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Digital Laser Doppler Flowmetry: Device, Signal Processing Technique, and Clinical Testing

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A method and a device for digital laser Doppler flowmetry are proposed. An approach to signal processing based on analysis of the power spectrum amplitude distribution over Doppler broadening frequencies is suggested. A prototype of the device is presented; its technical characteristics and settings used in tests are described. The method was tested in healthy volunteers of different ages and patients with type 2 diabetes mellitus. The research led to the development of binary classifiers for classifying volunteers and patients into groups according to the functional state of microcirculation.

Introduction

Laser Doppler flowmetry (LDF) is a non-invasive medical diagnosis technique, which has been actively developed and used in medical practice for over 40 years. The pioneering publication on LDF [1] showed that microcirculation parameters can be determined by analyzing coherent radiation scattering on moving blood particles [2]. Further studies demonstrated the possibility of skin microcirculation monitoring using the LDF modulation method, based on the physiological mechanisms of active regulation of the microvascular bed. Subsequent years saw development and improvement of equipment for laser Doppler flowmetry; methods for signal detection and processing, as well as for mathematical modeling of signals, were developed.

Laser Doppler flowmetry is used both in scientific research and in practical medicine to diagnose complications in diabetes mellitus (diabetic foot, diabetic retinopathy), rheumatologic diseases (Raynaud's disease, scleroderma, systemic lupus erythematosus), and gum diseases (gingivitis) [3]. Laser Doppler flowmetry owes the increase in its medical application to a number of studies (for example, [4]) on the correlation of blood perfusion oscillations with physiological processes. A number of works showed that LDF can be used to measure endothelium-dependent and endothelium-independent rhythms, microvessel muscle activity, and blood flow fluctuations associated with cardiac and respiratory activities.

It is usually impossible to reliably diagnose the functional state of microcirculation without special functional tests (heat, cold, electrical stimulation, or medicinal). These tests are based on activating a particular physiological system by exposure to an external or internal factor leading to a change in its initial state. Many works (in particular, [5]) substantiate the use of thermal tests. Cold tests often accompany heat tests. Another functional test used in medical practice is based on the electrophoretic transfer of active substances through mucous membranes and skin [6]. Although electrical stimulation is rarely used, there are works suggesting diagnostic procedures based on electrical stimulation [7].

Today, development of LDF devices and signal processing techniques continues within the framework of the research into distributed monitoring of blood perfusion. Multichannel recording is used to study the compensatory capabilities of the microcirculation system simultaneously in different skin areas exposed to changing environmental conditions (ambient temperature, body position in space) and internal factors (medication, forced breathing, exercise, etc.) [8].

In a number of works on the processing of the recorded LDF signal, data on the power spectrum of the photocurrent are used. In [9], the results of calculation of blood perfusion rate in several velocity ranges are present-

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ed. The calculations took into account the theoretical distribution of red blood cell velocities in the diagnostic volume. Another group of researchers adopted a different approach [10]: the phase scattering function and model power spectra were modeled using the probability distribution of the angle between the incident and scattered laser waves. To calculate the model power spectra, the probability distributions of Doppler shifts at different velocities of scattering particles were represented as a linear combination.

However, the method based on calculation and subsequent processing of the perfusion rate within narrow Doppler broadening bands has been so far rather poorly covered in the literature [11]. Presentation of the measurement results in a time–frequency scale makes it possible to determine and visualize changes in blood perfusion rate and its redistribution caused by functional tests. The use of such a distribution provides an additional feature space for analyzing the received signal, which increases the diagnostic capabilities of LDF.

Validation of the Proposed Method

It is well known that the Doppler shift from moving red blood cells can be estimated from the photodiode photocurrent. The blood perfusion rate is an integral characteristic proportional to the number of red blood cells involved in the formation of the Doppler shift of the optical signal within a given diagnostic volume, as well as to the average velocity of movement of this ensemble. Thus, the results of LDF measurements are, in the first approximation, linear with respect to the velocity and number of moving red blood cells in the diagnostic volume. The perfusion rate in the frequency range of f_1 to f_2 is calculated using the following expression:

$$I_m = \frac{1}{i_{dc}} \int_{f_1}^{f_2} f \cdot S(f) df, \quad (1)$$

where I_m is the blood perfusion rate, f is the frequency of the Doppler broadening of laser radiation, $S(f)$ is the photocurrent power spectrum, and i_{dc} is the constant component of the photocurrent.

Currently available laser Doppler flowmeters use techniques for power spectrum processing within a wide range of power spectrum distribution over Doppler broadening frequencies (for example, 20-12000 Hz), which leads to the loss of potentially useful diagnostic information. This distribution carries important physiological information about local and systemic processes that affect microcirculation. In [12], the effect of local heating and pressure on the optical probe was investigated, and the Doppler broadening spectra were studied using skin probes at various stages of occlusive and respiratory tests. These studies demonstrated the effect of blood perfusion redistribution over the Doppler broadening frequencies during a forced inhalation–exhalation cycle.

LDF Device with Digital Signal Processing

A prototype of the LDF device was assembled (Fig. 1a). An LPS-785-FC laser diode with a wavelength of 785 nm was used as the radiation source. The signal was sampled using an NI USB 6211 data acquisition card with a sampling rate of 50 kHz per channel in differential recording mode. The duration of the recording and processing cycle was 0.05 s; it included 2500 measurements. A custom-made amplifier with stabilized supply voltage was used to amplify the signal before ADC processing by

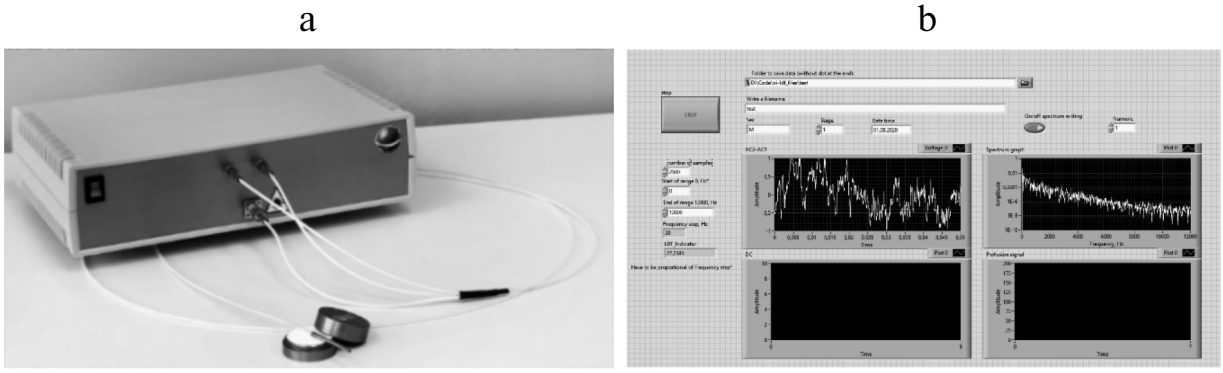

Fig. 1. Prototype device: a) external view; b) control interface.

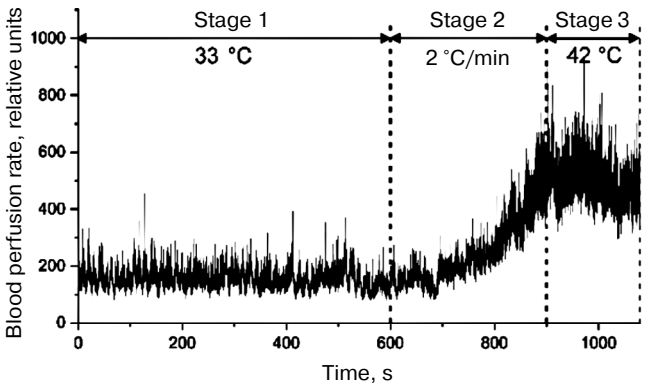

Fig. 2. Research protocol: an example of blood perfusion recording.

the data acquisition card. The device was controlled via a LabVIEW interface (Fig. 1b). The interface included the following windows: visualization of the calculated power spectrum, perfusion graph, oscillogram of the difference between signals from two channels, and address bar for saving data.

Patient and Volunteer Research Protocol

The developed protocol is based on a thermal test. During the thermal test, a strong vasodilator, nitric oxide, is released. The vasodilator systemically affects the microvascular bed. The vasodilator-induced changes in the perfusion rate and the phase and amplitude spectra are measured. Based on the measurement results, criteria for the diagnosis of microcirculation failure can be elaborated. The dorsal surface of the foot was chosen as the area of interest, because trophic ulcers and necrotic lesions in patients with type 2 diabetes mellitus most often occur on the feet and toes.

Before the measurements, a fiber guide was attached to the subject's foot. The guide bore a heat probe based on a Peltier element. At the first stage of the test, the blood perfusion rate was recorded at a temperature of 33 °C for 10 min, in order to equalize the temperature conditions in all subjects. At the second stage, the temperature was gradually increased to of 42 °C within 5 min, at a rate of 2 °C/min. At the third stage, the blood perfusion rate and the heat-induced effects on the capillary blood flow were recorded for 5 min (Fig. 2).

The measurements were performed using the prototype digital Doppler flowmeter and a LAKK-TEST device for local functional tests (NPP LAZMA, Moscow). The volunteers and patients were divided into three groups: group 1 – 7 volunteers aged (22 ± 0.5) years; group 2 – 6 volunteers aged (51 ± 6) years; group 3 – 10 patients aged (61 ± 7) years with more than 10-year history of type 2 diabetes mellitus. All patients gave their informed consent for the study.

Test Results

Before further processing, the amplitude values of the power spectra were summed over frequency bands with a step of 200 Hz. The range from 0 to 12800 Hz was selected for data processing. Thus, each measurement result was represented as an array of 64 perfusion records determined for the frequency sub-bands.

Cumulative sums of the spectra sequences averaged over a certain time period were used to assess the effects associated with the redistribution of perfusion over the frequency ranges caused by local heating. The cumulative sums were calculated as follows:

$$C_n = C_{n-1} + \frac{A_n}{\sum_m A_i}, \quad (2)$$

where n is the serial number of given frequency in the power spectrum, C_n is the cumulative sum of the sequence from 1 to n, A_n is the power spectrum amplitude at the nth frequency, and m is the maximum serial number (Fig. 3).

For further analysis of the data, the periods recorded at the first stage of the experiment and the manifestations of the axon reflex at the beginning of the third stage were

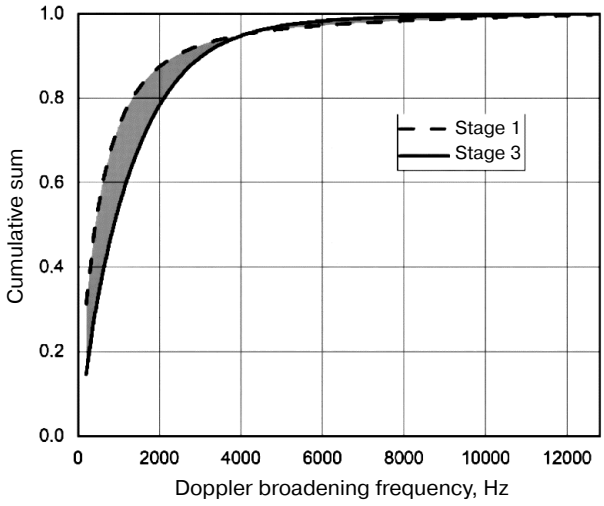

Fig. 3. An example of cumulative sum graphs for stages 1 and 3 and the area between them.

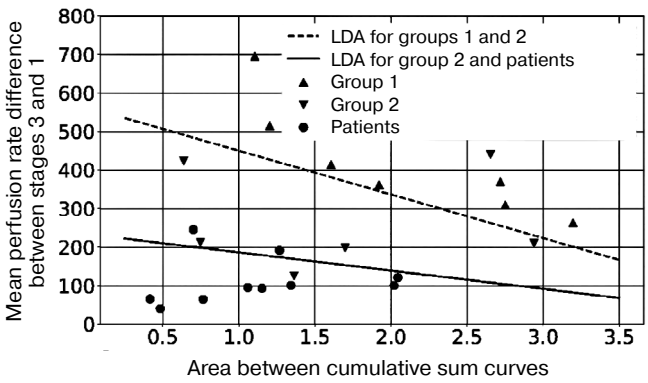

Fig. 4. LDA results for the groups of apparently healthy volunteers and patients.

identified. The area between the graphs of the cumulative sums calculated by the trapezoidal method is a quantitative characteristic of the signal amplitude redistribution over the frequencies for the averaged spectra recorded at the first stage and during the manifestation of the axon reflex.

Based on the area between the curves of cumulative sums and the mean perfusion for the selected period, binary classifiers were constructed by linear discriminant analysis (LDA) for group 2 (aged volunteers) and patients ($Y1$), and group 1 (young volunteers) and group 2 ($Y2$). The area under curve (AUC) was estimated (Fig. 4):

$$Y1 = -5.0622 + 0.84X1_{2p} + 0.0177X2_{2p}; \quad (3)$$

$$Y2 = -4.28022 + 0.86X1_{12} + 0.0076X2_{12}. \quad (4)$$

The AUC for the ROC curve was 0.86 and 0.9 for the binary classifiers $Y1$ and $Y2$, respectively.

Thus, the developed device, research protocols, and binary classifiers make it possible to classify the test participants according to the age-related changes in the microcirculation and the disorders associated with type 2 diabetes mellitus.

Conclusions

Digital LDF tests using the proposed sequence of photocurrent power spectra have shown that the developed research protocol holds much promise for the use in medical practice. The proposed approach to the LDF signal processing does not require additional measurement channels (temperature, fluorescence, diffuse reflectance spectroscopy, etc.) to be used. The test procedure is relatively simple. Its implementation for mass functional diagnostic testing does not require highly qualified personnel. The method is sufficiently accurate to provide correct classification of subjects into groups according to the state of microcirculation. Further development of the method will involve additional research into the diagnostic value of the power spectrum distribution over the Doppler broadening frequencies and, in particular, the substantiation of new diagnostic criteria based on the frequency distribution of perfusion oscillations.

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REFERENCES

1. Cummins, H. Z. and Swinney, H. L., III Light Beating Spectroscopy, Vol. 8, Elsevier (1970), pp. 133-200.
2. Forrester, A. T., "Photoelectric mixing as a spectroscopic tool," J. Opt. Soc. Am. OSA, **51**, No. 3, 253-259 (1961).
3. Leahy, M. J. and Nilsson, G. E., "Laser Doppler flowmetry for assessment of tissue microcirculation: 30 years to clinical acceptance," Proc. SPIE, **7563**, 75630E-75630E-5 (2010).
4. Kvandal, P., Landsverk, S. A., Bernjak, A., Stefanovska, A., Kvernmo, H. D., and Kirkebøen, K. A., "Low-frequency oscillations of the laser Doppler perfusion signal in human skin," Microvasc. Res., **72**, No. 3, 120 (2006).
5. Mizeva, I., Zharkikh, E., Dremin, V., Zherebtsov, E., Makovik, I., Potapova, E., and Dunaev, A., "Spectral analysis of the blood flow in the foot microvascular bed during thermal testing in patients with diabetes mellitus," Microvasc. Res., **120**, 13-20 (2018).
6. Stefanovska, A., Bracic, M., and Kvernmo, H. D., "Wavelet analysis of oscillations in the peripheral blood circulation measured by laser Doppler technique," IEEE Trans. Biomed. Eng., **46**, No. 10, 1230-1239 (1999).
7. Dremin, V., Zherebtsov, E., Makovik, I., Kozlov, I., Sidorov, V., Krupatkin, A., Dunaev, A., Rafailov, I., Litvinova, K., Sokolovski, S., and Rafailov, E., "Laser Doppler flowmetry in blood and lymph monitoring, technical aspects and analysis," Proc. SPIE, **10063**, 10063-03-10063-08 (2017).
8. Zherebtsov, E. A., Zharkikh, E. V., Kozlov, I. O., Loktionova, Y. I., Zherebtsova, A. I., Rafailov, I. E., Sokolovski, S. G., Sidorov, V. V., Dunaev, A. V., and Rafailov, E. U., "Wearable sensor system for multipoint measurements of blood perfusion: Pilot studies in patients with diabetes mellitus," in: Clinical and Preclinical Optical Diagnostics II. Proc. SPIE (Optical Society of America), Paper No. 11079_62 (2019).
9. Fredriksson, I., Larsson, M., and Strömberg, T., "Model-based quantitative laser Doppler flowmetry in skin," J. Biomed. Opt., **15**, No. 5, 57002-57012 (2010).

10. Wojtkiewicz, S., Liebert, A., Rix, H., Sawosz, P., and Maniewski, R., "Estimation of scattering phase function utilizing laser Doppler power density spectra," Phys. Med. Biol., **58**, No. 4, 937 (2013).
11. Sokolov, V. G., Korsi, L. V, and Egorov, S. Y., "Method of assessing blood oxygenation in microcirculation vessels based on Doppler approach," in: Priezzhev, A. V. and Cote, G. L (eds.) Optical Diagnostics and Sensing of Biological Fluids and Glucose and Cholesterol Monitoring, SPIE, **4263**, 98-105 (2001).
12. Dremin, V. V., Kozlov, I. O., Zherebtsov, E. A., Makovik, I. N., Dunaev, A. V., Sidorov, V. V., and Krupatkin, A. I., "Possibilities of laser Doppler flowmetry in assessing the state of microcirculation of blood and lymph," Region. Krovoobr. Mikrotsirk., **16**, No. 4, 42-49 (2017).
13. Kozlov, I. O., Zherebtsov, E. A., Zherebtsova, A. I., and Dunaev, A. V. "Analysis and decomposition of the laser Doppler spectrum for the assessment of microvascular complications in type 2 diabetes mellitus," in: Proc. XIVth Int. Sci. Conf. Physics and Radio Electronics in Medicine and Ecology (PhREME'2020), July 1-3, 2020, Vladimir–Suzdal, Vol. 1 [in Russian], pp. 51-55.