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A System of Local Analyzers for Noninvasive Diagnostics of the General State of the Tissue Microcirculation System of Human Skin

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A system of wearable analyzers for simultaneous monitoring of blood microcirculation and oxidative metabolism in the tissue microcirculation system in several areas of the human body has been developed. Each wearable analyzer implements the diagnostic methods of laser Doppler flowmetry (monitoring of blood microcirculation) and fluorescence spectroscopy (measurement of fluorescence of coenzyme biomarkers of oxidative metabolism). A distributed system of several wearable devices provides detection of systemic disorders of the physiological state of human skin.

Introduction

The tissue microcirculation system (TMS) of the skin is anatomically heterogeneous. The vascular tone of the microvasculature (arterioles, precapillaries, arteriovenular shunts) may change depending on the state and functioning of the skin in different areas of the human body. Systemic disorders of the TMS can be monitored by analyzing the totality of data on microcirculation obtained simultaneously in several local areas. A system of wearable devices for monitoring the general state of the TMS has been developed [1]. The system combines two methods for monitoring blood microcirculation and oxidative metabolism: the well-known method of laser Doppler flowmetry (LDF) [2, 3] and fluorescence spectroscopy (FS) [4, 5]. When tissue is exposed to laser radiation in the course of LDF, the reflected signal has components produced by radiation scattering on red blood cells. The reflected signal is processed to determine the Doppler frequency shift, which is proportional to the velocity of particles moving in the microvasculature.

Fluorescence of restored nicotinamide adenine dinucleotide (NADH), a coenzyme biomarker of metabolism, is measured to assess the oxidative metabolism [6, 7]. An increase in the amplitude of NADH fluorescence in comparison with the reference values is indicative of a decrease in the utilization of the substrate and coenzymes in the initial state of the tissue and, therefore, of a decrease in the oxidative metabolism. Conversely, an increase in the oxidative metabolism is accompanied by a decrease in the amplitude of NADH fluorescence. The oxidative metabolism is normalized as the utilization of the substrate and coenzymes is restored to its normal level. Reference values of the coenzyme fluorescence amplitudes are determined statistically. They depend on the area of the study and the participant's age. Under otherwise identical conditions, reference values increase with age due to the age-related decrease in metabolic activity.

Methods, Hardware Implementation, and Results

The hardware for monitoring the general state of the TMS uses the available technology to achieve the goals of monitoring. Local monitoring of the TMS is usually carried out using a stationary device with an optical fiber probe, which delivers laser radiation to the tissue and receives backscattered radiation [8]. The desktop unit

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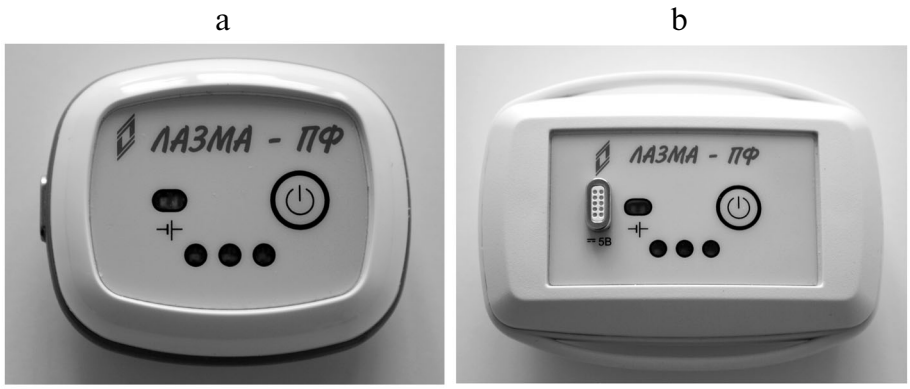

Fig. 1. LAZMA PF wearable analyzer modifications: a) for monitoring microhemodynamics (LDF); b) for monitoring both microhemodynamics (LDF) and oxidative metabolism (FS).

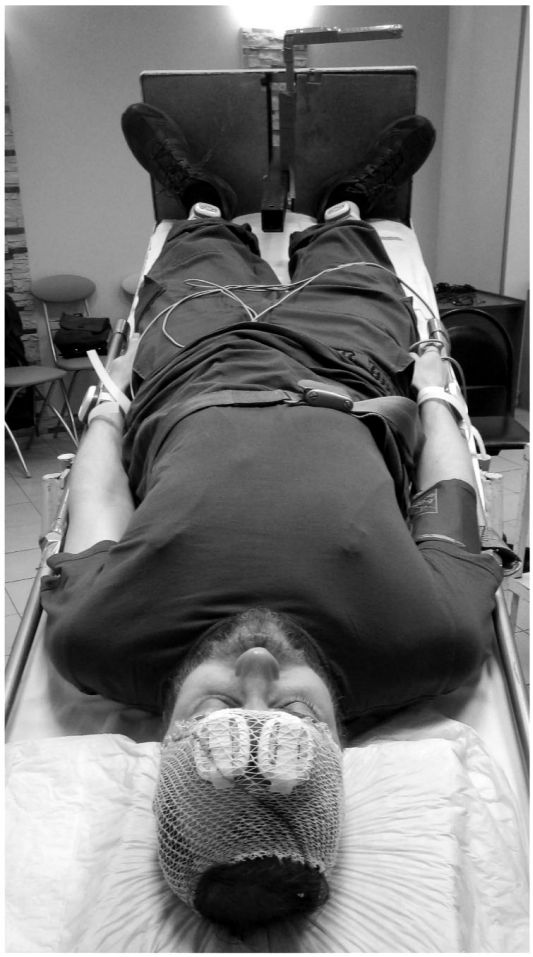

Fig. 2. Analyzers attached to six areas of human body: forehead (supraorbital arteries), right and left forearms, and right and left shins.

comprises the laser and optical and electronic units. There are no significant restrictions on the dimensions of the stationary device. However, devices with external probes are rather cumbersome and inconvenient for monitoring the state of skin simultaneously in several areas to detect systemic disorders. Portable (wearable) devices without optical fiber probes have been developed to meet this goal. These devices have built-in power supplies and provide data transmission via Bluetooth or Wi-Fi. The developed software makes it possible to work simultaneously with up to 8 wearable devices. Wearable devices facilitate simultaneous monitoring of symmetrical areas. This approach makes it possible to increase the efficiency of diagnosis of systemic disorders. Comparing microcirculation in different areas allows for detecting the areas with compromised physiological functioning.

Comprehensive diagnostic index of oxidative metabolism (IOM) is a measure of the state of blood microcirculation and oxidative metabolism monitored via NADH [8]:

$$\text{IOM} = C \cdot M_{\text{nutr}} / A_{\text{NADH}},$$

where M_{nutr} is the nutritive blood flow, A_{NADH} is the NADH fluorescence amplitude, and C is the proportionality coefficient (calibration-dependent);

$$M_{\text{nutr}} = M_{\text{mean}} \cdot A_{\text{m}} / (A_{\text{n}} + A_{\text{c}}),$$

where M_{mean} is the mean microcirculation index; A_{n}, A_{m}, and A_{c} are the blood flow oscillation amplitudes in the neurogenic, myogenic, and cardiogenic ranges, respectively. The obtained results are compared with the reference values.

TABLE 1. Reference Values of Parameters

Parameters \ Area	Hand, third finger, palm surface	Forearm, outer surface	Shin, inner surface	Foot, thumb, plantar surface
		Age: 18-50		
M_{mean}	15.4-23.1	3.5-9.5	3.5-6.0	10.6-15.8
M_{nutr}	5.1-6.2	1.5-3.5	1.0-2.0	2.8-3.4
IOM	3.3-4.7	0.7-1.7	0.7-1.7	2.3-2.8
		Age: >50		
M_{mean}	16.8-25.2	6.0-11	3.0-6.0	10.2-15.4
M_{nutr}	4.2-5.1	1.0-3.5	1.0-1.6	1.9-2.3
IOM	3.6-4.1	0.4-1.4	0.4-1.4	0.6-1.62

The wearable analyzer LAZMA PF (Certificate No. RZN 2018/7853 issued by the Federal Service for Surveillance in Healthcare (Roszdravnadzor), November 26, 2018) implements up-to-date technologies of photonics and microelectronics. It is available in two modifications: using LDF only (Fig. 1a) and using both LDF to assess blood flow perfusion and FS to monitor NADH fluorescence as a biomarker of oxidative metabolism (Fig. 1b). Both modifications use small-sized single-frequency vertical-external-cavity surface-emitting lasers (VECSEL). Use of these lasers made it possible to significantly reduce the device size to make it wearable. Each analyzer has a built-in power supply, does not use optical fiber probes, is wireless, and exchanges data with a computer via Bluetooth or Wi-Fi.

Figure 2 shows as an example how analyzers are attached to six areas of human body.

A wearable wireless analyzer can be conveniently attached to any surface of the body. The developed software makes it possible to process data from up to 8 wearable devices simultaneously. The wearable analyzers have temperature and motion sensors. When processing motion sensor data, recordings simultaneous with the subject's movements are identified as potential sources of distortion of the LDF-gram and filtered using special software. Figure 3a shows an example of recordings with motion-induced noise; Fig. 3b shows the same recordings after filtering out the noise.

The filtered recordings are compared with the reference values (Table 1) obtained by statistical pro-

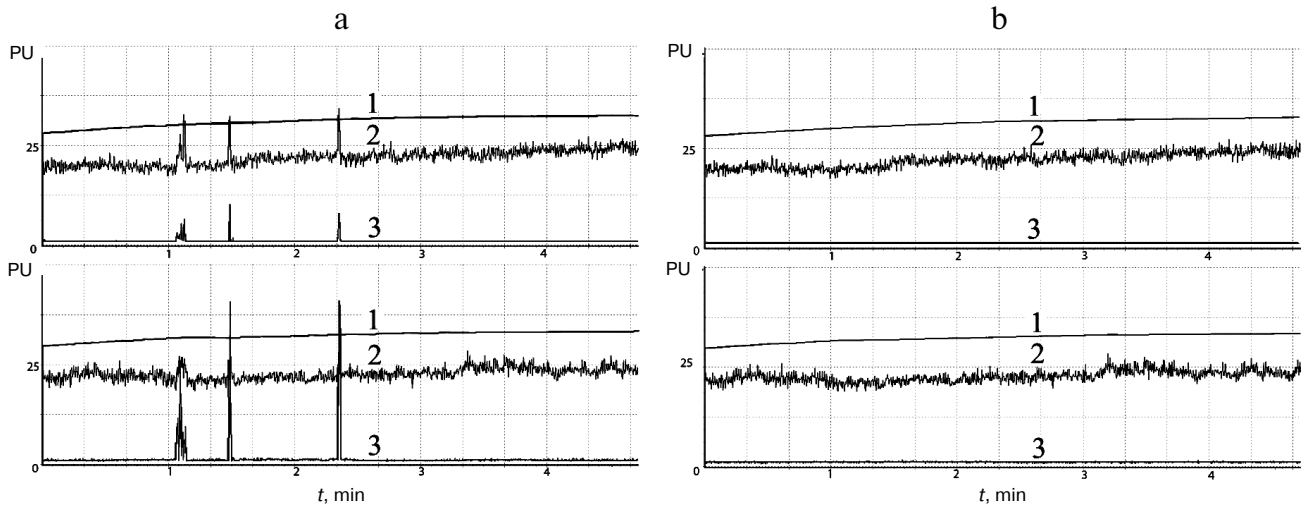

Fig. 3. An example of simultaneous recordings from two analyzers: a) with motion-induced noise; b) after filtering out the noise. 1) Temperature; 2) LDF-gram; 3) motion sensor recordings.

cessing of the results of tests carried out in healthy volunteers.

The software processes deviations of the obtained data from the reference values, after which it generates and displays on the computer monitor the conclusion on the type of disorders of blood microcirculation: arterial hyperemia, venous stasis, spasm of the arteries bringing blood to the microcirculatory bed, or stasis.

The diagnostic method considered in this work uses a system of wearable analyzers to identify the area with the most pronounced disturbances in the metabolism energy supply under current physiological conditions. The method is noninvasive and has no contraindications. The method is based on monitoring general physiological processes in tissues, so that it can be used to solve a variety of problems. In particular, it can be used for adjusting the treatment of patients with hypertension [9, 10].

Discussion and Conclusions

Tissue microcirculation systems of the human body are heterogeneous. It is advisable to assess the general state of the TMS of human skin from the totality of data on microcirculation obtained simultaneously in several local areas using a distributed system of analyzers for combined monitoring of two physiologically related processes: blood microcirculation and oxidative metabolism. For example, simultaneous monitoring of symmetrical areas allows identifying pathological developments accompanied by right-to-left asymmetry of diagnostic parameters measured in the upper extremities of patients with arterial hypertension [10]. To assess the general state of the tissue microcirculation system, it is recommended to use up to six analyzers distributed over symmetrical areas: two on the forehead in the vascularization zones of the supraorbital arteries, two analyzers on the upper and two on the lower extremities. As compared with stationary devices widely used in medical practice to monitor local areas of human body, wearable wireless analyzers present new opportunities for studying TMSs with due regard for their physiological heterogeneity.

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