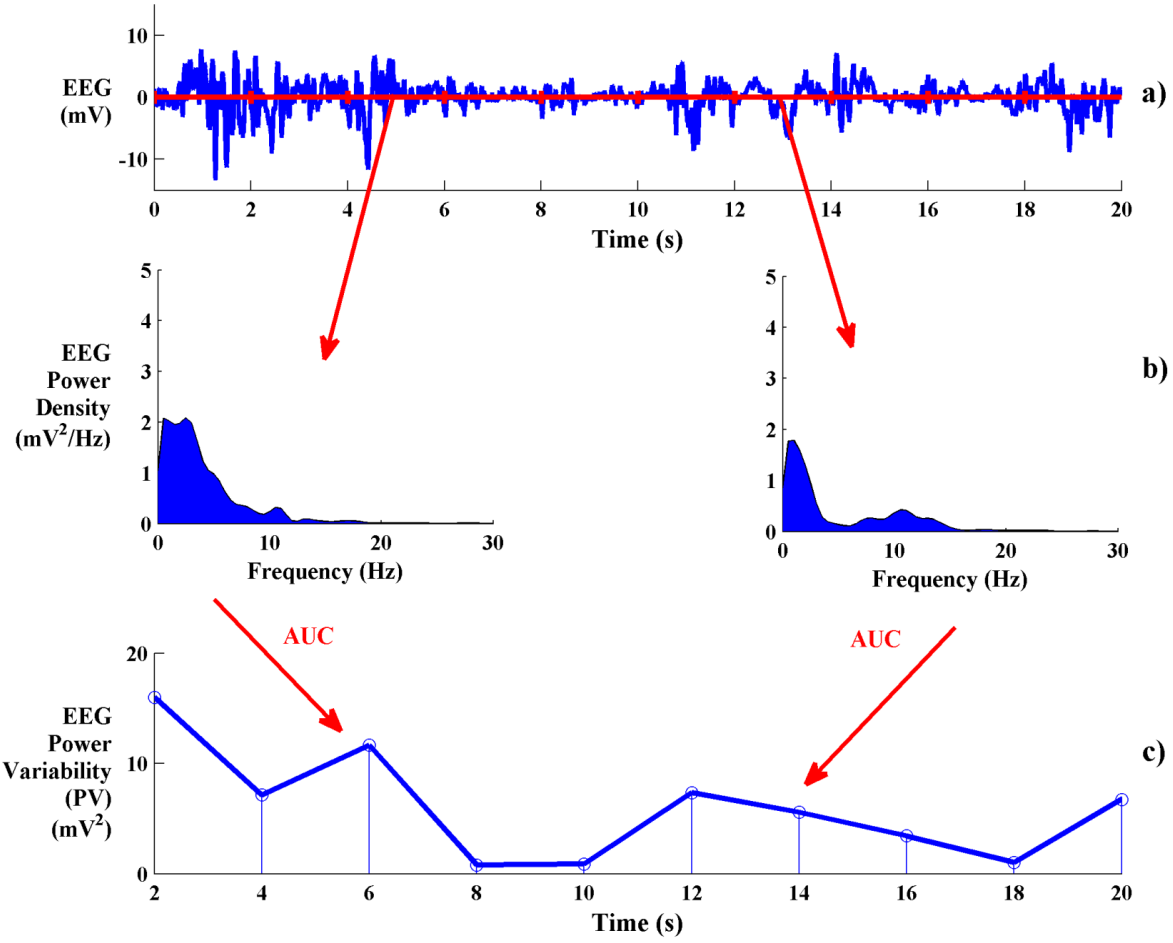

Figure 1. Derivation of EEG power variability (PV) signal from EEG recordings through steps (a) EEG is divided into 2s segments; (b) for each segment, EEG power density is evaluated; (c) power of each segment, calculated as the area-under-the curve (AUC) of the power density, provides samples of EEG-PV signal.

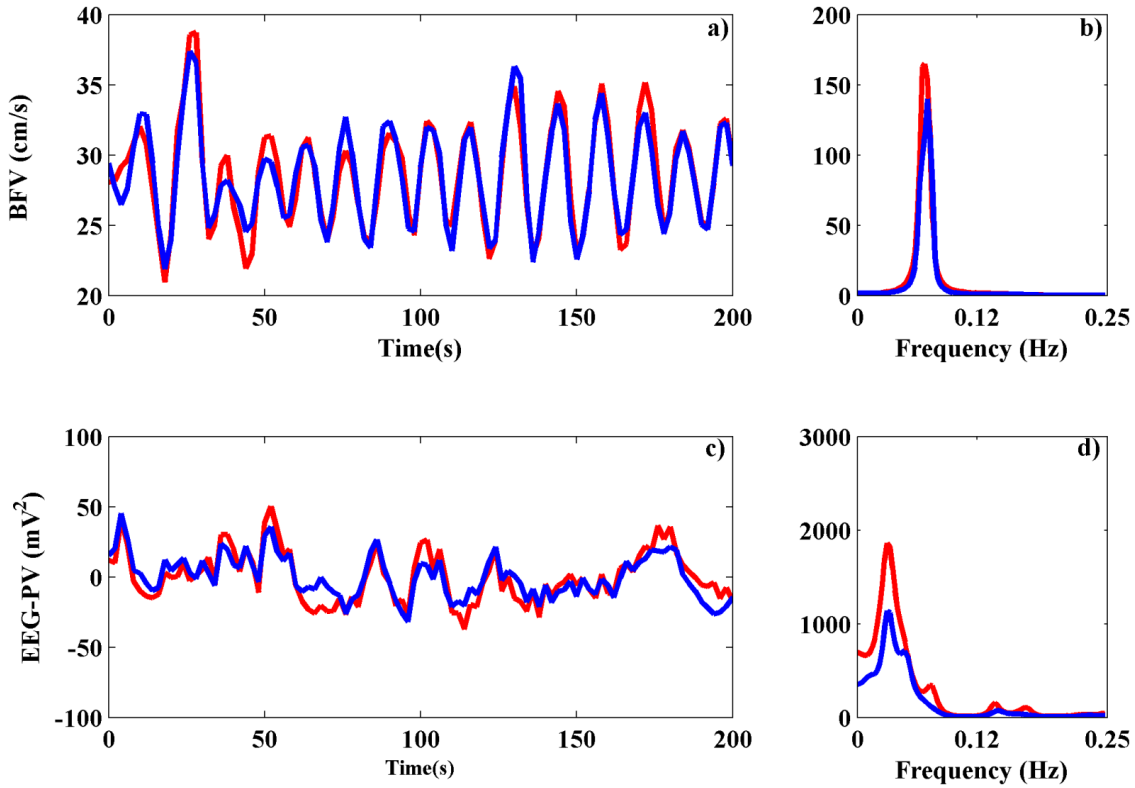

Figure 2. BFV and EEG-PV signals in moderate anaesthesia detected bilaterally in a representative study (red - left- and blue – right). Panels (a) and (c) show the time domain representation, panels (b) and (d) the frequency domain representation.

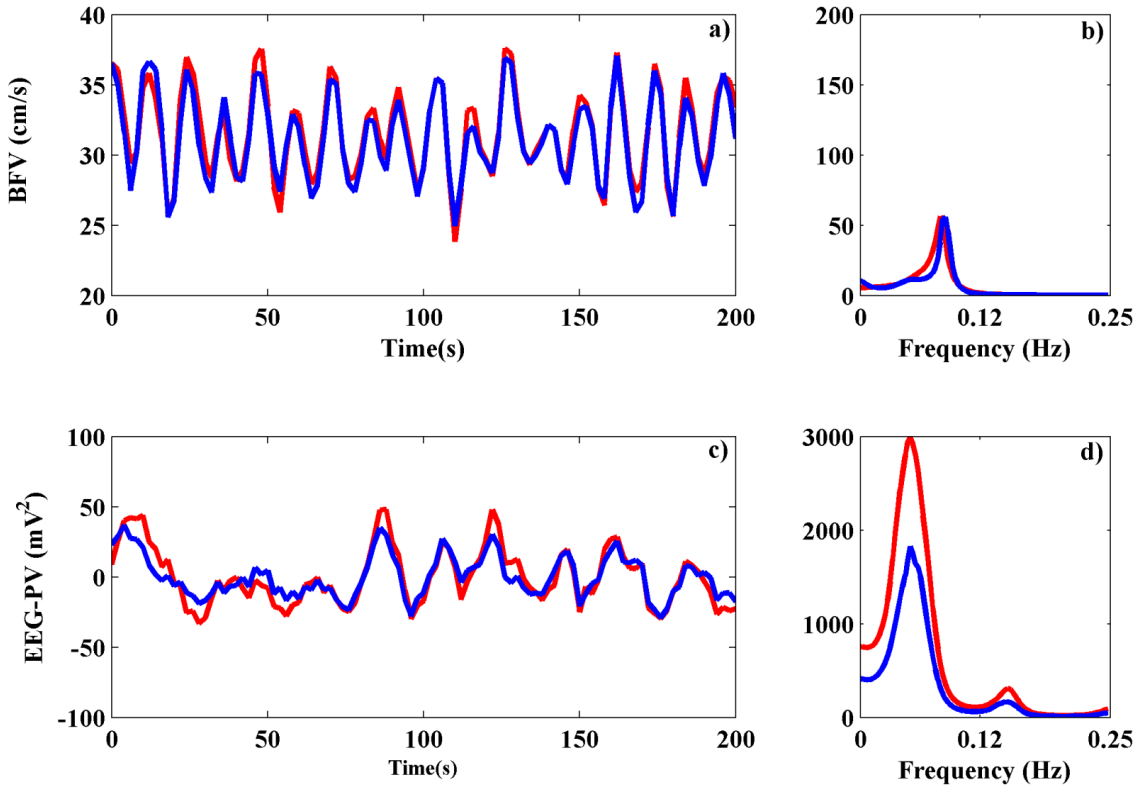

Figure 3. BFV and EEG-PV signals in deep anaesthesia detected bilaterally in a representative study (red - left- and blue – right). Panels (a) and (c) show the time domain representation, panels (b) and (d) the frequency domain representation.

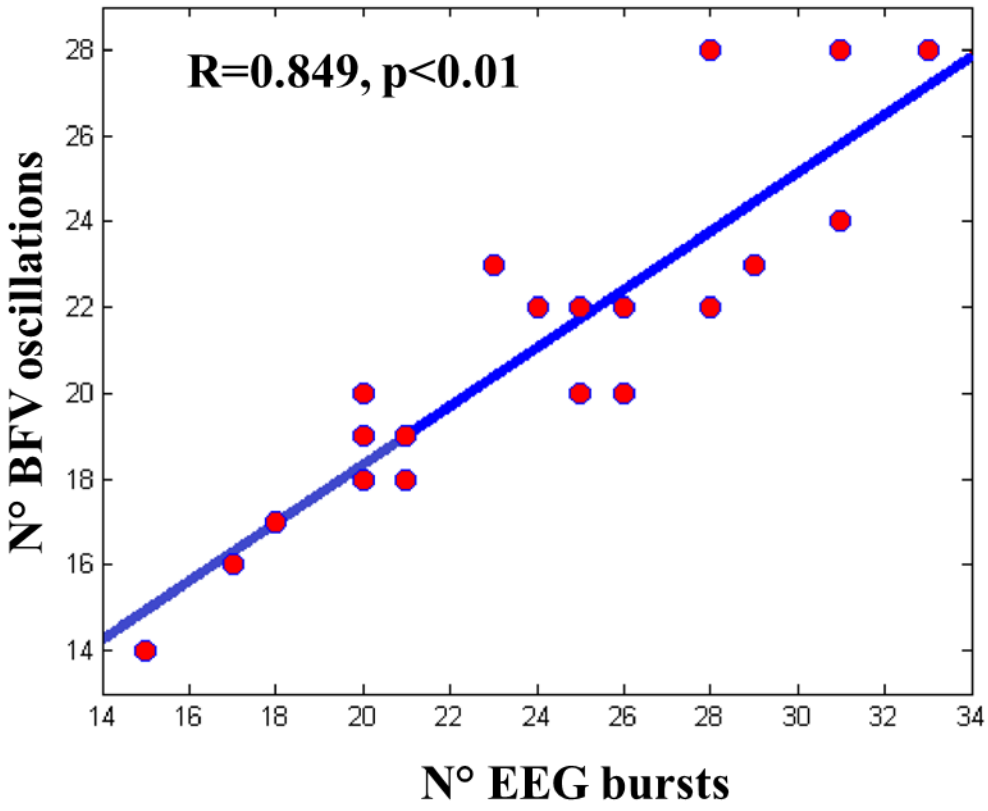

Figure 4. Numbers of EEG bursts vs. numbers of BFV fluctuations in 5 min recording of 28 subjects during deep anaesthesia (dots) and linear regression (line).

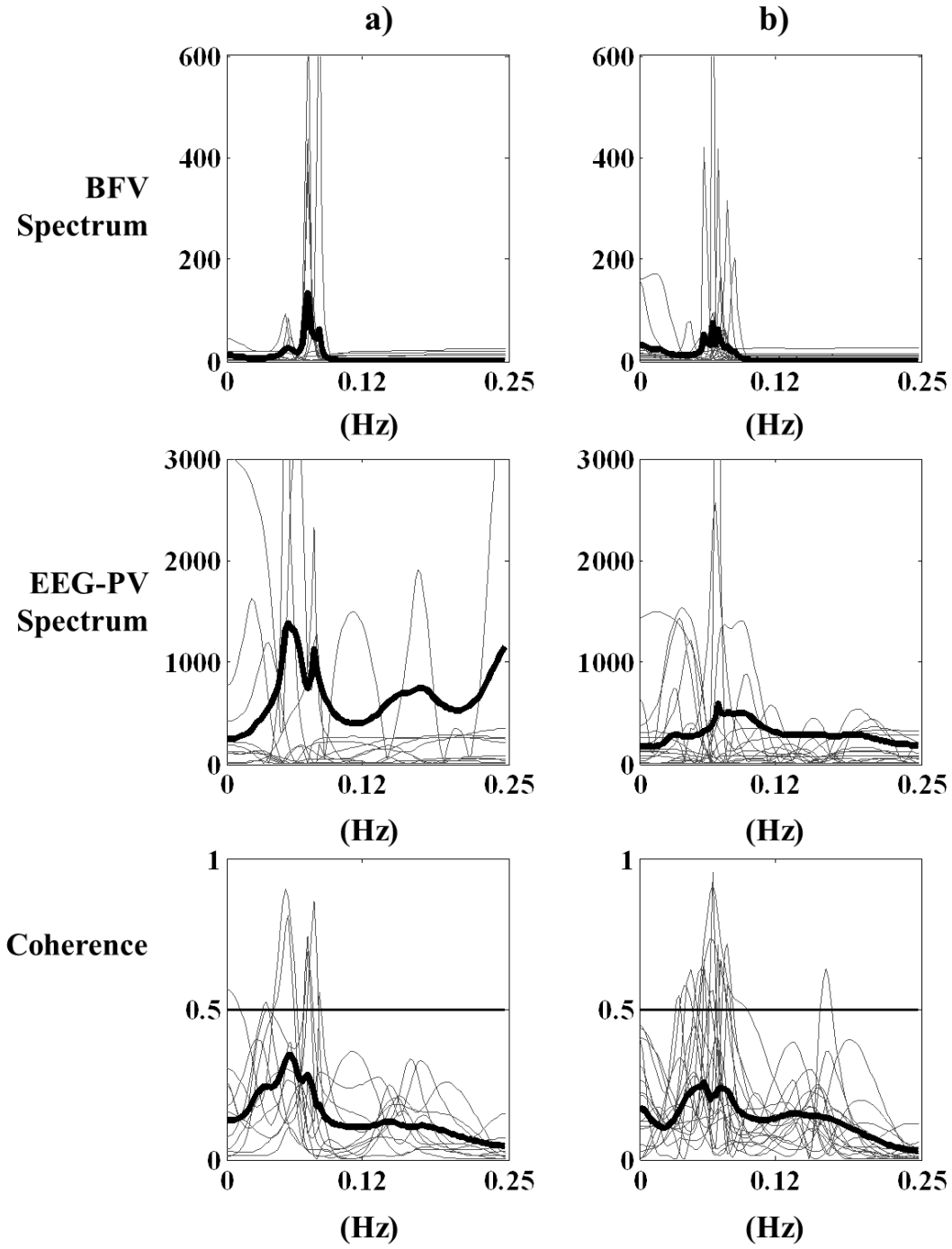

Figure 5. Individual spectra of BFV and EEG-PV and Coherence in (a) moderate and (b) deep anaesthesia. Bold line evidences the grand average.

Video Legends

Video 1. TCD bilateral monitoring during moderate anaesthesia. Spectral view upper; trend view lower. Note the regular oscillations of the mean BFV and the typically oscillatory sound of BFV vasomotion.

Video 2. Corresponding video of Figure 2. Integrated online multimodality monitoring (TCD upper, EEG middle, CSA lower) during moderate anaesthesia. Note the regular oscillations of the mean BFV (time base 6 min) on the lower portion of TCD and on the BFV spectrogram (time base 7 s) on the upper portion of TCD. Note the presence of a EEG theta band (6.8 Hz) on the CSA. Note the relationship between oscillatory patterns of EEG theta band power and BFV (TCD). The CSA display has 2 s delay in respect of EEG and TCD signals.

Video 3. TCD bilateral monitoring during deep anesthesia of the same patients showed in Video 1. Spectral view upper; trend view lower. Note the regular oscillations of the mean BFV with reduced amplitude in respect to video 1 and the typically oscillatory sound of BFV vasomotion.

Video 4. Integrated online multimodality monitoring (TCD upper, EEG middle and CSA lower) during deep anesthesia of the same patient showed in Fig 2. Note the regular oscillations of the mean BFV (time base 6 min) on the lower portion of TCD and on the BFV spectrogram (time base 7 s) on the upper portion of TCD. The oscillation in BFV appeared with lesser amplitude in respect of video 2. Note the presence of an EEG burst suppression pattern on the EEG and his

relation with BFV fluctuations on TCD. The CSA display has 2 s delay in respect of EEG and TCD signals.

Video 5. Typical example of integrated online multimodality monitoring (TCD upper, EEG middle, CSA lower) and anaesthesia monitor (right lower) during deep anaesthesia and NP-CPB. Also visible are the EEG recording parameters on the right upper side. Note the coupling between EEG burst and vasomotion. Note on the anaesthesia monitor, the flat line corresponding to blood pressure (91–95 mmHg), heart frequency (0 beats/min), central venous pressure (4 mmHg), peripheral oxygen saturation (100%), pharyngeal and rectal temperature (28.1°C, 30.4°C).

Funding Source

This study was support by a grant from the Regione Veneto in Italy for a project on the Reduction of Neurodysfunction after Cardiac Surgery and Neurosurgery, Improvement in Multimodality Neuromonitoring for neurophysiological technicians.

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Disclosure Statement

All authors disclose any actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence their work.