Thermoheliox: effect on the functional hemodynamics of the human brain

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A kinetic study of the effect of thermoheliox (inhalation of a helium and oxygen mixture, 70 °C) on the functional hemodynamics of the human brain by functional magnetic resonance imaging was carried out. The dynamic responses of the BOLD signal were found to be biphasic. An empirical equation describing the first phase of the hemodynamic response to visual stimulus was proposed. It was shown that preliminary inhalation of thermoheliox stimulates the hemodynamic responses by slowing down the vasoconstriction.

Key words: kinetics, thermoheliox, BOLD-effect, functional magnetic resonance imaging, visual stimulus.

The functional hemodynamics of the brain is a key process in the human central nervous system. In response to a signal, a local impulsive increase in the concentrations of oxygen and glucose (the main energy substrate of nerve cells), mediated by a specific behavior of the brain microvessels (neurovascular coupling), takes place in the excitation region of the neuron system. The impulse duration is approximately 10 s. This process is a highly important electromechanical feature of the brain as a biocomputer, which forms the basis for energy processes of receptor sensing, memory, thinking, and neurophysiological responses.

The unique opportunities for studying the neurovascular coupling are provided by functional magnetic resonance imaging (fMRI) based on the recording of BOLD responses (BOLD is blood-oxygen-level-dependent), superparamagnetic characteristics of oxygenated hemoglobin.[1—6] Our studies of the detailed mechanism of neurovascular coupling are based on experimental investigation of the process dynamics, chemical kinetic approach, and analysis of kinetic models.[7]

An attractive and potentially efficient method to influence the efficiency of oxygen transfer to nervous tissues during excitation is the use of thermoheliox, a breathing mixture consisting of oxygen and helium, at 50—100 °C.

Thermoheliox as a new medical technique is used for the therapy of respiratory diseases, ischemic strokes, dysfunctions of pregnancy, *etc*. It should be emphasized that high-temperature thermoheliox is effective for the treatment of coronavirus infection.[8—11]

This communication presents a quantitative study of the effect of thermoheliox on the dynamics of the hemodynamic response of the cortex excitation region after a visual signal. The study included three volunteers (two males and one female). As experimental results, we obtained 30 dynamic sets of BOLD signals before and after inhalation of thermoheliox (21% oxygen, 79% helium, temperature of 70 °C) for 0.5 h.

Experimental

Thermoheliox (a mixture of helium (60—80%) and oxygen (20—40%) heated to 100 °C) was clinically tested and approved in various fields of modern medicine. The study was performed using the Heliox-Extreme apparatus.[12] The device is equipped with a set of sensing measuring devices and algorithms tailored to particular pathologies.

Functional magnetic resonance imaging data were obtained on a Philips Achieva dStream magnetic resonance scanner with a constant magnetic field strength of 3.0 T. An echo-planar pulse

sequence (EPI) with the following parameters was used: repetition time (TR) of 3000 ms, echo time of (TE) of 30 ms, EPI factor of 240, number of slices of 40—50 (depending on the size of the head of the test subject), slice thickness of 3 mm, number of acquisitions (NSA) of 1, time of one dynamics of 3 s, number of dynamics of 120.

The visual stimulation consisted in presenting a test subject with 15 blocks of alternating rest phases (the subject looks at a black display for 21 s) and visual stimulus phases (the subject looks at a chess board image flashing at a frequency of 4 Hz for 3 s). The stimuli were presented using a special attachment, the start of the visual stimulation paradigm was synchronized with the start of fMRI scanning. For each subject, three fMRI scans were successively run before and after thermoheliox inhalation.

The BOLD response maps were obtained and processed using the SPM12 program.[13] Comparison of the maps showed a statistically significant contrast increase in the visual cortex in all subjects, but no significant response to visual stimulation in other brain loci. For each subject, an individual zone of activated visual cortex was identified by multiplying all his/hers BOLD response maps. In these zones, the data were averaged over 15 dynamics and the error of the mean was determined. This gave an individual time dependence of the relative intensity of the BOLD signal for each subject: the BOLD values for time t were normalized to the value for $t = 0$ (the time of the start of visual stimulus presentation).

The statistical data were processed using the Graphpad Prism software.[14] Several specific features of BOLD signal dynamics were detected and studied.

Results and Discussion

Biphasic character of the functional hemodynamic response. The response of the excitation region to a visual signal has a complex pattern and includes, at least, two dynamic phases. Typical dependences of BOLD responses to short visual stimuli are depicted in Fig. 1.
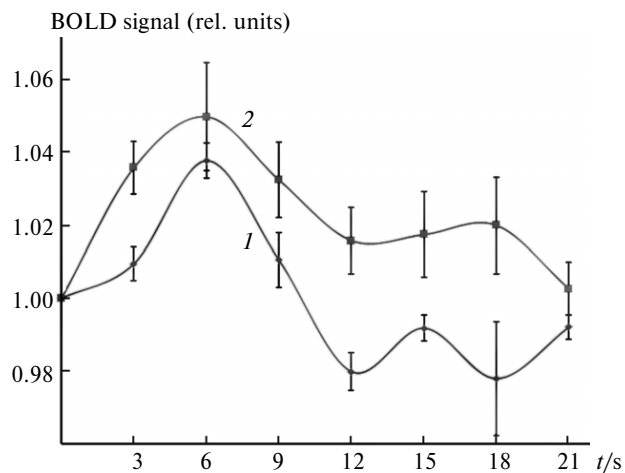
It can be seen that the BOLD signal includes two response waves (two phases) differing in intensity. The induction period (~2 s) is followed by an intense main hemodynamic surge (maximized at $t = 6$ s) followed by decay and a secondary, much weaker response (maximized at $t = 15—18$ s). The complex nature of the hemodynamic response is attributable to multipathway nature of coupling of the nerve impulse and vascular response. Note that the biphasic nature of the functional hemodynamic response was predicted from the kinetic modeling of the process.[15]

Empirical equation describing the first phase of the functional hemodynamic response. We proposed an empirical equation adequately describing the first phase of the hemodynamic response:

$$f(t) = 1 + At^n \cdot \exp(-kt), \tag{1}$$

where the induction period and the growth dynamics of the BOLD signal (vasodilation process) are reflected by the function At^n; the decay dynamics of the effect (vasoconstriction process) is described by the exponential function $\exp(-kt)$; the parameter n can correspond to the number of intermediate stages preceding accumulation of the vasodilator intermediate. A characteristic feature of function (1) is that it has a maximum. In addition,

$$n = kt_{max}, \tag{2}$$

where t_{max} is the time it takes to reach a maximum. Comparison of Eq. (2) with experimental data indicates that $n = 6$.

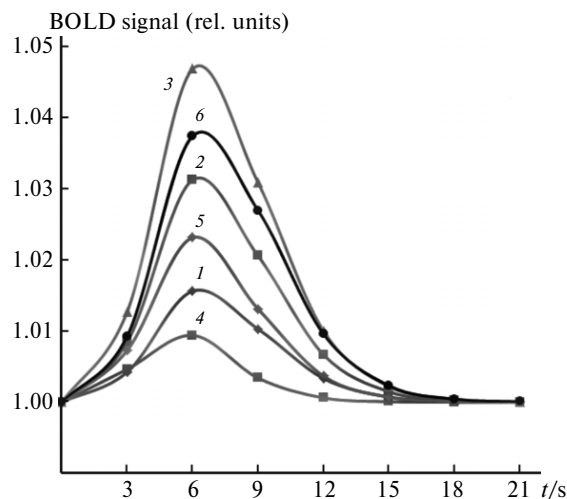The theoretical curves calculated from Eq. (1) upon variation of k and A are depicted in Fig. 2.

Fig. 1. Experimental data on the BOLD signal kinetics before (*1*) and after (*2*) the thermoheliox inhalation.

Fig. 2. Theoretical data on the BOLD signal kinetics derived from empirical function (1) by variation of the parameters A and k: $A = 0.0001$, $k = 0.95$ (*1*); $A = 0.0002$, $k = 0.95$ (*2*); $A = 0.0003$, $k = 0.95$ (*3*); $A = 0.0002$, $k = 1.15$ (*4*); $A = 0.0002$, $k = 1.00$ (*5*); $A = 0.0002$, $k = 0.92$ (*6*).

Thermoheliox stimulation of the hemodynamic response by slowing down the vasoconstriction. As can be seen from Fig. 1, preliminary inhalation of thermoheliox stimulates the BOLD signal. Using empirical equation (1), it is possible to identify the stage (vasodilation or vasoconstriction) that is affected by the preliminary thermoheliox inhalation. It follows from Eq. (1) that

$$\ln\{[f(t)_0 - 1]/[f(t)_{He} - 1]\} = \ln(A_0/A_{He}) + (k_{He} - k_0)t, \quad (3)$$

where $f(t)_0$ is the function BOLD(t) before thermoheliox inhalation, A_0 and k_0 are characteristics before the inhalation; $f(t)_{He}$, A_{He}, and k_{He} are the function BOLD(t) and parameters of the hemodynamic process after inhalation of thermoheliox heated to 70 °C for 30 min.
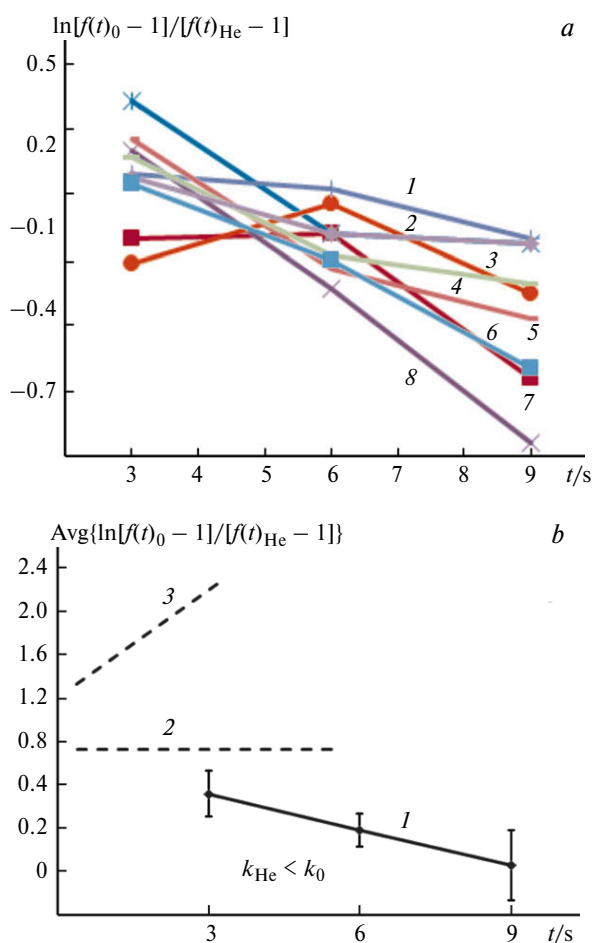
Fig. 3. Kinetics of the first phase of hemodynamic response in the coordinates of Eq. (3): (*a*) experimental data for several blocks collected from different volunteers (*1—8*); (*b*) averaged experimental data with statistical deviations calculated by the least squares method (*1*) and theoretical dependences for $k_{He} = k_0$ (*2*) and $k_{He} > k_0$ (*3*).

Experimental data on the hemodynamic response kinetics of the first phase of the BOLD signal in the coordinates of Eq. (3) are shown in Fig. 3. The straight line in Fig. 3, *b* has a negative slope; hence, $k_{He} < k_0$. This means that preliminary inhalation of thermoheliox slows down the vasoconstriction (relaxation) of the vascular dilation induced by the nervous impulse in the excitation region.

The conducted experimental study of the BOLD signal dynamics revealed the biphasic character of the process. It was shown that the preliminary inhalation of thermoheliox extends the hemodynamic impulse by slowing down the vasoconstriction.

All procedures involved in experiments with human subjects complied with the ethical standards of the National Committee for Research Ethics and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Informed consent was obtained from each of the participants included in the study.

The authors declare no competing interests.

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