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Study of 0.1-Hz vasomotion in microcirculation under local heating by means of imaging photoplethysmography

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ABSTRACT

Low-frequency oscillations in the human circulatory system is important for basic physiology and practical applications in clinical medicine. Our objective was to study which mechanism (central or local) is responsible for changes in blood flow fluctuations at around 0.1 Hz. We used the method of imaging photoplethysmography synchronized with electrocardiography to measure blood-flow response to local forearm heating of 18 healthy male volunteers. The dynamics of peripheral perfusion was revealed by a correlation processing of photoplethysmography data, and the central hemodynamics was assessed from the electrocardiogram. Wavelet analysis was used to estimate the dynamics of spectral components. Our results show that skin heating leads to multiple increase in local perfusion accompanied by drop in blood flow oscillations at 0.1 Hz, whereas no changes in heart rate variability was observed. After switching off the heating, perfusion remains at the high level, regardless decrease in skin temperature. The 0.1 Hz oscillations are smoothly recovered to the base level. In conclusion, we confirm the local nature of fluctuations in peripheral blood flow in the frequency band of about 0.1 Hz. A significant, but time-delayed, recovery of fluctuation energy in this frequency range after cessation of the skin warming was discovered. This study reveals a novel factor involved in the regulation microcirculatory vascular tone. A comprehensive study of hemodynamics using the new technique of imaging photoplethysmography synchronized with electrocardiography is a prerequisite for development of a valuable diagnostic tool.

1. Introduction

The human cardiovascular system is characterized by the presence of oscillations in a wide range of frequencies. Central and peripheral circulation are under the control of a multilevel system, including neurohumoral regulation of arterial pressure (AP) and heart rate (HR) by the autonomic nervous system [1]. Regulation of blood circulation due to variations in vascular tone provides an adaptive response of the cardiovascular system to physiologic and pathologic factors. At the functional level of vascular tone regulation, oscillations at a frequency of ~0.1 Hz are of particular interest [2]. In this regard, the study of low-frequency oscillations in the human circulatory system is of great importance both for fundamental physiology and for practical application in clinical medicine, especially for high physiological tasks (space, diving medicine), as well as for understanding the causes of vascular regulation disorders in essential hypertension, aging, progression of diabetic angiopathy, vasculitis, etc.

The origin of ~0.1 Hz oscillations in cardiovascular system remains uncertain and involve different physiological processes depending on blood vessel morphology. On the one hand, the presence of such oscillations in the spectrum of HR is established. HR fluctuations at ~0.1 Hz, associated with spontaneous variations of AP, are called Mayer waves

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[2]. Several theoretical models of dynamic arterial pressure control have been developed to explain the nature of Mayer waves [3–6]. In these models, it was assumed that the multiple dynamic components and time delays present in the baroreflex loop would produce a resonant, self-supported arterial pressure oscillation. Thus, the non-local nature of these low-frequency waves is well established. However, at the moment, the issue of Mayer waves source is not definitely understood [2].

On the other hand, spontaneous oscillations of cutaneous blood flow, which are closely related to fluctuations in the lumen of blood vessels, were observed both *in-vivo* and *in-vitro* [7,8]. These oscillations are referenced to as vasomotion and characterized by a wider spectrum than Mayer waves. They are presumably generated locally by spontaneous periodical constriction and dilatation of vascular walls [7]. However, various groups reported about phase synchrony between vasomotion at 0.1 Hz and rhythmic variations in HR at the same frequency [9–11]. These observations indicate that the mechanisms involved are complex and interacting in ways that are difficult to address in observations [12]. Nevertheless, it has been demonstrated that the assessment of ~0.1 Hz vasomotion is of practical importance for the development of early diagnostic methods of such socially significant diseases as diabetes and essential arterial hypertension [13–15]. Experimental evaluation of vasomotion in most cases was carried out using spectral analysis of a laser Doppler flowmetry (LDF) signal [10,11,14–17], the technique that has an advantage of being noninvasive and easy in use. However, when assessing blood flow, LDF probes are in mechanical contact with the circulatory system, which has a significant impact on the measured parameters of blood flow [18]. In the vast majority of measurements already performed using the LDF sensor, the pressure exerted by this sensor on the skin (and, consequently, on the blood vessels) was not controlled.

Various physiological tests (Valsalva maneuver, deep breathing, arterial occlusion, posture change, local heating and cooling, etc.) were used to identify the interaction between different mechanisms regulating peripheral microcirculation. Among them, a local heating test with LDF assessment of cutaneous blood flow was often used to reveal the relationship between vasomotion at different sites and Mayer waves representing centralized vascular regulation [16,17,19,20]. In particular, increased sympathetic activity to local skin warming has been reported [17]. In contrast, another group have shown that local contributions to vasomotion was more prominent during rapid heating stimulus [19].

Imaging photoplethysmography (iPPG) is a contactless method for measuring tissue perfusion that have drawn attention of researchers due to the capability to measure at once blood flow parameters over large area [21–23]. The latter advantage is especially useful since it allows one to assess spatial distribution of blood flow parameters and its dynamics, which may vary with long-term measurements. A modified iPPG technique featured by synchronous recording of skin images and electrocardiogram (ECG) was recently proposed in our group [24]. This method is characterized by an improved signal-to-noise ratio during *in-vivo* measurements. Another advantage of this modification (especially important when carrying out local heating tests) is the possibility of using a heater of extended area, which allows us both to minimize the pressure exerted on the tissue under study and to control it during prolonged experiments [25]. More recently we demonstrated efficacy of the modified iPPG technique for assessment of the difference in endothelial associated oscillations of blood flow between smokers and non-smokers during local heating test enhanced by subsequent wavelet analysis of iPPG signals [26].

Since the modified iPPG technique has a distinctive feature of simultaneous recording of ECG (determined by systemic cardiovascular processes) and cutaneous perfusion (capable of assessing peripheral vascular tone) [24], the aim of this study was to find a relationship between low-frequency fluctuations in peripheral microcirculations and central hemodynamics while monitoring the response to local skin heating. Our findings are the following: (i) a significant difference in the dynamics 0.1 Hz fluctuations of the cutaneous blood flow and the heart rate; and (ii) an increase of 0.1 Hz vasomotion began only after switching off the local heating.

2. Materials and methods

2.1. Participants and study protocol

The study involved 18 healthy male volunteers, whose average age was 45.0 ± 6.2 years. Exclusion criteria were: age less than 18 years, significant overweight, arterial hypertension, smoking, diabetes, cancer, systemic diseases including cardiovascular, respiratory, hepatic and renal failure, metabolic factors, skin diseases and patients with a history of drug dependence or continuous alcohol consumption, which may adversely affect patient compliance with study procedures and outcome. The characteristics of the subjects are given in Table 1.

The site of the study was the Private Healthcare Institution “Central Clinical Hospital Russian Railways Medicine in Vladivostok” and the Institute of Automatics and Control Processes of the Far East Branch of the Russian Academy of Sciences. The study was performed in accordance with the ethical standards presented in the 2013 Declaration of Helsinki, protocol approved by the Interdisciplinary Ethics Committee of Pacific State Medical University, Vladivostok, Russia. All subjects were acquainted with the testing process and signed a written informed consent form.

Measurements were carried out under appropriate sanitary conditions in a darkened room at an air temperature of 23 ± 1 °C. The period of subject’s adaptation to the conditions of the study was at least fifteen minutes. The subject was comfortably positioned in a special chair with head and leg support to ensure a relaxed posture throughout the experiment. The subject conveniently placed his right hand on the table so that the forearm was at the level of the heart. A transparent heating module was placed on top of the lower third of the forearm (Fig. 1*A*). At least two hours before the experiment, subjects abstained from taking food and liquid, as well as substances affecting vasomotor properties of blood vessels. During the experiment, neither talking nor sleeping was allowed.

In this study, we performed an in-depth analysis of experimental data obtained recently for the control group when assessing the reaction of blood flow to local heating [26]. Measurements of each subject lasted from 40 to 60 min, during which the video of the heated forearm area was recorded continuously and synchronously with ECG and skin temperature. The study protocol consisted of (i) 5 min baseline recording; (ii) heating to 40–42 °C with the rate of about 3.5 °C per minute; (iii) maintaining the maximum skin temperature for 20 min; and (iv) switching off the heating while continuing to monitor blood flow and heart rate during relaxation. The recorded video, ECG and skin temperature were uploaded to a personal computer for further offline processing.

2.2. Measuring system

To assess the blood flow reaction on local heating, we used a homemade iPPG system [25,26]. A picture of the experimental setup and typical graphs representing the dynamics of the main variables are

Table 1
Characteristics of subjects involved in the study.

Parameter	Value
Number	(n = 18)
Age (years)	45.0 ± 6.2
Body mass index (kg/m^2)	27 ± 3
Systolic blood pressure (mmHg)	125 ± 9
Diastolic blood pressure (mmHg)	83 ± 8

Data are reported as mean ± standard deviation.

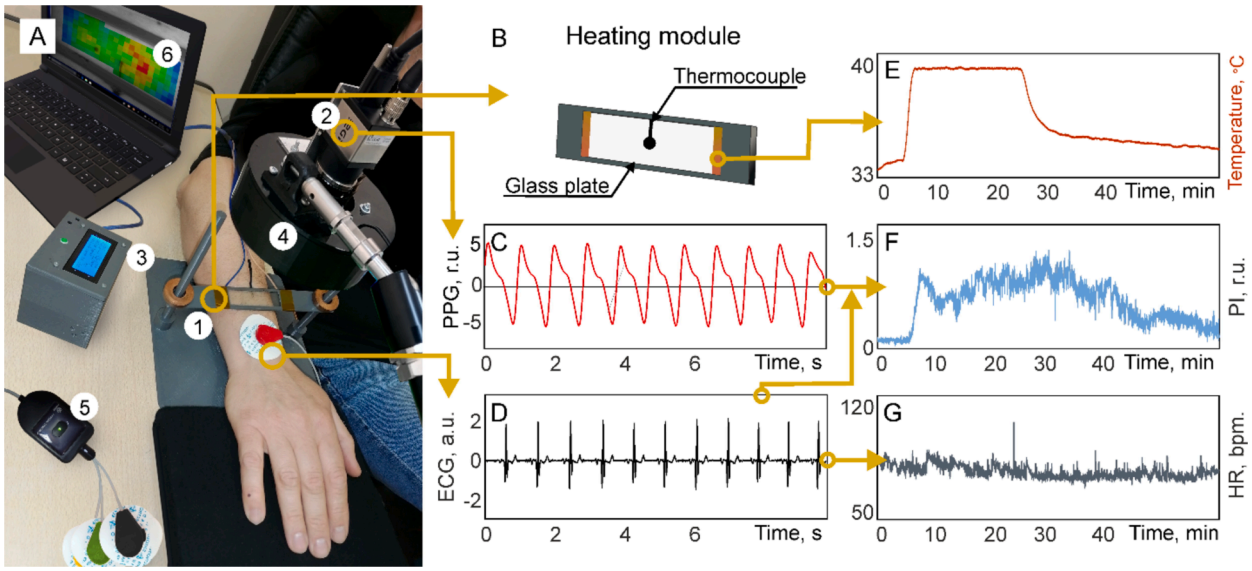

Fig. 1. Laboratory system for evaluating perfusion response to local heating. (*A*) Picture of the imaging photoplethysmography (iPPG) measuring system, which includes a transparent heating module (1), digital monochrome camera (2), skin temperature control unit (3), an illumination module (4), digital electrocardiograph (5), and personal computer (6) for system management and data acquisition and processing. (*B*) Drawing of the heating module. (*C*) An example of the photoplethysmographic (PPG) waveform recorded during 11 cardiac cycles. (*D*) ECG recorded synchronously with the PPG waveform. (*E*) Evolution of the skin temperature during the local heating test. (*F*) Changes in the mean perfusion index during the local heating test. (*G*) Heart rate variability during the local heating test.

shown in Fig. 1. In our system, the skin was heated using a transparent heating module (3 in Fig. 1*A*) and shown in detail in Fig. 1*B*. This arrangement allowed us to minimize and stabilize the contact force affecting the cutaneous blood flow due to a sufficiently large contact area of the skin with a $70 \times 20 \times 2$ mm^3 glass plate. The contact pressure did not exceed 15 mmHg. Video recording of this area by a digital camera (2 in Fig. 1*A*) with subsequent data processing makes it possible to compensate for the heterogeneity of the blood flow response to heating. The skin temperature was regulated by a control unit with a feedback system (3) in which the temperature was measured by a K-type thermocouple placed between the glass and the subject's skin. For better thermal conductivity, Vaseline oil (Flora Kavkaza, Russia) was added to the contact area. The video was recorded at a distance of 20 cm with a monochrome digital camera (Imaging Development Systems GmbH, Obersulm, Germany) at a frequency of 36 fps and resolution of 380 × 256 pixels with an M1214-MP2 lens (Computar, Tokyo, Japan). The camera was rigidly mounted in the center of an illumination module (4) consisting of four rings of Light-Emitting-Diode's ribbon (250 LEDs operating at the wavelength of 530 ± 25 nm) and mounted on a variable friction support for precise positioning. To improve the signal-to-noise ratio, object illumination and video data recording were performed through a linear-polarizing film with mutually orthogonal orientation of polarization directions for the light source and video camera. Simultaneously, a digital electrocardiograph (5 in Fig. 1*A*) Kardiotechnika-EKG-8 (Incart Ltd., St. Petersburg, Russia) recorded the patient's ECG in two leads at a frequency of 1 kHz. To synchronize the video and ECG recordings, we used synchronous pulses generated by the camera at the beginning of each frame. These pulses were continuously received by one of the input channels of the digital electrocardiograph and were digitized in this device in parallel with the signals from the standard ECG leads. By this way, the synchronization accuracy of 1 ms was achieved. Skin temperature changes were monitored at a frequency of 5 Hz. Synchronization of the ECG signal, video record, and skin temperature data was performed manually by an operator, who simultaneously pushed two buttons on the computer to start capturing the video and temperature data. Data collection and the management of the entire system were carried out by a personal computer (6 in Fig. 1*A*).

2.3. Data processing

Quantitative assessment of changes in perfusion during the local heating test was carried out offline using an algorithm described in details in our previous paper [27], which includes the graph with processing pipeline (see Fig.S1 in [27]). Recorded videoframes and ECG were processed using custom software implemented in MATLAB® platform (version R2020a, The MathWorks, MA, USA). Briefly, there are four stages of data processing. At the first, most important stage, the recorded images were stabilized using the optical flow algorithm [28] in order to reduce the impact of unavoidable motion artifacts. Considering the multidirectional nature of the tissue sections motion, mainly due to cardiac and respiratory activity, the entire frame of the raw image was divided into 64 segments measuring 32 × 47 pixels, followed by compensation for the displacement of each segment independently. The motion-related displacement vector was calculated by averaging frames within a floating time window with a duration equal to the mean cardiac cycle. Whole frame was partitioned into Regions of Interest (ROI) of 7 × 7 pixels (or 1 by 1 mm in the plane of the forearm), the positions of which was adjusted according calculated displacement vectors. Already at this stage we exploited the synchronicity of ECG and videorecord, thereby increasing the efficiency of compensation for motion artifacts [24].

At the second stage, a PPG waveform was calculated as an evolution of the mean pixel value in every ROI considering its adjusted position in each frame. These waveforms were used to assess the spatial distribution of the blood pulsation amplitude over the heating area. In iPPG systems, the pulsation amplitude is estimated as the ratio of the PPG-waveform component modulated at the HR to the mean value of the waveform, which takes into account possible nonuniformity of the illumination intensity [24,29]. From the resulting spatial distribution, half of the ROIs with a higher pulsation amplitude are selected thus accounting for the heterogeneity of the perfusion distribution. Then, the dynamics of the normalized waveforms averaged over the selected ROIs was evaluated during the entire time of the local heating test, which allowed us to assess the perfusion dynamics. A typical fragment of the mean PPG-waveform is shown in Fig. 1*C*.

At the third stage, we calculated the perfusion index (*PI*) in every cardiac cycle as the difference between the maximum and minimum

values of the normalized PPG waveform while determining the boundaries of each cycle by R-peaks of the synchronously recorded ECG. Synchronous video signal acquisition with ECG data is illustrated in Fig. 1 in which the time axes on the graphs on panels *C* (PPG waveform) and *D* (ECG) are linked to each other. An example of the perfusion dynamics assessed during the local heating test is shown in Fig. 1*F*. As it was demonstrated in [29], the *PI* parameter reflects the tone of blood vessels supplying the capillary network under study, despite the fact that green light interacts only with capillaries due to the shallow depth of its penetration. This is explained in the alternative model of the PPG signal formation, according to which the modulation of the blood volume in the capillary bed at the heart rate occurs due to mechanical compression/decompression of the density of capillaries by adjacent arteries [30]. Of course, the formation of PPG signals is highly dependent on concurrent, interdependent, and intertwined physiological effects, among which blood volume variation, tissue compression by vascular wall movement, and red blood cells deformation are the most important factors that can be appreciated from a recent review paper [31].

While iPPG is an instrument for assessing local changes in blood flow, HR variations reflect systemic effects. An example of HR dynamics, which is evaluated as the inverse time difference between adjacent R-peaks is shown in Fig. 1*G*.

At the fourth stage, a wavelet analysis of perfusion dynamics, $PI(t)$, and heart rate, $HR(t)$, was carried out [26]. The spectral composition of $PI(t)$ and $HR(t)$ was evaluated in eleven time-intervals, the duration of each of which was 4 min. Of the eleven intervals, the first (designated as *A*) was on the baseline, the intervals from the second to the sixth (*B* to *F*) covered the heating phase, and the rest (*G* to *K*) were in the relaxation phase. Given the strong unsteadiness of the initial moment of increasing perfusion after switching on the heater, at which the averaging of the parameters is incorrect, we introduced a gap between the intervals *A* and *B*. For every subject we calculated wavelet coefficients for the entire sequence of both $PI(t)$ and $HR(t)$ [26]. The power spectral densities of the perfusion index $M_i^P(\nu)$ and heart rate $M_i^H(\nu)$ were estimated by integrating the wavelet coefficients in each of time interval *i*. Next, we calculated the normalized spectra of the perfusion index, NS_i^P, using normalization by the mean value of the $PI(t)$ in the respective time interval as follows

$$NS_i^P(\nu) = M_i^P(\nu)/\langle PI^2(t)\rangle_i \tag{1}$$

Since the perfusion index *PI* is proportional to the amplitude of blood flow oscillations at the heart rate, such normalization shows the ratio of the oscillation energy of the selected frequency band to the cardiac wave energy in the studied tissue volume. The normalized spectra of the HR heart rate dynamics, $NS_i^H(\nu)$, were calculated as

$$NS_i^H(\nu) = M_i^H(\nu)/\langle HR^2(t)\rangle_i \tag{2}$$

Here $\langle HR^2(t)\rangle_i$ is the mean value of the energy $HR(t)$ in the time interval *i*.

2.4. Statistical analysis

Before the analysis, we tested the normality of the distribution by Shapiro-Wilk test, which identified that samples under consideration are non-Gaussian. In this regard, the further analyses were conducted by methods of nonparametric statistic and results are presented as median and quartiles. For statistical data analyses we utilized Fridman criterion with further post-hoc tests based on Bonferroni correction. A 95 % confidence interval was used. The level of significance of all of the statistical indicators is $P < 0.05$. Statistical analysis of the data was performed using Mathematica 10.3 software (Wolfram research, USA).

3. Results

Fig. 2 shows the typical dynamics of the perfusion and heart rate during the local heating test. The heating leads to a multiple increase in $PI(t)$ in a healthy subject. Dependence $PI(t)$ has a typical biphasic shape with fast vasodilation, followed by a nadir and then by a long plateau. After switching off the heating element, skin temperature rapidly decreases whereas the perfusion does not follow the temperature, and in some subjects even increasing. It was found that $PI(t)$ decreases at a very low rate: it does not return to the baseline level even after a long relaxation period (more than 30 min).

Comparison of the dynamics of low-frequency components of $PI(t)$ and $HR(t)$ waveforms can be performed using a spectrogram, on which the calculated wavelet coefficients graphically represent the time–frequency waveform sweep. On the spectrogram, the power spectral density components are shown for each moment in time and are color-coded in such a way that red indicates a higher power, while blue corresponds to a lower one.

The wavelet spectrograms (Fig. 3) of the $PI(t)$ and $HR(t)$ have several notable features. Starting from the 30th minute, an increase in spectral energy of $PI(t)$ in the frequency band of 0.05–0.14 Hz is clearly observed (Fig. 3*A*), which appears five minutes after turning off the heating element. On the contrary, the spectral energy of $HR(t)$ in this frequency band (as well as at other frequencies) remains unchanged throughout the whole heating test (Fig. 3*B*).

To compare the dynamics of the power spectral densities among the subjects, we calculated the normalized spectra NS_i^P and NS_i^H in every time interval (*A*−*K*) according to Eqs. (1) and (2), and presented the obtained spectra in Fig. 4 in the form of the box plots for a few representative time intervals. Note that the chosen time intervals correspond to different stages of the heating test. The time interval *A* (0.5–4.5 min), indicated in purple, coincides with the baseline recording; the interval *B* (7–11 min), indicated in brown, is associated with the initial stage of vasodilation, caused by the axon reflex; the intervals *C-F* (11–23 min), marked by orange boxes, correspond to the period during which the heating module remained switched on; and remained stage of the test is covered by the intervals *G-K* (23–55 min), and shown by green boxes. Seeking the clarity of presentation, we plotted in Fig. 4 only four representative intervals *A*, *B*, *E*, and *K* in the frequency range from 0.01 to 0.6 Hz. Perfusion spectra in the selected time intervals are shown in Fig. 4*A*. The spectral composition during the baseline (purple boxes) does not statistically differ from that at the end of the test (green boxes). Moreover, a pronounced peak in the band around 0.1 Hz, marked by a vertical blue bar, is clearly seen. In contrast, fluctuations in this frequency band are significantly lower during the heating (brown and orange boxes). It is worth noting that spectral properties in these frequencies are similar during both phases of vasodilation.

Unlike $PI(t)$, the wavelet spectra of $HR(t)$, assessed in the same time intervals, does not show any statistically significant difference as one can see in Fig. 4*B*. Considering observed peculiarities, we focused our analysis on the frequency band from 0.05 to 0.14 Hz, which is centered to 0.1 Hz.

By averaging the normalized spectra NS_i^P in the frequency range of 0.05–0.14 Hz in each of the time intervals, we obtain 11 values to demonstrate the dynamics of changes in the mean spectral energy of perfusion variations in the frequency band around 0.1 Hz. Similarly, 11 more values were calculated for the normalized heart rate spectra, NS_i^H, in the same frequency band. The statistical distribution of the spectral components of $PI(t)$ and $HR(t)$ for the whole group is presented as box-whisker diagram in Fig. 5 by blue and dark-grey boxes, respectively. As one can see in Fig. 5, the dynamics of the energy of myogenic fluctuations in the *PI(t)* (peripheral hemodynamics) differs significantly from that in the *HR(t)* representing the central hemodynamics.

While no statistically significant difference in the 0.1 Hz spectral energy of $HR(t)$ between two different time intervals was found in any

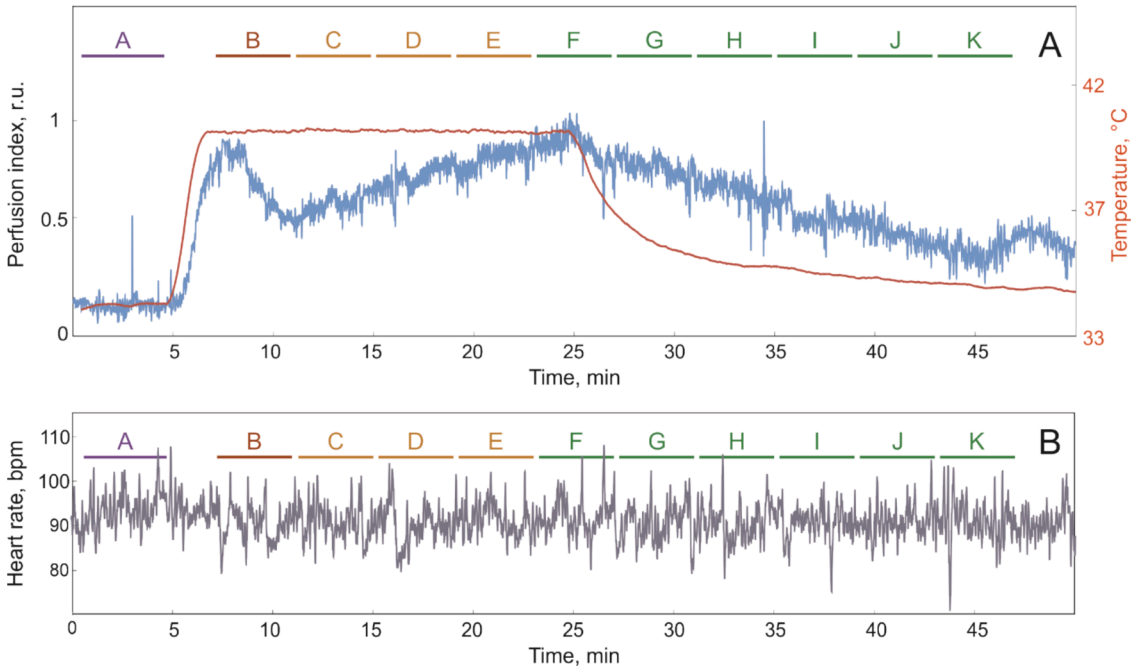

Fig. 2. Synchronously recorded dynamics of skin temperature, perfusion, $PI(t)$, and heart rate, $HR(t)$, during a forearm local heating test. (A) An example of simultaneously recorded skin temperature (red curve) and $PI(t)$ (blue curve). (B) Dependence $HR(t)$ synchronously recorded with $PI(t)$. The time intervals in which the wavelet transform of the recorded signals was calculated are shown at the top of each panel. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

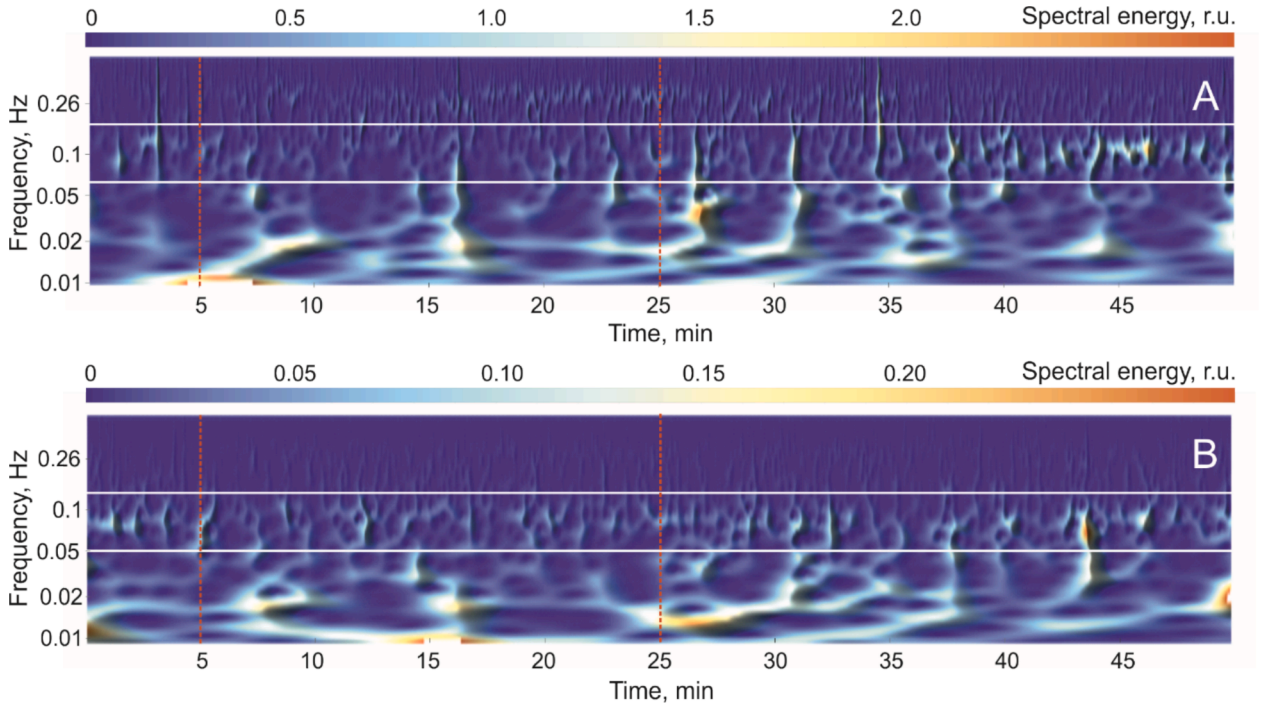

Fig. 3. Wavelet spectrograms of the perfusion and heart rate responses to local heating. (*A*) Time-frequency dependence for the perfusion waveform, $PI(t)$. (*B*) Time-frequency dependence for the heart rate, $HR(t)$. Both measured waveforms are shown in Fig. 2. Red vertical lines mark the moments when the heating module is switched on and off. The horizontal white lines show the frequency range (0.05–0.14 Hz). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

pair of time intervals, the pattern is completely different for spectral energy of $PI(t)$. The values of statistical significance of differences of 0.05–0.14 Hz spectral component of $PI(t)$ is presented in the inset of the Fig. 5. It is seen in Fig. 5 that the energy of perfusion fluctuations in the 0.05–0.14 Hz frequency band significantly decreases immediately after the start of skin heating (time interval *B* compared to *A*). Between these intervals, there was a fivefold decrease in group median spectral energy with $P = 0.002$.

After first drop, the energy of PI fluctuations stays on this low level during all time the heater is switched on. The difference between all the

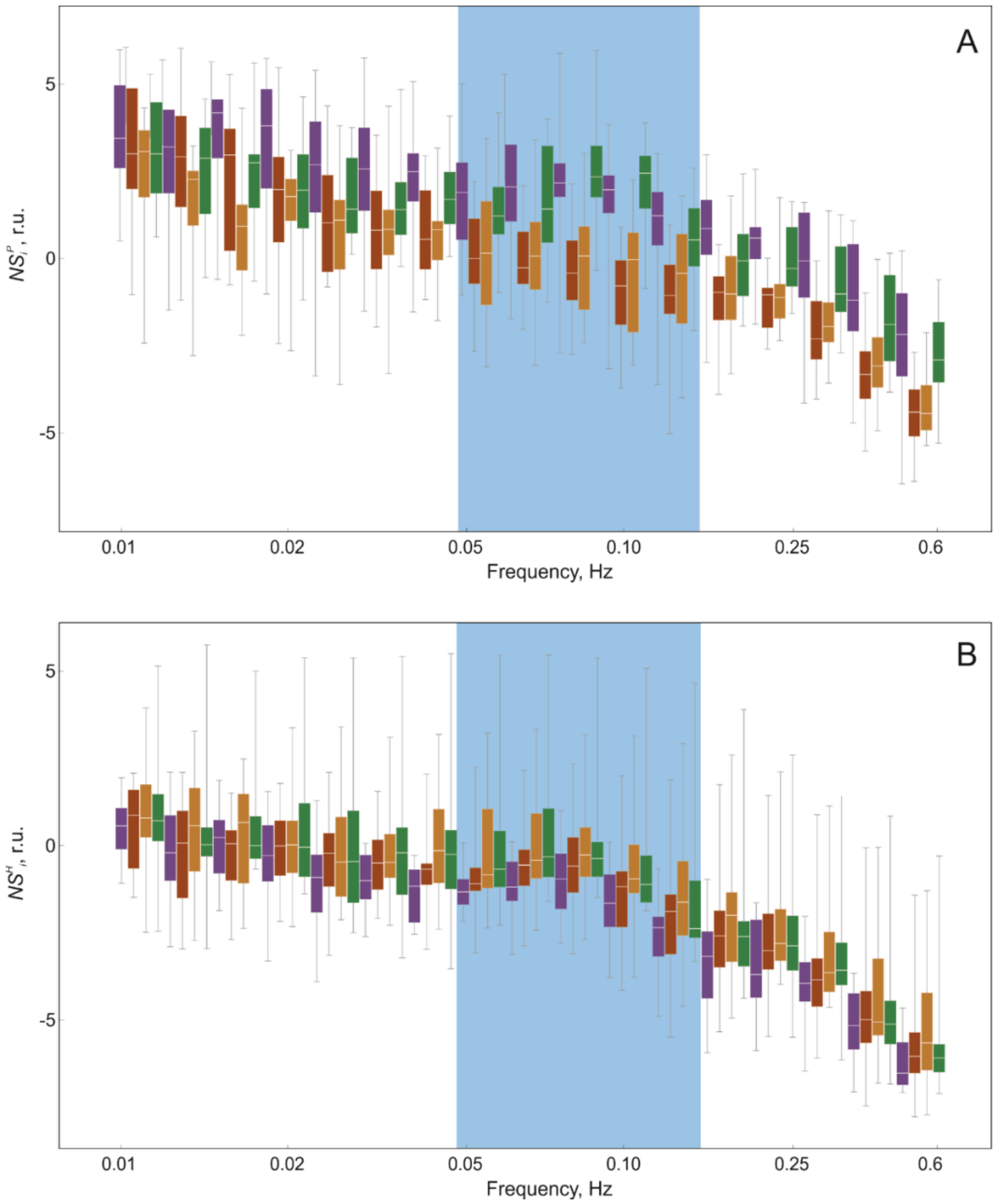

Fig. 4. Normalized spectral energy of the perfusion index and heart rate (NS_i^P and NS_i^H, respectively) in four representative time intervals, averaged over all subjects under study. (*A*) Wavelet spectra NS_i^P of the perfusion index, $PI(t)$. (*B*) Wavelet spectra NS_i^H of the heart rate, $HR(t)$. The representative time intervals in the heating test *A* (0.5–4.5 min), *B* (7–11 min), *E* (19–23 min), and *K* (43–47 min) are colored purple, brown, orange, and green, respectively. Blue vertical bars indicate the frequency band of 0.05–0.14 Hz. The data are presented in the logarithmic scale. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

intervals, during which the heater was switching-on, is insignificant. After turning off the heater, ~0.1 Hz oscillations gradually intensify and their significant changes are confirmed by a statistically significant difference in pairs (*G*–*I*, *H*–*J*, *I*–*K*). This means that at least over every 8 min the spectral energy increases significantly. The difference becomes nonsignificant only in the relaxation time interval of *K* corresponding to 43–47 min or the heating test. Therefore, the oscillation restores only after 30 min of relaxation. This result is proved by statistically equivalence of the intervals *A* and *K*.

4. Discussion

In this study, we used two time-synchronized experimental modalities, iPPG and ECG, to assess the response of the cardiovascular system to the local heating test. While the former method allows us to reveal the features of peripheral hemodynamics, the latter shows the contribution of the autonomic nervous system to the regulation of central hemodynamics. Our study has confirmed previously reported observations [32–34] that mild heating of a forearm skin area leads to a multiple increase in perfusion. Such kind of vasodilation results in almost complete disappearance of rhythmic oscillations in blood cell flux at a frequency of around 0.1 Hz, which was first discovered in 1987 by Kastrup et al. [35] and confirmed in this study, as well. The wavelet analysis of microcirculatory blood flow dynamics during the local heating test revealed a sharp, statistically significant drop in the energy of blood flow fluctuations in the frequency range from 0.05 to 0.14 Hz.

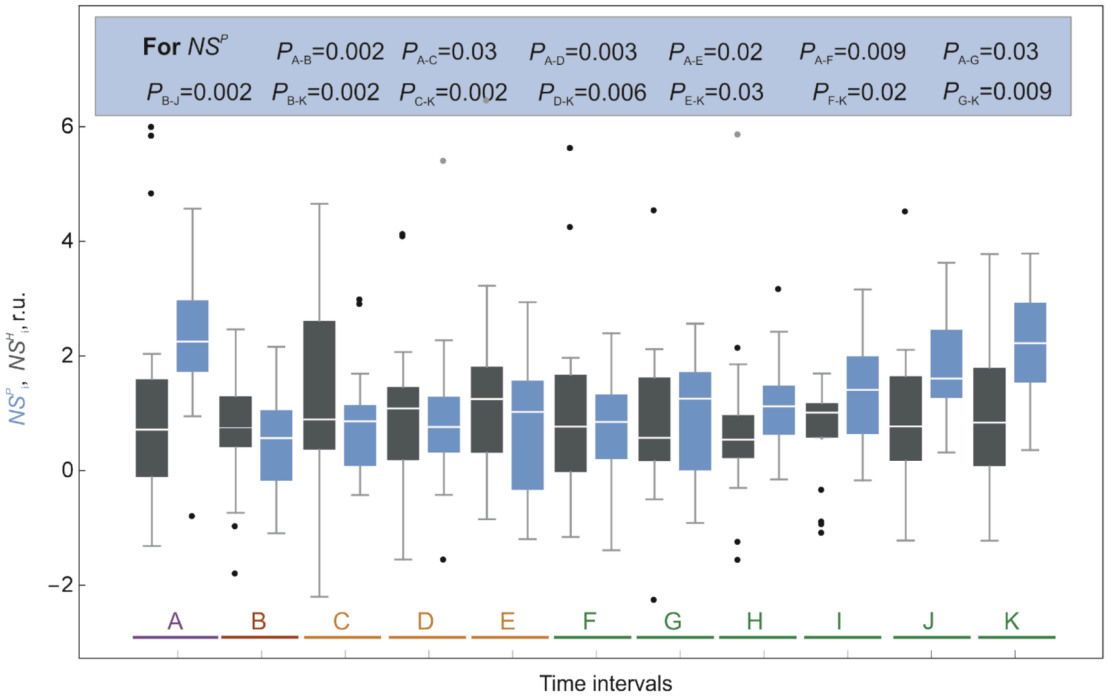

Fig. 5. Dynamics of normalized spectral components of *PI(t)* (NS_i^P, shown by blue boxes) and HR(t) (NS_i^H, shown by dark-grey boxes) in the frequency band of 0.05–0.14 Hz for all subjects. The spectral components are represented on a logarithmic scale. The position of the time intervals on the time scale of the local heating test is shown in Fig. 2. The values of statistical significance of differences of normalized spectral components of perfusion (NS_i^P) in pairs are presented in the Figure inset. We show the value of P only for pairs in which the difference is significant ($P < 0.05$). The difference of HR(t) spectral components is not significant for all possible pairs of intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Significant decrease in the energy of blood flow fluctuations in this spectral band in response to local heating was also reported by Geyer et al. [36], although they used a slower skin heating protocol.

Variations in the tone of small vessels due to contraction and relaxation of muscular components of the vascular wall play a significant role in the regulation of skin blood flow. Under the conditions of performing the test of prolonged local hyperemia in the first minutes of heating, there is an increase in blood flow due to relaxation of vascular smooth muscle and a decrease in sympathetic influence on the vascular wall of arterioles, which, as a consequence, leads to a multiple increase in perfusion (vasodilation due to the axon reflex). The rapid increase in blood flow in the vascular bed creates shear stress on the luminal surface of the vessels. In response to this stimulus, endothelial cells react by increasing the synthesis of primarily nitric oxide, prostacyclin, bradykinin [37]. Increased production of these substances leads to a decrease in the concentration of intracellular Ca^{2+} and relaxation of smooth muscle of the vessel wall [38]. Subsequent heating increases nitric oxide release by causing a mild inflammatory reaction, in which local chemical mediators increase the permeability of capillaries and postcapillary venules, which also leads to vasodilation of resistive vessels. Despite the difference in mechanism of dilatation between the first and second phases of the response to skin heating, we did not find a statistically significant difference in blood flow fluctuations at frequencies of around 0.1 Hz between these phases, (Fig. 5 for the time-intervals *B – E)*. These fluctuations of the blood flow remain at a very low level for 5 min even after turning off the heating element and only then begin to gradually recover to baseline values. It is worth noting that the restoration of fluctuations in this frequency band up to the baseline level takes more than 25 min for all subjects.

At the same time, after turning off the heater, we observed continued dilatation, PI did not restore up to the initial level up to the end of our measurements (Fig. 2). It should be emphasized that there is a high level of prolonged perfusion regardless of a sharp (within 2 min) drop in skin temperature. Such a significant discrepancy between the dynamics of skin temperature and evolution of perfusion after switching off the external heating was first reported by Minson et al., who called this observation paradoxical and left it without interpretation [39]. The protocol of the local heating test with the cessation of skin warming is rarely used, but there are few reports of continued vasodilation after a sharp decrease in skin temperature [21,25,26]. Our study has revealed for the first time that in the post-heating period, simultaneously with continued vasodilation, there is a significant increase in the energy of blood flow fluctuations in the low-frequency range of 0.05–0.14 Hz. Such an increase in myogenic fluctuations has not been reported in previous studies [35,36]. We speculate that the gradual increase in these oscillations and prolonged perfusion after turning off the heater are interrelated phenomena.

The spectral analysis of heart rate dynamics, associated with the central mechanism of hemodynamics regulation, did not reveal any changes in the energy of *HR(t)* fluctuations in this frequency range throughout the test. Therefore, we suggest that the observed activation of blood flow fluctuations at the frequency of about 0.1 Hz after cessation of heat exposure is unlikely to be associated with the regulation of vascular tone by centrally originated mechanisms. Our experimental data confirm the theoretically established fact that a small change in microcirculatory parameters can lead to either suppression or significant enhancement of blood flow fluctuations at the frequency of about 0.1 Hz [40]. As suggested, such behavior of the microcirculatory system is due to the strong nonlinearity of the response of smooth muscle that regulates arteriolar tone to changes in vascular intraluminal pressure [41,42].

To our mind, three aspects might be considered as limitations of our study. First, the PI parameter, estimated using iPGG, cannot be used to directly compare the perfusion in different subjects. This is a key limitation of all noninvasive methods of blood flow measurement in microcirculation system, in which the measured parameters only indirectly characterize cutaneous perfusion. Nevertheless, our previous experimental observations [26,27], supported by an alternative model

of the PPG-signal formation predominantly due to vascular wall movement [30], show the adequacy of evaluating changes in perfusion by this method in response to various functional impacts. It is worth noting that the perfusion response to local heating, estimated using iPPG [25,26], corresponds to the typically measured by other techniques [32]. In this study, we compare the relative changes in the normalized spectral power of the perfusion signal, which seems to be weakly dependent on the topology of the microcirculatory network. Second, in our measurements, we used Vaseline oil, which might affect microvascular regulation. However, as far as we know, studies on the effect of Vaseline oil on vasomotor activity have not been carried out. In addition, we assume that the oil has little effect on the measured relative changes in the vasomotion. At future work, we are planning to experimentally assess the effect of Vaseline oil on microvascular regulation. Third, the study was carried out only among men. We assume that the gender does not affect results, but this assumption needs to be validated in future research.

5. Conclusions

Synchronized iPPG and ECG techniques reveal a significant difference in the dynamics 0.1 Hz fluctuations of the cutaneous blood flow and the heart rate. In addition, a significant, but time-delayed, recovery of fluctuation energy in this frequency range after cessation of the skin warming was discovered for the first time. Thus, the reliable measurements of blood flow parameters in the forearm area performed by the iPPG system allowed us to experimentally confirm the local nature of fluctuations in peripheral blood flow in the frequency range of about 0.1 Hz.

CRediT authorship contribution statement

Irina A. Mizeva: Writing – original draft, Software, Formal analysis, Conceptualization. **Natalia P. Podolyan:** Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Oleg V. Mamontov:** Methodology, Formal analysis, Conceptualization. **Anastasiia V. Sakovskaia:** Resources, Investigation. **Alexei A. Kamshilin:** Writing – review & editing, Software, Resources, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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