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Functional Status of Microcirculatory-Tissue Systems during the Cold Pressor Test

I. N. Novikova[a], A. V. Dunaev[a], V. V. Sidorov[b], and A. I. Krupatkin[c]

[a] *State University—Education-Science-Production Complex, Oryol, Russia*
[b] *LAZMA Research and Production Company, Moscow, Russia*
[c] *Priorov Central Research Institute of Traumatology and Orthopedics, Moscow, Russia*
e-mail: aikrup@mail.ru

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Abstract—The time course of changes in the parameters of microcirculatory–tissue systems (MTSs) during the cold pressor test (CPT) was investigated in 32 conventionally healthy volunteers by noninvasive optical methods of laser Doppler flowmetry (LDF), tissue reflectance oximetry (TRO), and pulse oximetry. Depending on the oxygen consumption recovery rate in the CPT, the subjects were conventionally divided into two groups, one with a normal physiology and the other with a tendency to vascular spasm and lack of functional recovery of the MTSs. Blood flow oscillations were analyzed in detail to identify the possible causes of vascular spasm. The causes might include a distortion of the tone-shaping myogenic mechanisms that regulate resistive microvessels, blood congestion in microcirculation, or a combination of both of the factors. The CPT used to assess the MTS function was assumed to report the MTS reserve and to detect a propensity for vascular spasm at a preclinical stage, thus being of a potential applied significance.

Keywords: noninvasive diagnosis, laser Doppler flowmetry, tissue reflectance oximetry, pulse oximetry, microcirculatory-tissue system, cold pressor test, tissue respiration

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INTRODUCTION

Assessing the microcirculatory–tissue systems (MTSs), their parameters, functions, and processes is involved in the diagnosis of many human disorders. The MTSs are a structural and functional component of all organs and act to ensure tissue respiration as one of their key functions. Tissue respiration includes oxygen exchange with the blood and a set of redox reactions with the mitochondrial cytochrome system and is aimed at producing adenosine triphosphate (ATP). Oxygen extraction and consumption rates are the main parameters of tissue respiration [1].

Various noninvasive optical technologies are currently used to diagnose the MTS status and to evaluate tissue respiration [2], including laser Doppler flowmetry (LDF) [3, 4], tissue reflectance oximetry (TRO) [5], and pulse oximetry [6]. The gist of LDF is probing tissue optically and analyzing light reflected and scattered on moving erythrocytes. An important feature is that LDF makes it possible to study in vivo the total range of rhythmic microvascular processes from pulse to circadian rhythms, which play a great role in the function of the blood microcirculatory system [7]. TRO is based on measuring different hemoglobin fractions spectrophotometrically and is used to study the time course of oxygen transport and the blood saturation in microvessels in vivo. Pulse oximetry takes advantage of the fact that oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (Hb) absorb at different wavelengths, reporting the percent oxyhemoglobin (oxygen saturation saturation) in the blood in vivo. Employed together, the methods allow a complex evaluation of the MTS parameters in the human body.

Asymptomatic abnormalities of hemodynamics are diagnosed and possible MTS responses to external challenges are studied using a variety of functional stress tests. An occlusion test accesses the blood flow in the absence of the arterial supply and evaluates the microvasculature reserves by the increase in blood flow during reactive postocclusion hyperemia [8]. A respiratory functional test reports the vascular wall reactivity to activation of the sympathetic system, which is a component of the autonomic nervous system and causes constriction of afferent microvessels to temporally reduce the blood flow [9]. There are also a postural test, which reports the response of venous and arterial microcirculatory vessels [10]; a heat test [11, 12]; etc. A cold pressor test (CPT) is performed by immersing hands in cold water and is of particular interest in studying the MTSs [3, 13]. However, the time-related changes and possible alterations in microcirculation and tissue respiration in the CPT

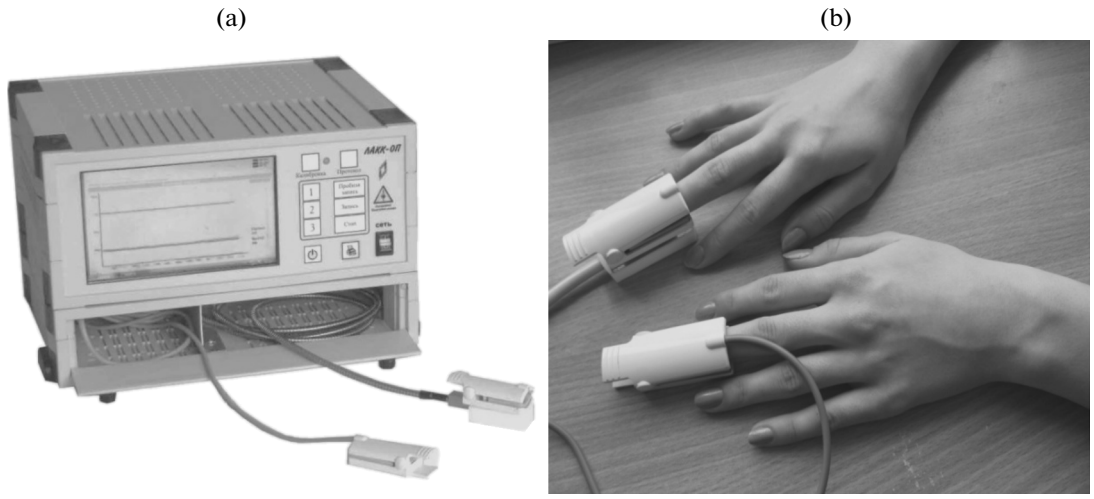

Fig. 1. (a) Outside appearance of a LAKK-OP laser microcirculation analyzer for a general practitioner and (b) positioning of the sensors on the subject's fingers during the examination.

have not been assessed using laser diagnostic technologies.

The objectives of this work were to study the changes in complex parameters of the human MTSs during the CPT and to analyze their possible causes.

METHODS

Our experimental study involved 32 conventionally healthy volunteers, including 16 males (mean age 21.7 ± 1.4 years) and 16 females (mean age 21.6 ± 1.6 years). Measurements were performed on the skin with arteriovenous anastomoses on the palmar surface of the distal phalanx of the right middle finger at physical and mental rest, 2 h after meal. All measurements were taken at the same time to exclude circadian fluctuations in blood flow. The subjects were preliminarily adapted to ambient temperature (20–23°C) and sat with the right forearm resting on the desk at the level of the heart. The study was carried out using a LAKK-OP laser microcirculation analyzer for a general practitioner (LAZMA, Moscow) (Fig. 1a). The analyzer is designed to assess the biological tissue status simultaneously by LDF with a laser probing wavelength of 1064 nm, TRO at wavelengths of 530 and 630 nm, and pulse oximetry. Optical sensors were placed on fingers for the examination as in Fig. 1b. A frequency analysis of various microcirculation-regulating mechanisms, that is, the endothelial, neurogenic, myogenic, respiratory, and cardiac oscillations [14] recorded by LDF and TRO was carried out using the program LDF 2.3.514.602, which performs a continuous wavelet transform and utilizes the complex-valued Morlet wavelet as an analytic wavelet [15].

Only one CPT was carried out in one day. Six basic records (BRs) of 5 min each were obtained during the CPT, including two BRs taken prior to the cold exposure and four BRs taken after the end of exposure. Both of the hands were immersed in cold water in the CPT. The duration of exposure (hand chilling) was 5 min. To obtain reliable diagnostic information, BRs were recorded with 5-min intervals. The total duration of one experimental examination was 55 min. The water temperature was 14.9 ± 0.1°C in the CPT. The water and subject's skin temperatures were checked using a NB-401 non-contact thermometer (Sensitec, Netherlands).

The main MTS parameters recorded during the experimental examination included a blood microcirculation index (I_m), tissue oxygen saturation (S_tO_2), relative blood volume (V_b), and arterial oxygen saturation (S_aO_2).

Example LDF and TRO records obtained prior to and after the cold exposure and their amplitude–frequency spectra are shown in Fig. 2. It should be noted that the first BR minute was excluded when constructing the amplitude–frequency spectra of the post-exposure LDF and TRO records (Fig. 2d) because of the transitional processes due to tissue heating after the physiological exposure. As is seen, the CPT substantially changed the main MTS parameters under study.

A method based on analyzing the blood flow oscillation amplitudes [1, 16] was used to calculate the oxygen extraction (OE) and oxygen consumption rate (OC):

$$OE = \left(S_aO_2 - S_vO_2\right)/S_aO_2, \quad (1)$$

where S_vO_2 is the venous blood oxygen saturation.

To estimate the venous blood oxygen saturation, we analyzed the amplitudes of oscillations related to passive mechanisms regulating the tissue oxygen saturation (S_tO_2), namely, the amplitudes of cardiac ($A(S_tO_2)_c$) and respiratory ($A(S_tO_2)_r$) oscillations.

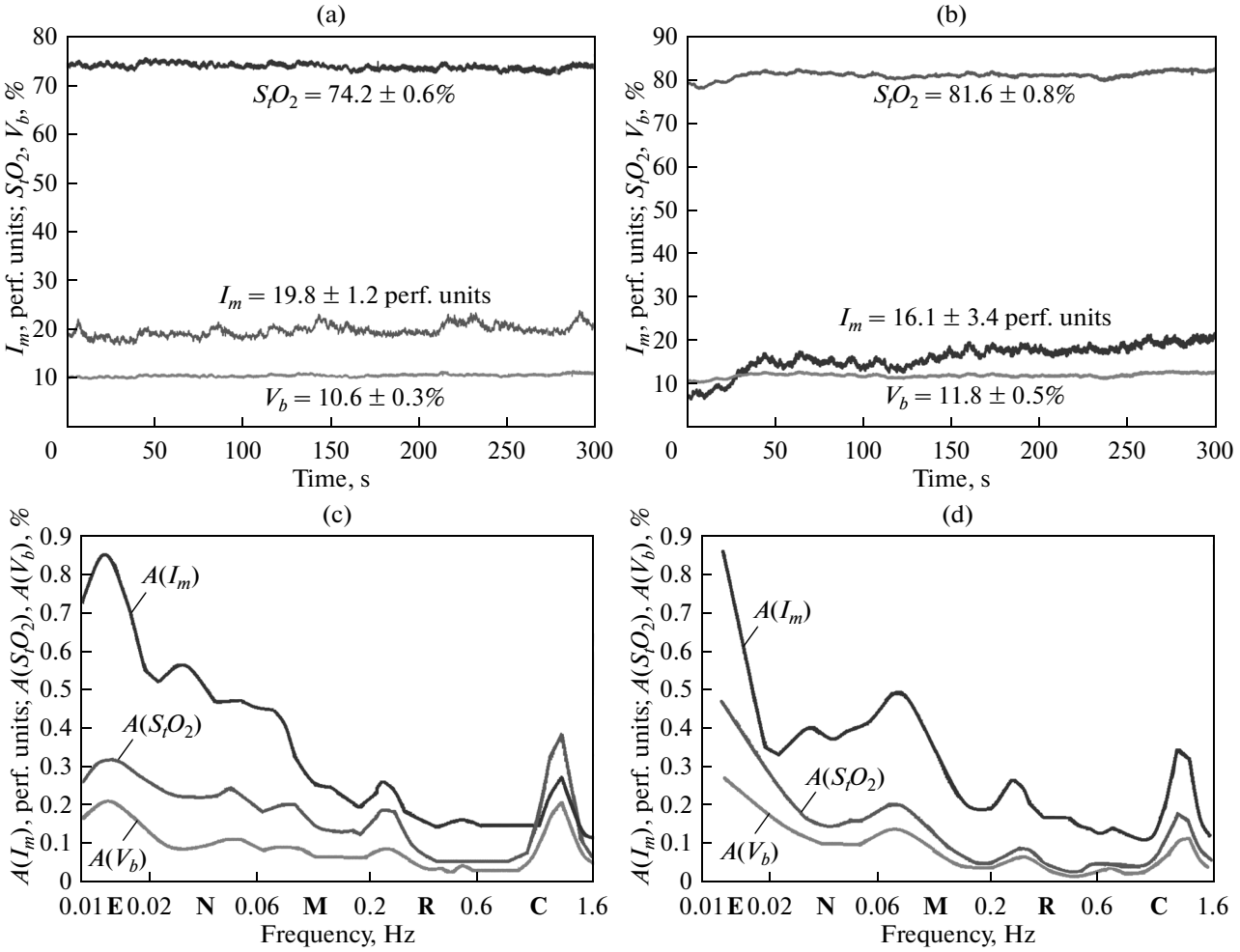

Fig. 2. LDF and TRO sample records and their amplitude–frequency spectra obtained (a, c) before and (b, d) after cold exposure in the CPT. Oscillation frequency ranges associated with endothelial (E), neurogenic sympathetic (N), myogenic (M), respiratory (R), and cardiac (C) regulatory mechanisms are indicated. Perf. units, perfusion units.

When $A(S_tO_2)_c/A(S_tO_2)_r > 1$, the venous blood oxygen saturation is obtained as

$$S_vO_2 = \frac{S_tO_2}{A(S_tO_2)_c/A(S_tO_2)_r}, \quad (2)$$

where $A(S_tO_2)_c$ and $A(S_tO_2)_r$ are the maximal amplitudes of cardiac (0.8–1.6 Hz) and respiratory (0.2–0.4 Hz) oscillations of tissue oxygen saturation, respectively.

This variant is prevalent in the majority of records from skin with arteriovenous anastomoses.

Calculations of $S_vO_2$have several specifics in the case of resonance with tissue oxygen saturation oscillations due to active regulatory mechanisms, when high-amplitude oscillations are observed only in one range, while oscillations of other ranges are dramatically suppressed and have lower amplitudes. In the case of oscillation resonance in the total myogenic (0.047–0.145 Hz) or respiratory ranges, venous blood oxygen saturation is calculated as

$$S_vO_2 = \frac{S_tO_2}{BI(S_tO_2)}, \quad (3)$$

where $BI(S_tO_2)$ is the bypass index (BI) obtained from the S_tO_2 plot:

$$BI(S_tO_2) = 1 + \frac{A(S_tO_2)_n}{A(S_tO_2)_m}, \quad (4)$$

where $A(S_tO_2)_n$ and $A(S_tO_2)_m$ are, respectively, the amplitudes of tissue saturation oscillations in the neurogenic (0.021–0.046 Hz) and myogenic ranges.

The oxygen consumption rate (*OC*) is obtained using LDF records and the venous blood oxygen saturation calculated at the previous step:

$$OC = I_{mnutr}(S_aO_2 - S_vO_2), \quad (5)$$

where I_{mnutr} is the portion of the nutritive flow in the total microvascular flow:

$$I_{mnutr} = M/BI(I_m), \quad (6)$$

where M is the mean perfusion I_m and $BI(I_m)$ is the bypass index calculated from the LDF record as

$$BI(I_m) = BI(I_m)_1 + BI(I_m)_2. \quad (7)$$

The component $BI(I_m)_1$ is calculated using Eq. (4) and perfusion data (I_m). When blood flow oscillations due to endothelial regulatory mechanisms dominate, their amplitude (A_e) is used in place of the amplitude of neurogenic oscillations (A_n) to calculate the BI.

The $BI(I_m)_2$ component is calculated as

$$BI(I_m)_2 = A(I_m)_{pass}/A(I_m)_m, \quad (8)$$

where $A(I_m)_{pass}$ is the maximal amplitude of blood flow oscillations due to passive regulatory mechanisms (cardiac or respiratory oscillations).

$BI(I_m)_2$ is included in calculating BI when $BI(I_m)_2 \geq 1$ [1].

To estimate the oscillatory component of microvascular tone, we determined the endothelial (ET), neurogenic (NT), and myogenic (MT) tone values [3].

$$ET = \sigma/A(I_m)_e, \quad (9)$$

where σ is the mean square deviation of the microcirculation index I_m, and $A(I_m)_e$ is the maximal amplitude of perfusion oscillations in the endothelial range.

$$NT = \sigma/A(I_m)_n, \quad (10)$$

where $A(I_m)_n$ is the maximal amplitude of perfusion oscillations in the neurogenic range.

$$MT = \sigma/A(I_m)_m, \quad (11)$$

where $A(I_m)_m$ is the maximal amplitude of perfusion oscillations in the myogenic range.

Measurements were used to calculate the relative perfusion oxygen saturation in microcirculation as a complex MTS parameter of the human body:

$$S_m = S_tO_2/I_m. \quad (12)$$

The parameter characterizes the relationship between the blood flow (perfusion) in microcirculation and the amount of oxygen not consumed by tissues; i.e., the parameter is inversely proportional to oxygen consumption.

RESULTS AND DISCUSSION

The experimental findings showed that the subjects differed in changes observed in MTS parameters during the CPT and especially during recovery. Using the change in oxygen consumption rate after the CPT as a main criterion of response, we conventionally divided the subjects into two groups. Group 1 ($n = 16$) showed a relatively normal pattern with OC reaching the baseline level by the end of testing. Group 2 ($n = 12$) displayed a propensity for vascular spasm, OC being not restored to the baseline.

An additional small group ($n = 3$) was isolated, where the subjects did not show any considerable changes in MTS parameters affecting tissue respiration, in particular, the oxygen consumption rate. One subject had a skin temperature of 25°C in the test region during the test and was diagnosed with the cold hand syndrome in further examination. The results obtained for the four subjects were excluded from further analysis of the MTS response to the CPT.

Mean MTS parameters (with their mean square deviations) were plotted against time of the CPT for subject groups 1 and 2 (Fig. 3).

As is seen from the time dependences, the two groups similarly displayed a decrease in total perfusion (Fig. 3a), nutritive blood flow (Fig. 3c), and oxygen consumption rate (Fig. 3d) after the CPT (minute 25), while differing in the response of tissue oxygen saturation (Fig. 3b). To identify the possible factors that determine the difference in MTS response to cold exposure during the CPT, we analyze in detail the amplitude–frequency spectrum of blood flow and tissue saturation oscillations.

Table 1 summarizes the results of a statistical analysis of data obtained in the two subject groups, which were isolated by the tissue respiration response to the CPT. Differences in parameters measured before the CPT (BR 2), immediately after cold exposure (BR 3), and at the end of examination (30 min after exposure, BR 6) were tested for significance by the Mann–Whitney test [17].

In the CPT, the skin temperature in the test region decreased in both of the groups. Hypothermia caused constriction of muscle-containing vessels, namely, arteries and arterioles [3], thus decreasing total perfusion.

Cold receptors are excited in the functional CPT, resulting in substantial activation of adrenergic sympathetic nerves [18] and, consequently, triggering blood flow oscillations in the sympathetic range. Cold-induced vasodilation due to hand cooling stimulates the endothelial production of nitric oxide, thus increasing the amplitude of oscillations of the endothelial origin [19]. An increase in the amplitude of low-frequency oscillations in the CPT increases the BI (from 2.6 ± 0.5 rel. units at baseline to 4.7 ± 2.7 rel. units after exposure in group 1, $p < 0.05$, and from 2.7 ± 0.5 to 3.3 ± 1.0 rel. units in group 2) and myogenic tone (from 2.9 ± 1.0 rel. units at baseline to 6.7 ± 4.0 rel. units after exposure in group 1, $p < 0.05$, and from 2.8 ± 0.7 to 4.0 ± 0.9 rel. units in group 2, $p < 0.05$). Thus, the blood flow through arterioles and arteriovenous anastomoses starts to predominate, and a major portion of the blood flows through bypasses, resulting in a relative decrease in nutritive blood flow (from 6.8 ± 2.5 perfusion (perf.) units at baseline to 3.5 ± 2.7 perf. units after exposure in group 1, $p < 0.05$,

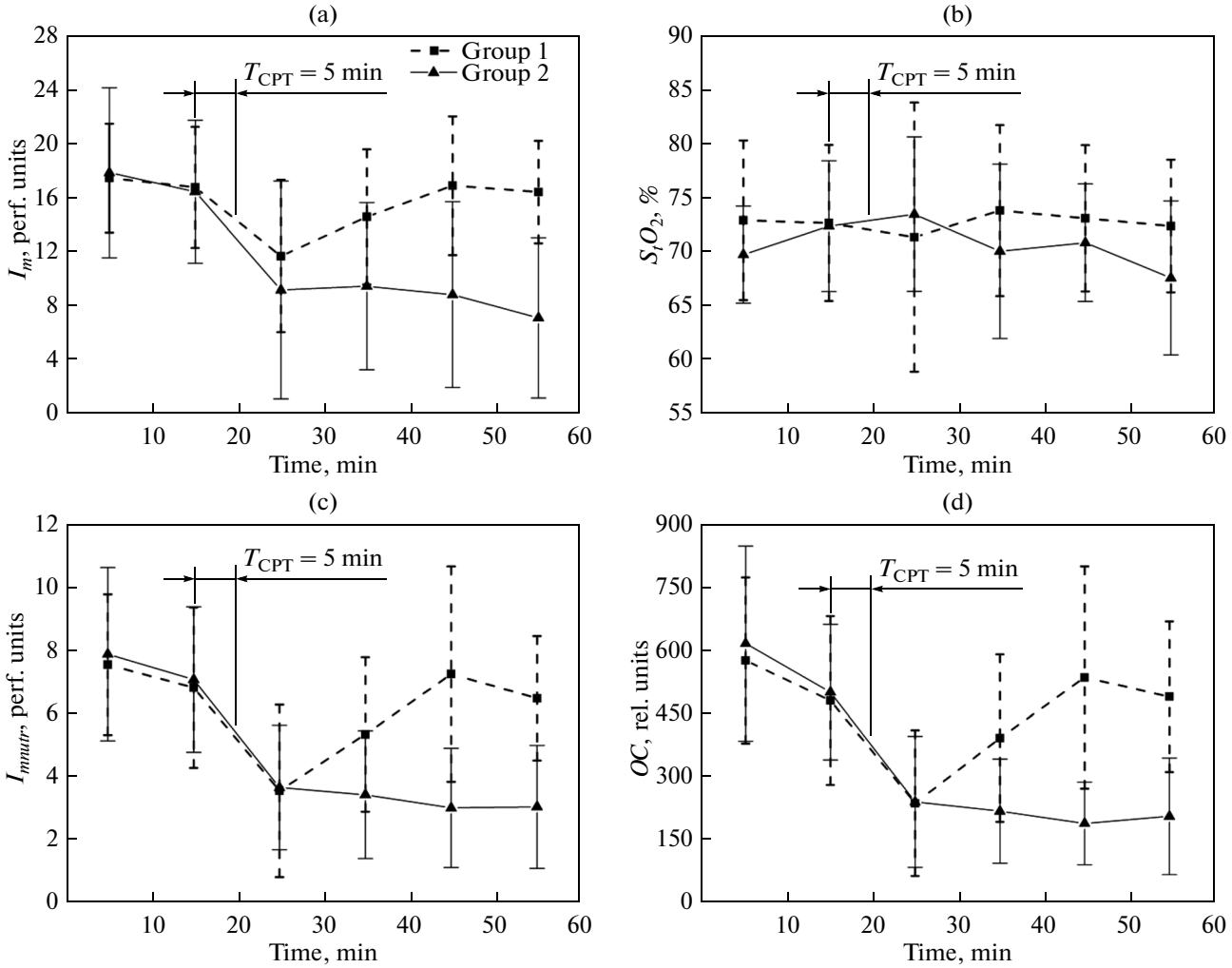

Fig. 3. Time-related changes in main MTS parameters during the CPT as averaged for the two subject groups. See text for detail.

and from 7.1 ± 2.3 to 3.7 ± 2.0 perf. units in group 2, $p < 0.05$). A lower nutritive blood flow results in a decrease in oxygen consumption rate (from 481.1 ± 202.6 rel. units at baseline to 234.7 ± 175.0 rel. units after exposure in group 1, $p < 0.05$, and from 501.3 ± 162.8 to 237.8 ± 157.6 rel. units in group 2, $p < 0.05$). At the same time, appreciable changes in oxygen extraction (the oxygen portion removed from the arterial blood via diffusion into tissues) are not observed. In group 1 with a relatively normal response, blood flow oscillations grow normal 30 min after cold exposure (BR 6), the myogenic tone of precapillaries decreases to approximate the baseline value (2.7 ± 0.6 rel. units), and capillary perfusion is activated (16.4 ± 3.8 perf. units). As a result, the BI decreases (2.6 ± 0.5 rel. units), the nutritive blood flow increases (6.5 ± 2.0 perf. units), and the oxygen consumption rate is consequently normalized (490.4 ± 180.8 rel. units).

Vasoconstriction-related changes in the CPT are greater in the group 2 subjects, and the MTS parameters under study are not restored. Because constriction of the vascular wall is intense and prolonged, examination at the end of the experiment still reveals a lower total perfusion (10.1 ± 5.1 perf. units), a lower BI (4.4 ± 2.6 rel. units), and a higher myogenic tone (4.6 ± 2.7 rel. units). The changes determine a lower nutritive blood flow (3.0 ± 2.0 perf. units) and a lower oxygen consumption rate (203.3 ± 140.2 rel. units) as compared with the values observed before the CPT. This response may result from intense muscle contraction and delayed membrane repolarization (which normally precedes muscle relaxation) [20], which together render the arterial wall constricted for a long time. Such alterations can arise in the case of imbalance between the production and degradation of vascular tone-regulating humoral factors or a higher sensitivity of the vascular wall to vasoconstrictor influences.

To identify the factors potentially responsible for the propensity for vascular spasm, we analyzed the oscillatory components of tone-determining mechanisms and the amplitude ratio between pulse and res-

Table 1. Evaluation of changes in tissue respiration in the CPT

Parameter	Type of the tissue respiration response to the CPT					
	relative norm ($n = 16$)			propensity for vascular spasm ($n = 12$)		
	BR 2	BR 3	BR 6	BR 2	BR 3	BR 6
T_B, °C	34.7 ± 3.0	19.1 ± 2.0*	33.1 ± 4.1	35.2 ± 1.7	18.6 ± 3.9*	29.2 ± 5.5
I_m, perf. units	16.8 ± 4.5	11.7 ± 5.6*	16.4 ± 3.8	18.1 ± 4.6	11.8 ± 6.9*	10.1 ± 5.1*
S_tO_2, %	72.5 ± 7.2	71.2 ± 12.5	72.3 ± 6.1	72.3 ± 6.1	73.4 ± 7.2	67.5 ± 7.1
V_b, %	8.7 ± 1.5	7.7 ± 1.8	8.4 ± 1.4	10.7 ± 1.7	8.4 ± 1.6*	9.6 ± 1.9
S_aO_2, %	98.1 ± 0.7	98.4 ± 0.7	98.3 ± 1.0	97.3 ± 1.9	98.5 ± 0.8	98.5 ± 0.8
$BI(S_tO_2)$, rel. units	3.1 ± 0.7	5.6 ± 3.4*	3.3 ± 1.6	3.3 ± 0.9	5.1 ± 1.8	4.5 ± 1.6
$BI(I_m)$, rel. units	2.6 ± 0.5	4.7 ± 2.7*	2.6 ± 0.5	2.7 ± 0.5	3.3 ± 1.0	4.4 ± 2.6*
S_vO_2, %	26.6 ± 12.3	30.3 ± 12.3	23.5 ± 11.2	26.1 ± 10.5	35.5 ± 14.5	29.5 ± 16.2
ET, rel. units	2.0 ± 0.6	2.7 ± 1.1	2.4 ± 1.1	1.9 ± 0.3	2.3 ± 0.6*	2.0 ± 0.9
NT, rel. units	2.3 ± 0.5	4.1 ± 3.2	2.3 ± 0.9	2.3 ± 1.0	2.3 ± 0.8	2.2 ± 0.8
MT, rel. units	2.9 ± 1.0	6.7 ± 4.0*	2.7 ± 0.6	2.8 ± 0.7	4.0 ± 0.9*	4.6 ± 2.7*
I_{mnutr}, perf. units	6.8 ± 2.5	3.5 ± 2.7*	6.5 ± 2.0	7.1 ± 2.3	3.7 ± 2.0*	3.0 ± 2.0*
S_m, rel. units	4.7 ± 1.3	7.8 ± 4.2*	4.7 ± 1.3	4.2 ± 1.1	8.5 ± 4.5*	8.6 ± 4.3
OE, rel. units	0.73 ± 0.13	0.69 ± 0.12	0.76 ± 0.11	0.73 ± 0.11	0.64 ± 0.15	0.70 ± 0.16
OC, rel. units	481.1 ± 202.6	234.7 ± 175.0*	490.4 ± 180.8	501.3 ± 162.8	237.8 ± 157.6*	203.3 ± 140.2*

BR, basic record.

* The difference between the values obtained after the CPT and prior to exposure was significant at $p < 0.05$ by the Mann–Whitney test.

piratory oscillations of the blood flow [21]. The results of the analysis are summarized in Table 2.

A decrease in the myogenic regulatory factor was found to cause vascular spasm in 10 out of 12 subjects. When the vasomotion amplitude is lacking or dramatically decreased, myogenic tone increases. The MTSs persist in this state for a long time, in particular, when the function of muscle cell membranes in the vascular wall is distorted because of defects in the function of ionic channels. The distortion leads to an abnormal alternation of the constriction and relaxation phases in the muscular layer of vessels; i.e., vasoconstriction grows more intense and long term.

A decrease in the amplitude ratio of pulse and respiratory blood flow oscillations ($A_c/A_r \leq 1$) was observed along with a lower myogenic regulatory factor in two subjects. In these cases, venular perfusion prevails over arteriolar perfusion in microcirculation, possibly, as a result of microcirculatory congestion. A combination of the myogenic and congestive factors determined vascular spasm in the subjects. Considerable venous congestion was not observed in the other ten subjects ($A_c/A_r > 1$). Yet the amplitude ratio between cardiac and respiratory flow oscillations was close to unity in six of these subjects, suggesting a conventionally borderline condition.

It should be noted that congestion was not identified as the only cause of alterations in any of the subjects, but was always combined with a high myogenic tone. Congestion is only a sign of more intense myogenic activation, which causes a more significant hemodynamic alteration in the form of venular congestion. The myogenic component was a key vascular spasm-determining factor responsible for the difference between subject groups 1 and 2.

Thus, the CPT used to assess the MTS function makes it possible not only to evaluate the MTS reserves, but also to detect the propensity to vascular spasm at a preclinical stage. Such studies are of importance for investigating the pathogenesis of the disorders that involve dysfunction of microcirculation-regulating mechanisms and vasoconstriction as a main microvascular abnormality (e.g., diabetes mellitus,

Table 2. Analysis of the factors potentially responsible for the propensity for vascular spasm and insufficient functional recovery

Parameter	Factors responsible for the propensity for vascular spasm and insufficient functional recovery of the MTSs ($n = 12$)	
	myogenic ($n = 10$)	myogenic and congestive ($n = 2$)
$A(I_m)_m$	↓	↓
$A(I_m)_c/A(I_m)_r$	↑ (>1)	↓ (≤1)

(↑) increase, (↓) decrease.

atherosclerosis, Raynaud's disease, vibration disease, etc.). It is expedient to further study the CPT potential in the clinical setting.

CONCLUSIONS

To summarize, the time course of changes in MTS parameters during the CPT was investigated in 32 conventionally healthy volunteers by noninvasive optical methods: LDF, TRO, and pulse oximetry. Depending on the oxygen consumption recovery rate in the CPT, the subjects were conventionally divided into two groups, one with a normal physiology and the other with a tendency to vascular spasm and lack of functional recovery of the MTSs. Blood flow oscillations were analyzed in detail to identify the possible causes of vascular spasm. The causes might include a distortion of the tone-shaping myogenic mechanisms that regulate resistive microvessels, blood congestion in microcirculation, or a combination of both of the factors. The CPT used to assess the MTS function was assumed to report the MTS reserve and to detect a propensity for vascular spasm at a preclinical stage, thus being of a potential applied significance.

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