Spontaneous Low-Frequency Oscillations in Cerebral Vessels: Applications in Carotid Artery Disease and Ischemic Stroke

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The etiology behind and physiological significance of spontaneous oscillations in the low-frequency spectrum in both systemic and cerebral vessels remain unknown. Experimental studies have proposed that spontaneous oscillations in cerebral blood flow reflect impaired cerebral autoregulation (CA). Analysis of CA by measurement of spontaneous oscillations in the low-frequency spectrum in cerebral vessels might be a useful tool for assessing risk and investigating different treatment strategies in carotid artery disease (CAD) and stroke. We reviewed studies exploring spontaneous oscillations in the low-frequency spectrum in patients with CAD and ischemic stroke, conditions known to involve impaired CA. Several studies have reported changes in oscillations after CAD and stroke after surgery and over time compared with healthy controls. Phase shift in the frequency domain and correlation coefficients in the time domain are the most frequently used parameters for analyzing spontaneous oscillations in systemic and cerebral vessels. At present, there is no gold standard for analyzing spontaneous oscillations in the low-frequency spectrum, and simplistic models of CA have failed to predict or explain the spontaneous oscillation changes found in CAD and stroke studies. Near-infrared spectroscopy is suggested as a future complementary tool for assessing changes affecting the cortical arterial system. **Key Words:** Cerebral autoregulation—low frequency oscillations—stroke—carotid artery disease—transcranial Doppler—near-infrared spectroscopy.

Cerebral autoregulation (CA)[1] is controlled and affected by neurogenic,[2,3] metabolic,[4,5] and myogenic[6,7] mechanisms, making it complex to study and interpret. Various neurologic disorders exhibit changes in CA.[8-11] CA can be studied by static[12] and dynamic[5] interventional methods, but the use of these methods requires a certain level of compliance and can be stressful or even harmful to the patient. Over the last 10 years, an increasing number of studies have assessed CA by recording spontaneous oscillations in mean arterial blood pressure (MAP) and cerebral blood flow (CBF). This approach to assessing CA can be termed spontaneous dynamic CA. Spontaneous changes in MAP and CBF can be oscillations at respiratory and cardiac frequencies. Numerous studies[13-28] have focused on changes in low-frequency oscillations (LFOs, known as Mayer waves,[29] at 0.1 Hz) and very low-frequency oscillations (VLFOs, known as B-waves,[30] at 0.04 Hz). These studies have reported interesting findings indicating impaired CA in neurologic pathologies. Investigating the level of CA impairment assessed through the analysis of spontaneous oscillation is of clinical interest, because this analysis might provide a useful tool for assessing risk and

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evaluating treatment strategies in cerebrovascular disease. In this article, we discuss the etiology behind spontaneous oscillations in the low-frequency spectrum and review studies that have investigated spontaneous oscillations in MAP and CBF in carotid artery disease (CAD) and ischemic stroke.

Etiology of Oscillations in the Low-Frequency Spectrum

Although spontaneous oscillations in the low-frequency spectrum in systemic blood pressure were discovered more than 130 years ago,[29] the driving mechanisms responsible for these LFOs is unclear. Interventional studies have shown that neurogenic,[31] metabolic[32] and myogenic stimuli[33] all affect LFOs. LFOs are believed to reflect changes in sympathetic tone[34] based on human[35] and animal[36] studies, in which oscillations were found to be strongly attenuated by alpha-adrenoceptor blockade.

The pacemaker hypothesis is derived from observations in experimental animal studies of efferent sympathetic nervous activity and MAP oscillations in the absence of sensory input from the periphery.[37-39] The exact location and function of a possible central pacemaker is unknown. It is known that CBF can be altered by electrical stimulation of brainstem centers.[40] Serotonergic nerves from the brainstem's median and dorsal raphe nuclei project to major resistance vessels,[41] and electrical stimulation of the dorsal raphe nucleus leads to serotonergic activity in major cerebral arteries.[42] These findings suggest that a central pacemaker may be located in the brain stem.

Guyton and Harris[43] originally proposed a baroreceptor reflex effect on LFOs. This was later confirmed in animal studies showing that sinoaortic deafferentation attenuates Mayer waves.[44,45] Interestingly, a study evaluating both sinoaortic baroreceptor denervation and sympathetic blockade in rats found that ~80% of the LFO power of MAP depended on the sympathetic nervous system activity, whereas the baroreflex accounted for ~50% of this power.[46] This suggests that both a central pacemaker and the baroreflex might modulate LFO.

VLFOs, often referred to as B-waves, were originally observed by Lundberg[30] as spontaneous oscillations in intracranial pressure (ICP) at frequencies below 0.04 Hz in patients with various intracranial diseases. VLFOs also have been observed as a normal physiological phenomenon in healthy persons measuring ICP,[47] intraventricular cerebrospinal fluid flow,[48] and flow velocity in the middle cerebral artery,[49] suggesting a vascular myogenic mechanism based on the basic properties of the type of smooth muscle cells in cerebral vessels. Other studies have suggested that VLFOs, like LFOs, are caused by a central pacemaker.[47,50] Given that VLFOs in CBF are mostly independent of MAP,[51] a myogenic mechanism should be considered. Conversely, bilateral assessment of VLFOs by transcranial Doppler ultrasonography (TCD) showed that the changes are synchronized, suggesting a central pacemaker mechanism.[47] Thus, the main difference between the different oscillation frequencies lies in the fact that LFOs are driven by spontaneous MAP changes, whereas VLFOs seem to be generated by mechanisms independent of MAP.

Functional Purpose of Oscillations in the Low-Frequency Spectrum

Very little data are available addressing the question of a physiological functional purpose of LFOs and VLFOs. Roche-Labarbe et al[52] found associations between oscillations in the LFO range and spontaneous electroencephalogram bursts in neonates, suggesting that changes in oscillations are coupled to neuronal activity. In terms of blood flow and oxygen delivery, a mathematical model has shown greater oxygen conductance in vessels with an oscillating diameter compared with vessels with a constant diameter.[53] A rat in vivo model examining the femoral artery found that during critical perfusion conditions, oscillations of arterioles at 0.034 Hz preserved nutritive perfusion.[54] Whether these findings apply to the synchronized LFOs and VLFOs in systemic and cerebral vessels remains to be investigated. The finding that LFOs play a role in oxygen delivery could mean that impaired oscillations in a neurologic pathology is a direct causal factor in the outcome of the pathology, and thus would be important to monitor.

Measurement of Systemic and Cerebral Vessel Oscillations

Oscillations in the low-frequency spectrum in systemic MAP[14,21,51] are commonly measured with a finger cuff system, using the volume clamp method of Penaz et al.[55] TCD can be performed at the patient's bedside and provides high-resolution measurement of velocity of the middle cerebral artery (VMCA), which supplies each hemisphere with up to 80% of the flow volume to the brain.[56] Because VMCA is easy to insonate, and the diameter of the MCA does not change even under strong blood pressure manipulations,[57] spontaneous changes in VMCA are believed to be caused by changes in CBF. VMCA may also be a reliable surrogate for blood flow changes in the internal carotid artery (ICA).[58]

A different approach to analyzing CA is through near-infrared spectroscopy (NIRS), which detects relative changes in cerebral oxygenation and blood volume over the cerebral cortex.[59] Because the most comprehensive research on spontaneous dynamic CA to date has been done through analysis of changes seen on TCD, we focus on those studies in the following sections. We then address investigations of spontaneous dynamic CA performed with NIRS.