Wearable Devices for Multimodal Optical Diagnostics of Microcirculatory-Tissue Systems: Application Experience in the Clinic and Space

Andrey Dunaev
Research and Development Center of Biomedical Photonics, Orel State University, 95 Komsomolskaya str., Orel 302026, Russia

e-mail: dunaev@bmecenter.ru

Abstract. This work demonstrates some results of the successful experience of using wearable devices for multimodal optical diagnostics of microcirculatory-tissue systems both in clinical practice and in the conditions of a Space experiment. The multimodal approach based on simultaneously applying a minimum of 2 optical diagnostic methods, for example, laser Doppler flowmetry and fluorescence spectroscopy, allows analysing of blood flow and metabolic processes in biological tissue more systematically. Combining several wearable devices into a distributed diagnostic system allows placing them simultaneously on symmetrical parts of the body (such as opposite limbs) thus providing a possibility to study the symmetry of the measured signals. The obtained data on the state of the microcirculatory-tissue systems of the human body recorded with wearable multimodal devices make it possible to assess the relationship and dynamics of oxygen delivery and utilization by tissues more comprehensively and reliably in a variety of diagnostic tasks. © 2023 Journal of Biomedical Photonics & Engineering.

Keywords: wearable devices; microcirculatory-tissue systems; multimodal optical diagnostics; laser Doppler flowmetry; fluorescence spectroscopy; Space experiment; zero gravity.

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1 Introduction

In recent decades, the knowledge about tissue optical properties in the healthy and pathological state has reached a sufficient level to develop and implement the methods of optical non-invasive diagnostics in clinical practice [1–3]. Lately, there has been a steady increase in interest in the problems of non-invasive research not only of the microcirculatory bed as the final segment of the cardiovascular system, but also of the microcirculatory-tissue systems (MTS) of the human body from the point of view of maintaining homeostasis and homeokinesis of tissues in a single holistic organism. MTS of the human body are the smallest functional unit of the vascular system, where microvessels are in close relationship with the surrounding tissue and regulatory elements. MTS is the functional element of an organ and is a structural and functional complex composed of specialized parenchyma cells, cells of the connective tissue suspended in a non-cellular matrix, blood and lymphatic microvessels, and fiber nerve endings, which are combined into a single system by regulatory mechanisms [4]. Violations in the MTS play a key role in the pathogenesis of various diseases complications (for example, rheumatological and endocrinological [5–7], dermatological [8], and otolaryngological [9] ones). Even during minimally invasive surgical operations, it is necessary to assess the state of MTS, for example, in case of organ ischemia, etc. [10]. In view of the above, timely diagnosis of MTS of the human body is a subject of extensive research.

At present, there is a surge of interest in wearable electronic diagnostic devices, because daily monitoring of parameters (for example, MTS parameters) promises a new quality of diagnostics [11–13]. Recently actively developed multimodal approach allows clinicians to obtain *in vivo* values of individual physiological and biochemical parameters, as well as to conduct a comprehensive assessment of the viability of MTS [14–17]. One of the first developments of wearable devices for estimating MTS parameters is the analyzer “LAZMA PF” (LAZMA Ltd, Russia; in EU/UK this device is produced by Aston Medical Technology Ltd., UK as “FED-1b”) [18, 19], which combines a multimodal approach, namely, consisting of 2 channels – laser Doppler flowmetry (LDF) and fluorescence spectroscopy (FS).

The LDF method is based on laser probing of biological tissues and analysis of light scattered from moving erythrocytes. The main parameter recorded by this method is called the index of microcirculation or perfusion (I_m) [20]. This method allows one to evaluate the oscillatory processes in the microvasculature in a wide range of frequencies, which are calculated using the wavelet transform [21–23]. For more than 15 years, it has been customary to use adaptive wavelet analysis to assess fluctuations in the microvasculature, which implements a continuous wavelet transform using the complex-valued Morlet wavelet as an analyzing wavelet. Previously, the fast Fourier transform and Butterworth mathematical filters were also used for this purpose, however, due to the fact that the LDF-gram (perfusion) is a non-stationary process (short-term fragmentary episodes of vasoconstriction and vasodilation of the microvascular bed are recorded in it), it is now customary to use continuous wavelet transform, which provides the optimal “time – frequency” ratio for blood flow signals and allows to trace the frequency and amplitude of oscillations [22]. At present, it is customary to distinguish several (mostly 5) main frequency ranges (oscillations) that take into account the influence of various regulatory mechanisms: endothelial 0.0095–0.02 Hz (E), neurogenic 0.02–0.06 Hz (N), myogenic 0.06–0.16 Hz (M), breathing 0.16–0.4 Hz (B) and cardiac 0.4–1.6 Hz (C) [4, 24]. However, some authors (for example, Refs. [25–27]) distinguish 2 subranges in the range of endothelial oscillations – 0.005–0.0095 Hz and 0.0095–0.02 Hz, that reflect the vascular tone regulation due to the endothelium activity, both NO-dependent and independent. In addition, some authors [28, 29] consider it reasonable to distinguish two subranges of general myogenic oscillations – 0.047–0.069 Hz (low-frequency) and 0.07–0.145 Hz. In the former, the influence of peptidergic sensory fibers can be manifested, and the second reflects the proper myogenic oscillations or vasomotions. Thus, currently, it is possible to analyze 7 different ranges of microvasculature fluctuations.

The FS method is based on laser probing of tissues and registration of fluorescence spectra of metabolic coenzymes. This method, among others, implements the registration of the normalized amplitudes of the NADH (nicotinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide) fluorescence intensity depending on the excitation wavelength respectively [30]. Changes in these parameters are associated with changes in metabolic conditions due to different physiological and pathological processes, and therefore fluorescence monitoring can be used to detect cell metabolism disorders associated with the occurrence of various diseases [31].

Thus, the purpose of this work was to demonstrate the successful experience of using these wearable multimodal devices both in clinical practice and in the conditions of a Space experiment.

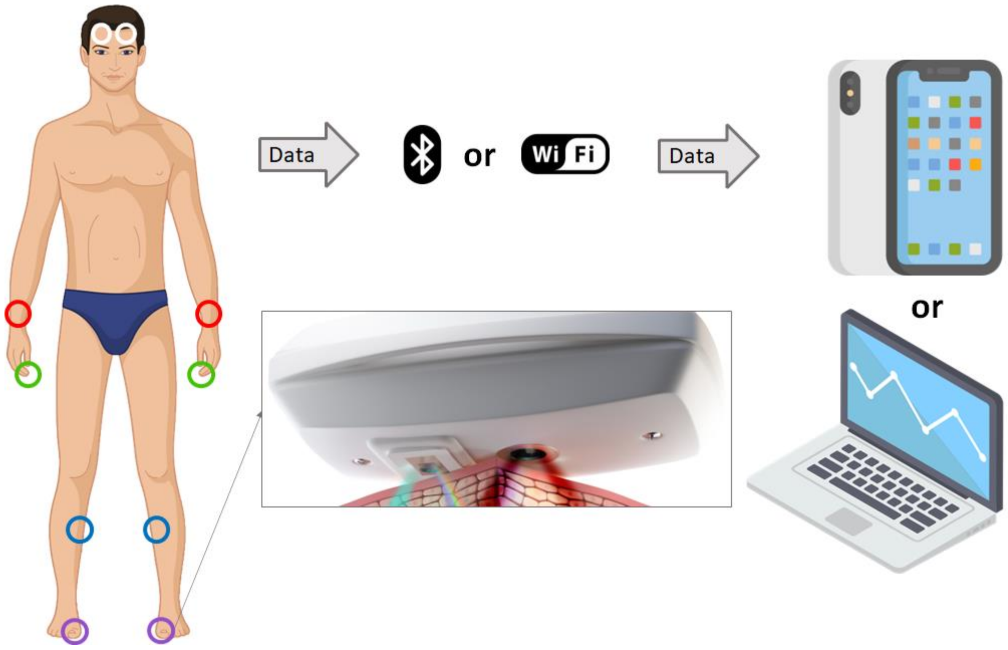


Fig. 1 Examples of location of wearable devices for diagnosing the MTS on symmetrical zones of the human body and their wireless connection to a personal computer or smartphone.

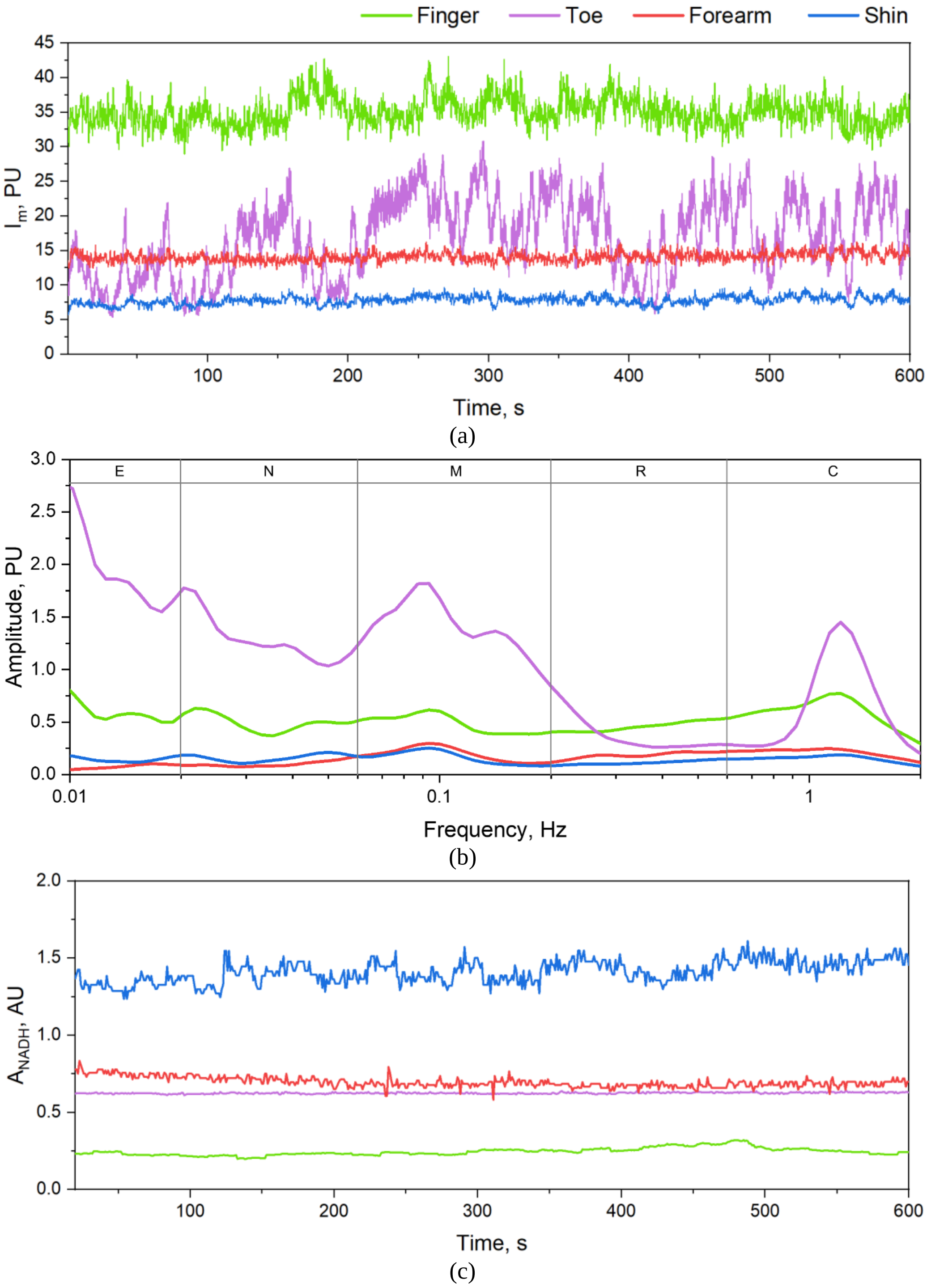


Fig. 2 A typical example of simultaneous registration from 4 skin zones of the right extremities of average perfusion (a), its wavelet analysis (b), and the normalized NADH fluorescence amplitude (c) of a conditionally healthy volunteer.

2 Design Features of a Wearable Device for Multimodal Optical Diagnostics

A distinctive feature of the wearable devices under consideration is the absence of optical fibers in their design, which allows to decrease the movement artefacts common in fibre-based LDF monitors [32]. Wearable devices are placed on the skin for direct irradiation from a window and registration of emitted (secondary) radiation from biotissue at the back of the instrument and transmitting measurement data to a PC using Bluetooth or Wi-Fi protocols (Fig. 1). Wearable device “LAZMA PF” with 2 optical diagnostic channels uses a VCSEL chip with a wavelength of 850 nm as a single-mode laser source (0.8 mW) in the LDF channel, delivering radiation directly to the skin [19]. In the FS channel it uses a 365 nm UV LED (pulse power – 1.4 mW, average power 0.35 mW with duty cycle 4) to excite endogenous fluorescence (NADH in the wavelengths range 460–470 nm) [33]. An amplitude of NADH fluorescence intensity (A_{NADH}) is normalized to back-scattered radiation to reduce the influence of different blood filling in biotissue [30], which arises, among other reasons, due to the artifacts associated with different pressure on the skin surface [34]. The distance between the windows of 2 channels is about 1 cm (as shown in Fig. 1), the examined diagnostic volume for each of the channels is different and depends on the design features of each channel (on the so-called "measurement base" – the distance between the radiation source and detector) – on average, it does not exceed 1 mm^3. Examples of location on symmetrical zones of the limbs of wearable devices for diagnosing the MTS of the human body and their wireless connection to a personal computer or smartphone are shown in Fig. 1. This figure also shows the most common locations for wearable devices on the biotissue of the subject's body (distributed monitoring system) depending on diagnostic tasks: these are often symmetrical points on the right and left sides of the upper and lower extremities, skin areas there are rich with arteriolo-venular anastomoses (hands or toes fingers pads) and with predominant nutritive blood flow (forearms or shins), and on the forehead at areas of supraorbital arteries.

A typical example of simultaneous registration during 10 min from 4 skin zones of the right extremities of average perfusion (a), its wavelet analysis with 5 frequency ranges (b), and the normalized NADH fluorescence amplitude (c) of a conditionally healthy volunteer (men 46 years) is shown in Fig. 2 (the colors of the graphs correspond to the colors of the device's location in Fig. 1).

The software allows to calculate the average value of nutritive blood flow (I_{mn}) according to the Eq. (1), measured in perfusion units (PU). Nutritive blood flow is a characteristic of blood flow in the capillaries, that directly provides trophic and oxygenation processes (unlike blood flow through arteriolo-venular anastomoses) [18]:

$$I_{mn} = \frac{I_m \cdot A_m}{A_n + A_c}, \tag{1}$$

where is the I_{mn} – nutritive blood flow, I_m – the average value of the index of microcirculation, A_m – the amplitude of myogenic oscillations, A_n – the amplitude of neurogenic oscillations, A_c – the amplitude of cardiac oscillations.

In addition, according to the multimodal approach, as a complex parameter for a comprehensive assessment of the relationship between the state of the microvasculature and oxidative metabolism in the tissue, an oxidative metabolism index (*OMI*) has been developed (due to the use of only one fluorescence excitation with wavelength 365 nm in this device, the proposed formula is adapted) [11, 18, 35]:

$$OMI = k\frac{I_{mn}}{A_{NADH}}, \tag{2}$$

where *k* is the coefficient of proportionality (determined by the calibration of the FS channel of the device), A_{NADH} – normalized fluorescence amplitude of coenzyme NADH.

This new diagnostic parameter makes it possible to assess the relationship between the supply of oxygenated blood to the capillary bed and the utilization of oxygen in tissues.

3 Application Experience in the Clinical Practice

Despite the relatively recent invention of wearable devices in 2 versions (with one LDF channel, as well as with both LDF and FS), since 2018 they have been actively introduced into clinical practice in various fields of medicine – functional diagnostics, endocrinology (diabetes mellitus), cardiology (arterial hypertension), rehabilitation, yoga therapy, and even Space medicine. Next, we will consider several examples of the successful use (in terms of increasing the information content of diagnostics) of these wearable devices in medicine.

Before starting to implement these new wearable devices for solving various diagnostic tasks, the possibilities of using the set of them for multipoint measurements of blood perfusion were investigated [36]. These devices were used to analyze the skin blood flow synchronization in homologous regions of the contralateral limbs, both in the basal state and during various functional (occlusion or breath holding) tests. Studies have shown a high synchronization of blood flow rhythms in the contralateral limbs of healthy volunteers. Portability and low sensitivity to motion artefacts make them more mobile and capable of use even outside the clinic. Furthermore, these wearable devices demonstrate high repeatability of measurements at rest and in physiological tests, which increases the diagnostic value of measurements.

One of the first researches using new wearable devices was the study of changes in blood microcirculation for different age groups. In presented study [37] a higher level of perfusion in areas with glabrous skin of the middle finger pad in the older age group was shown and the measurements taken from the forearms skin on the dorsal wrist surface demonstrated the same tendency. A higher signal level in the older group can be explained by skin thinning during the ageing process, because of which laser radiation is less scattered, increasing the diagnostic volume. In another research [38] the LDF signal was simultaneously recorded from the 3rd fingers' pads of both hands, and amplitudes of the blood flow oscillations and wavelet coherence of the signals were used for the data analysis. Wavelet coherence shows how much the blood flow oscillations coincide in frequency and amplitude. In this case, the magnitude of the amplitudes is not taken into account, the value is the ratio of the amplitudes of the oscillations. The closer the amplitudes are to each other, the higher the coherence (approaching 1), and the closer the similar amplitudes are in the frequency range, the higher the coherence. Thus, it was discovered that myogenic oscillations of blood perfusion in the younger group had a higher wavelet coherence parameter than in the older group. The obtained data can be considered further in the development of protocols for the studies of MTS in patients with different pathologies.

Another example of research in functional diagnostics is the study of differentiating cardiovascular parameters between healthy young non-smokers and smokers [39]. This study showed a higher level of blood perfusion in the non-smoker group compared to the smoker group and vice-versa for the variation of pulse frequency. This result can be useful to assess the sensitivity of the wearable devices in determining the effect of nicotine for smokers as compared to non-smokers and also the blood microcirculation in smokers with different pathologies.

As one of the examples of the successful use of these wearable devices in the form of a distributed system on the body of endocrinological patients can be this pilot study [40]. In this study, four wearable LDF devices for multipoint measurements of blood perfusion were utilized for microcirculatory function assessment in patients with 2 type diabetes mellitus (DM) and healthy controls of two distinct age groups. The results of the studies have shown that the average perfusion differs between healthy volunteers of distinct age groups and between healthy volunteers of the younger age group and patients with DM. It was noted that the average level of perfusion measured on the wrist in the two groups of healthy volunteers has no statistically significant differences found in similar measurements on the fingertips. This pilot study has shown that the implementation of the LDF as a fiber-free wireless wearable device is a very convenient solution to be applied as point-of-care testing. The measurements in the groups of different ages allowed for the registration of age specific changes in blood perfusion as well as changes that can be associated with the development of DM.

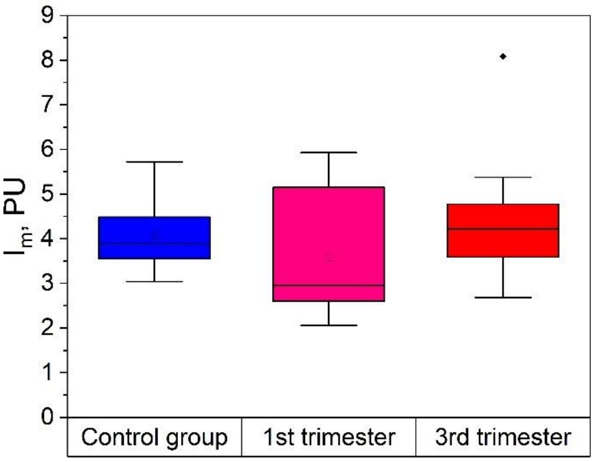
Another promising example of the use of these wearable devices in endocrinology may be the monitoring of the microcirculatory disorders therapy in DM during a standard course of intravenous infusions of alpha-lipoic acid solution [41]. The studies have demonstrated a tendency for a decrease in microcirculation and nutritive blood flow in patients during the course of the therapy and an increase in shunt blood flow. Since it is known that patients with DM show higher values of perfusion, these changes may be associated with a positive effect of the treatment. It was noted that after therapy, the parameters of the patients approximated their values to those of the control group. These changes are especially significantly expressed in the lower and less significantly in the upper limbs. This difference may be explained by the predominant involvement of the microvascular bed of the lower limbs in the development of diabetic complications, due to their higher susceptibility to different stress factors (more pressure due to wearing shoes and bipedalism, etc.).

One of the first examples of the application of multimodal wearable diagnostic devices in endocrinology is the study of the effect of pregestational type 1 DM on the state of MTS in patients at different stages of pregnancy [42]. This study is the first to show the combined use of LDF and FS together with glucose variability monitoring to assess vascular function and oxidative metabolic status in 10 pregnant patients with pregestational type 1 DM (the average age of the patients was 32, and all were between 7 and 22 weeks of gestation). All patients also underwent continuous glucose monitoring with the “Libre Freestyle” system (Abbott, US), which was preinstalled subcutaneously in the forearm area. An installed system measured the values of glucose concentration in the intercellular fluid every 15 min for 10–14 days. The LDF and FS data measured at the wrists and shins were also compared with data obtained in a similar way from 7 healthy nonpregnant women with a mean age of 32 years. Fig. 3 demonstrates obtained preliminary results from 2 channels of wearable multimodal devices measured at the shins.

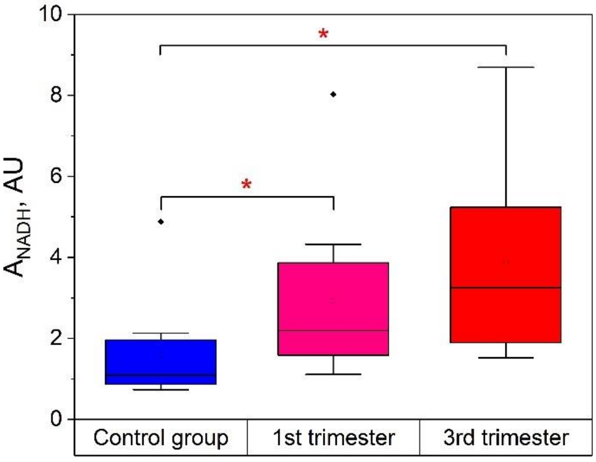
From the data presented in Fig. 3a, it can be seen that the average perfusion does not differ significantly in the analyzed groups. However, the analysis of perfusion frequency rhythms revealed a decrease in the oscillatory activity of the microvasculature in the legs in patients during pregnancy, which may indicate a deterioration in the functional state of microcirculation by the 3rd trimester. The data in Fig. 3b demonstrates a statistically significant increase in the amplitude of the NADH fluorescence intensity in the group of pregnant women, which may be a consequence of impaired tissue respiration. The development of this direction of using wearable multimodal devices is seen in the comparison of LDF and FS monitoring data of patients with their glucose variability monitoring data in order to analyze the possible effects of diurnal blood glucose changes on oxidative metabolism and microcirculation.

It is also worth noting that the authors [43] could demonstrate the use of peripheral blood flow oscillations analysis with wearable LDF devices to diagnose vascular disorders in patients who have undergone COVID-19 in their early and advanced stages of recovery. Obtained results show a significant increase in the amplitude of neurogenic oscillations in the upper extremities of patients undergoing COVID-19, which may be a factor preceding dilation of arterioles and venules and redirection of microcirculatory blood flow from the nutritive to the shunt pathways. But more research is needed to fully understand the changes in the mechanisms of blood flow regulation that occur after an infection.

The first successful application of wearable devices in cardiology is the study of the functional state of resistive skin microvessels in patients with newly diagnosed arterial hypertension [44]. According to the obtained LDF data, in men with arterial hypertension, there is a decrease in the amplitude (increase in the tone) of neurogenic and myogenic vasomotion, a decrease in the amplitude of pulse oscillations of microcirculatory flow, a decrease in perfusion efficiency of endothelial, neurogenic, myogenic and pulse mechanisms of tissue perfusion regulation. Of all tone-forming mechanisms, only the myogenic mechanism had a weak negative correlation with systolic blood pressure level. The amplitude of pulse oscillations demonstrated the highest degree of correlation with blood pressure parameters. Thus, the use of wearable devices even with only an LDF channel was suggested to be a useful method for the dynamic monitoring of patients with arterial hypertension.



(a)



(b)

Fig. 3 Average perfusion (a) and normalized NADH fluorescence amplitudes (b) for groups of pregnant women with DM in the 1st and 3rd trimesters at the shins in comparison with the control group. (* – statistical significance of differences was confirmed by the Mann-Whitney test, $p \leq 0.05$).

Another interesting example of using wearable devices is the study of the dynamics of cutaneous blood perfusion and the regulatory mechanisms of blood microcirculation depending on the body position changes. It is known, that changes in hemodynamic parameters depending on the position of the body significantly assist the homeostasis in the limbs and essentially in the sufficiency of blood supply for the brain [45]. Obtained results show the importance of taking into account the position of the body in space during the monitoring of physiological parameters interrelated with blood perfusion. The results can be further implemented for the development of the methodology for the wider use of wearable devices in functional diagnostics. Presented findings of the amplitude-frequency analysis of LDF signals measured in different body positions confirm the earlier assumptions of the measurement technique for the orthostatic test and diagnostic procedures based on it, and more specifically, for the use of this particular type of wearable device together with the physiological tests. The results obtained can be of particular interest for the development of new protocols for the study of microcirculation, including those related to daily monitoring.

4 Application Experience during Space Experiment for Microcirculatory-Tissue Systems Study

A unique example of the successful application of wearable multimodal devices was a Space experiment “LAZMA” aboard the International Space Station (ISS) during the 20th visiting expedition (December 8–20, 2021) [46]. The main goal of this Space experiment was to study for the first time tissue metabolic processes (oxygen utilization by tissues) and microcirculatory blood flow in human skin under zero-gravity conditions.

The “LAZMA” experiment was carried out with a crew of astronauts (2 participated) during the ISS visiting expedition. The measurements were carried out in 3 stages: stage 1 – before spaceflight; stage 2 – during the stay of the crew on the ISS; stage 3 – after the return from spaceflight. Each stage lasted at least 7 days with daily measurements of physiological parameters. The analyzers were placed on the pads of the middle fingers and big toes, on the back of the wrists, and attached to the temples. Each measurement of one study area lasted 8 min during which the astronaut was in a state of complete physical and psychological rest. Fig. 4 shows a typical example of average perfusion and normalized NADH fluorescence amplitude on the pad of the left big toe of one of the astronauts before, during, and after the Space flight.

The obtained preliminary data show an almost complete inversion (especially during Space flight) of 2 recorded signals by different measuring channels. Moreover, in the area selected for analysis (toe), we can see an acute reaction to microgravity in the first 2–3 days of flight, both in a decrease in perfusion and in an increase in the amplitude of NADH intensity. These changes may be related to the redistribution of blood flow in the microcirculation system from the lower to the upper part of the body under the influence of zero-gravity [47–49].

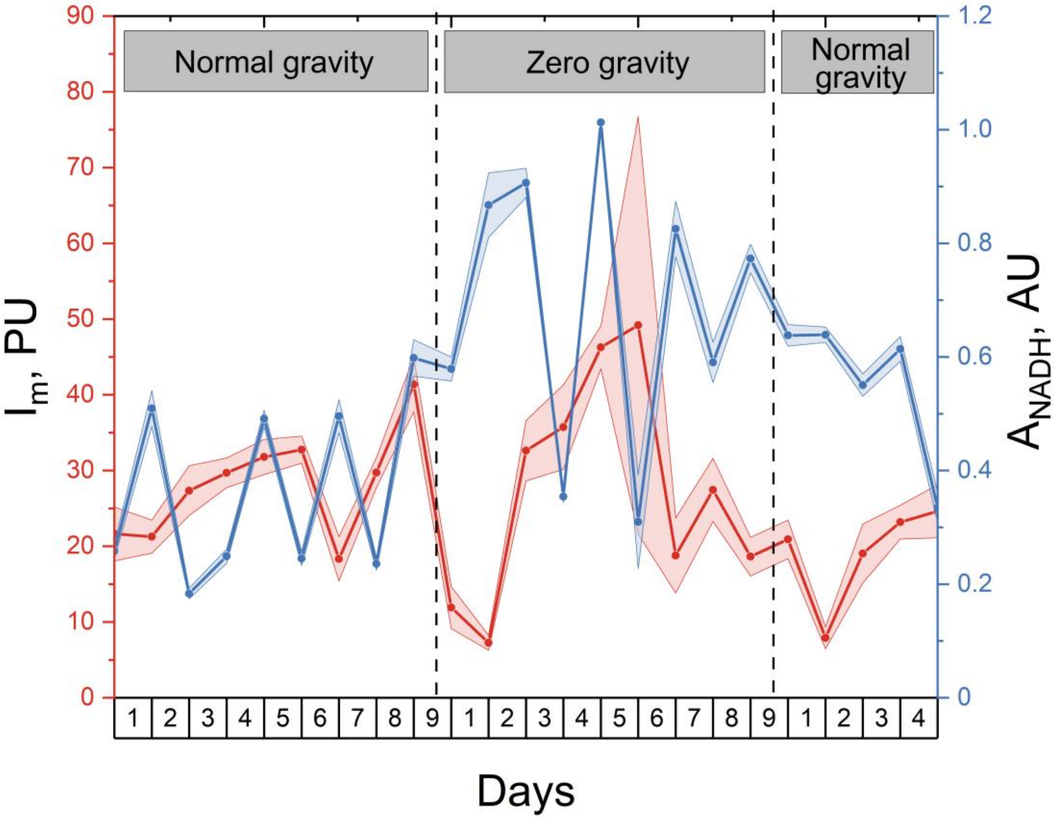


Fig. 4 Average perfusion (red) and normalized NADH fluorescence amplitude (blue) on the pad of the left big toe of one of the astronauts before, during and after Space flight.

Thus, for the first time, a technique has been developed for measuring MTS in the limbs of cosmonauts during the period of acute adaptation to microgravity conditions and readaptation after the completion of a Space flight. Obtaining the most important physiological information in real time under conditions of zero gravity will provide completely new data on the physiology of the MTS in humans under conditions of orbital flight.

5 Conclusion

Thus, in this review, the unique possibilities of using wearable devices to assess the state of the microcirculatory-tissue systems of the human body were demonstrated. In the examples presented over the past 5 years, the possibilities of their effective application in various fields of medicine – functional diagnostics, endocrinology, cardiology, and even in Space medicine have been clearly demonstrated. Moreover, in the case of using 2-channel devices based on a multimodal approach, it becomes possible to evaluate perfusion-metabolic disorders in the biological tissues of patients' limbs.

Thus, the data on the state of the MTS of the human body recorded with wearable multimodal devices make it possible to assess the relationship and dynamics of oxygen utilization more comprehensively and reliably by tissues in a variety of diagnostic tasks. In this regard, in the coming years, they are expected to be even more widely introduced into clinical practice, as well as for monitoring MTS at home, which is especially valuable during quarantine measures.

Disclosures

Author declares that there is no conflict of interests in this paper.

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