Spectral changes of near-infrared spectroscopy signals in migraineurs with aura reveal an impaired carbon dioxide-regulatory mechanism

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William Liboni · Filippo Molinari · Gianni Allais · Ornella Mana · Emanuela Negri · Gennaro Bussone · Giovanni D'Andrea · Chiara Benedetto

Abstract Subjects suffering from migraine with aura (MwA) present an altered cerebral autoregulation during migraine attacks. It is still unclear whether MwA sufferers present a normal autoregulation during attack-free periods. In this study, we characterized cerebral autoregulation in the frequency domain by analyzing the spontaneous oscillations superimposed on the cerebral hemodynamic signals, as detected by near-infrared spectroscopy (NIRS). Ten healthy women (age: 38.4 ± 9.5 years) and ten women suffering from MwA (age: 35.2 ± 10.5 years) underwent NIRS recording in resting conditions and during breath-holding (BH). Being the NIRS signals during BH nonstationary, we used the Choi–Williams time–frequency distribution to perform spectral analysis. We considered 256 s of signals and quantified the variation in the power of the very-low frequencies (VLF: 20–40 mHz) and of the low frequencies (LF: 40–140 mHz) as response to BH. Results showed that BH increases the power in the LF band both in healthy and MwA subjects. Considering the signal of the deoxygenated hemoglobin, the average power increase in the LF band was equal to 20% ± 15.4% for the healthy group and significantly lower, 4.8% ± 8.3%, in the MwA group (Student's t test, $P < 0.02$). No significant difference was observed in the VLF band or in the oxygenated hemoglobin signal power variations of the LF and VLF bands. The resulting data reveal a possible impairment in the carbon dioxide-regulatory mechanism in MwA subjects.

Keywords Near-infrared spectroscopy · Migraine with aura · Cerebral autoregulation · Time–frequency distributions

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Introduction

Over the last few years, there has been a growing interest in the investigation of cerebral autoregulation of migraine sufferers. Moreover, particular interest has been devoted to the cerebral hemodynamic assessment of patients suffering from migraine with aura (MwA). Even if cerebral autoregulation impairment has been observed during MwA attacks, it is still unclear whether MwA sufferers present a normal autoregulation during attack-free periods [1].

Cerebral hemodynamics can be effectively characterized in the frequency domain [2]. Spontaneous oscillations superimposed on the cerebral hemodynamic signals can be detected by near-infrared spectroscopy (NIRS). These oscillations can be subdivided into two frequency bands: very low frequencies (VLF), also known as B-waves, ranging from 20 to 40 mHz and low frequencies (LF), also called M-waves, ranging from approximately 40 to 140 mHz. At the brain level, VLF are thought to be generated by brain stem nuclei, which modulate the lumen of

the small intracerebral vessels; LF reflects the M-wave systemic oscillations of the arterial blood pressure and are modulated by the sympathetic system activity [3].

Functional stimuli modulate the amplitude of VLF and LF oscillations [2]. This study was aimed at the evaluation of the power changes of the VLF and LF oscillations, as assessed by NIRS, in a group of MwA sufferers, compared to a group of healthy subjects. Breath-holding (BH), which has already proven efficacious for cerebral autoregulation assessment, was used as an active stimulation [4].

Subjects and methods

Subjects

After having obtained written informed consent, ten healthy women (age: 38.4 ± 9.5 years) and ten women suffering from MwA (age: 35.2 ± 10.5 years) were enrolled into the study. MwA was diagnosed according to the International Classification of Headache Disorders, second edition (ICHD-II) [5]. The presence of vascular, neurological, psychological, cardiac pathologies and/or cardiac defects were excluded for all subjects on the basis of clinical and instrumental examinations. Breath-holding was performed in a quiet room with dimmed lighting and the subjects lying in a supine, comfortable position, with their eyes closed. Before and after BH, they rested for about 5 min.

An NIRO300 (Hammamatsu Photonics, Australia) was used to record the NIRS signals. The light source was positioned on the forehead, about 2 cm alongside the midline and 3 cm above the supraorbital ridge. The distance between the source and the receiver was equal to 5 cm, and the differential path length factor was set to 5.97. The sampling frequency of the signals was equal to 2 Hz.

Signal processing

Since during BH the concentrations of the oxygenated (O_2Hb) and reduced hemoglobin (HHb) change very rapidly, the NIRS signals are to be considered as nonstationary. This implies that the time–frequency distributions should be used instead of the traditional Fourier-based spectral analysis. We used the Choi–Williams distribution, which is a bilinear transformation belonging to the Cohen's class [6]. Essentially, a series of instantaneous spectra of the signal under analysis may be obtained using this technique. These instantaneous spectra are then aligned up side-by-side, one for each time instant. Hence, the spectral content of a signal is represented in a bidimensional plane, as a function of time (on the horizontal axis) and frequency (on the vertical axis). In this way, the nonstationary nature of the NIRS signals during BH may be managed, making it possible to carry out a precise observation of the spectral component of the NIRS signals, at each single specific time instant. A time–frequency representation of an HHb NIRS signal is reported in Fig. 1.

The O_2Hb and HHb signals were analyzed in the time–frequency plane and the percentage of signal power in the VLF and LF bands (referred to the total power of the signal) calculated before and after BH. We considered

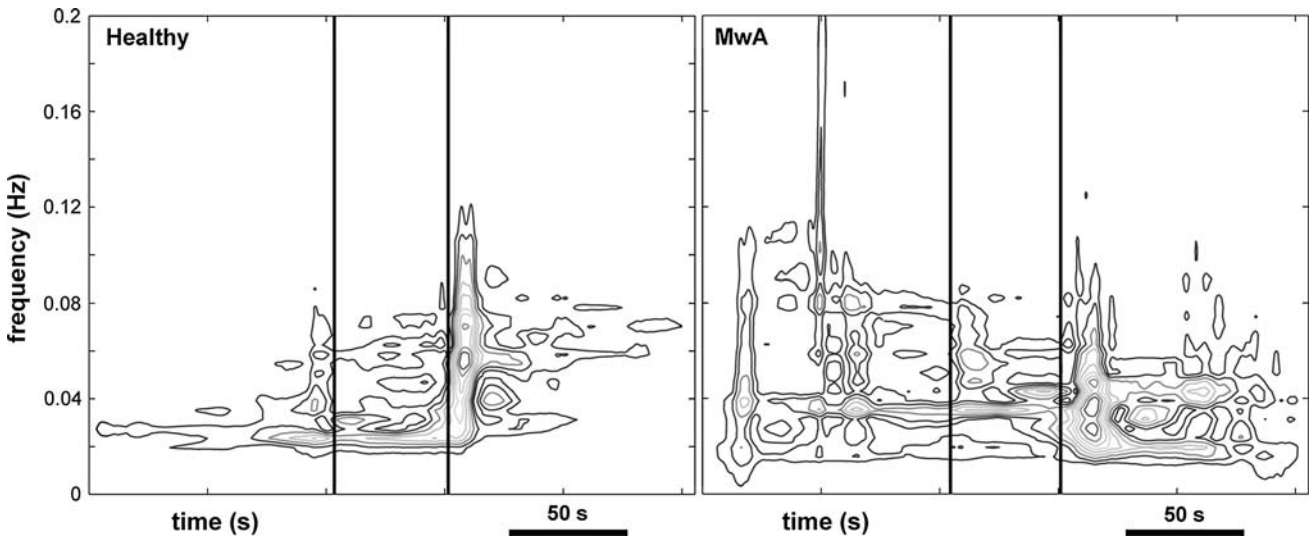

Fig. 1 Representation by level curves of the time–frequency transform of the HHb signal of a healthy subject (*left panel*) and an MwA patient (*right panel*). The *horizontal axis* reports time and the *vertical axis*, frequency. The *black vertical lines* represent the onset and offset of the BH. The BH caused the power in the LF band (0.04–0.14 Hz) to increase strongly in the healthy subject (+33%), with only a weak increase in the MwA subjects (+6%)

signals lasting 256 s, with the BH event in the middle of the analysis window (see Fig. 1). Hence, spectral resolution was better than 4 mHz, which has been shown to be a suitable value to clearly separate the two frequency bands.

Results and discussion

Figure 1 shows the TF distribution of the HHb signals in a healthy subject (left panel) and an MwA sufferer (right panel). The graph has been depicted by level curves. The black vertical lines indicate the onset and offset of the BH. Although it was observed that BH increases the power in the LF band in both the figures, in healthy subjects LF increased by about 33%, whereas in the MwA subjects there was only a 6% increase. Moreover, in healthy subjects the increase was sudden and instantaneous, whereas in the MwA subjects the LF power was dispersed over a larger time window.

On the global population, the average power increase in the LF band was equal to $20 \pm 15.4\%$ for the healthy group and $4.8 \pm 8.3\%$ in the MwA group. Healthy subjects showed a significant increase in the LF power compared to MwA patients (Student's t test, $P < 0.02$). No significant difference was observed in the VLF band, nor was there any statistically significant difference in the O_2Hb signal power variations of the LF and VLF bands.

The resulting data revealed a possible impairment in the carbon dioxide-regulatory mechanism in MwA subjects. In healthy subjects, at a microvascular level, the LF oscillations, which substantially reflect the sympathetic system activity, follow the macrovascular oscillations and become delayed in the presence of a hemodynamic impairment [7]. Hence, our results may show a possible impaired hemodynamic autoregulatory mechanism in MwA subjects.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

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