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Ratio of Perfusion in the Skin of the Index Finger and Big Toe in Patients with Type 2 Diabetes Mellitus

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Abstract—The aim of this study was to investigate the ratio of baseline perfusion levels in the skin of the palmar surfaces of the fingers and plantar surfaces of the big toe in healthy volunteers and patients with diabetes mellitus. Three study groups were included: healthy volunteers (group 1, $n = 29$), patients with type 2 diabetes mellitus (DM2) without diabetic foot syndrome (group 2, $n = 27$), and patients with diabetic foot syndrome (group 3, $n = 27$). All subjects were measured for the level of perfusion in the skin of the upper and lower extremities using the method of incoherent optical fluctuation flowmetry (IOFF). Perfusion was assessed in perfusion units (p.u.). The measurement was carried out sequentially, first on the left side of the body, then on the right. The baseline perfusion values from the index finger of the hand (BPh) and from the big toe of the foot (BPf) in perfusion units (p.u.) were assessed at rest. The BPh value in group 1 was 11.5 [5.4; 16.8] p.u.; in group 2, 17.4 [13.2; 24.8] p.u.; in group 3, 18.4 [13.2; 23.6] p.u. The BPh level was statistically significantly lower in group 1 than in groups 2 ($p_{1-2} < 0.001$) and 3 ($p_{1-3} < 0.001$). There was no statistically significant difference in finger perfusion between groups 2 and 3 ($p_{2-3} = 1$). The BPf values in groups 1, 2, and 3 were 4.4 [2.3; 8.8], 7.9 [5.4; 14.6], and 3.9 [1; 9.9] p.u., respectively. The BPf level in group 2 was higher than in group 1 ($p_{1-2} = 0.006$), but the parameter in group 3 was comparable to the values from group 1 ($p_{1-3} = 0.73$) and different from group 2 ($p_{2-3} < 0.001$). Thus, in group 3, there was a pseudonormalization of this index due to abnormally low BPf values in the extremities with hemodynamically significant stenoses. The baseline perfusion ratio (BPh/BPf) in groups 1, 2, and 3 was 2.11 [1.22; 3.03], 1.91 [1.18; 3.92], and 4.29 [1.8; 12.84], respectively. The BPh/BPf ratio in group 3 was significantly higher than in groups 1 ($p_{1-3} < 0.001$) and 2 ($p_{2-3} < 0.001$). The ability to detect the presence of hemodynamically significant lower limb arterial stenoses was analyzed by the BPf and BPh/BPf indices; the area under the ROC curve for BPf was 0.808 (0.729; 0.887); for BPh/BPf, 0.855 (0.782; 0.928). It was shown that an increase in the BPh/BPf ratio to exceed 3.7 with a sensitivity of 75.7% and a specificity of 81.4% indicates the presence of hemodynamically significant stenoses according to the ROC analysis. The presence of arterial blood flow abnormalities in the great arteries of the lower extremities leads to a significant reduction in BPf level. Calculation of the BPh/BPf ratio is more informative in identifying limbs with hemodynamically significant stenoses than the BPf level and can be used as a screening method for identifying patients with lower limb arterial disease.

Keywords: microcirculation, diabetes mellitus, diabetic foot, incoherent optical fluctuation flowmetry

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The blood microcirculation system embraces many functionally interconnected vessels and plays an important role in maintaining the homeostasis of all body systems, during many metabolic processes in tissues, including the processes of oxygen transport and consumption, both at the systemic and local levels [1].

Systemic microcirculatory disorders are a link in the pathogenesis of many diseases, such as diabetes mellitus (DM), arterial hypertension, etc. [2–4].

The study of microcirculation by most teams is carried out at the time of functional impacts, since the study of the average levels of basic perfusion is uninformative [5–7]. Thus, using the example of DM, some authors report a decrease in basal perfusion in patients with DM compared with the control group [8]; others do not find significant differences [9], and still others note a tendency for basic blood flow to increase in patients with DM [10]. Such heterogeneity of results may be related to the peculiarities of measurement localization, heterogeneity of cutaneous blood flow, different severity of the patient's condition, criteria for inclusion in the study, and many other factors [11]. This partly determines the low clinical relevance and applicability of modern methods of noninvasive diagnostics of the state of the microvasculature, for example, laser Doppler flowmetry (LDF). The possibility of an individual assessment of the state of microvasculature in a particular patient due to poor reproducibility and high variability is reduced [12].

During this study, on the way to finding approaches to creating a personalized diagnostic algorithm, the task was to assess the ratio of the level of baseline perfusion on the skin of the palmar and plantar surfaces of the fingers and toes of the upper and lower extremities in healthy volunteers and patients with DM2. Unexpectedly, the analysis of this ratio appeared to be more informative for the formation of an individual conclusion than the assessment of baseline perfusion parameters in the upper and lower extremities separately. This article is devoted to the description of this result.

MATERIALS AND METHODS

The study included three groups of subjects. The inclusion criteria for group 1 (healthy volunteers) were as follows: age from 18 to 44 years, absence of carbohydrate metabolism disorders, absence of chronic cardiovascular and pulmonary diseases, absence of kidney damage, normal body mass index (body mass index less than 25 kg/m^2), and normocholesterolemia (low-density lipoproteins within the reference values).

Group 2 (DM2 patients without diabetic foot syndrome) included patients who met the following criteria: age from 45 to 74 years, a verified diagnosis of DM2, the presence of peripheral neuropathy (autonomic neuropathy is an exclusion criterion), the absence of a history of cardiovascular events (heart attack, stroke, coronary/carotid revascularization), and absence of diabetic foot syndrome.

Group 3 (patients with diabetic foot syndrome) included patients aged 45 to 74 with diabetic foot syndrome and diagnosed neuropathy.

The exclusion criteria were common for all groups of patients: diagnosed malignant neoplasms in the last 5 years; diagnosed systemic autoimmune diseases; severe heart rhythm disturbances (atrial fibrillation, frequent extra beats); acute viral infections, such as acute respiratory viral infection, influenza, etc.; fever of any origin; exacerbation of concomitant chronic diseases; blood diseases, such as thrombocytopenia and anemia (hemoglobin less than 90 g/L); skin diseases that prevent the study from being conducted; current/a history of vascular thrombosis or a high risk of thrombosis (except for group 3 patients); pregnancy; chronic stage 5 kidney disease (GFR <15 mL/min/1.73 m^2 according to MDRD and CKD-EPI); and regular intake of steroid, nonsteroidal anti-inflammatory drugs (with the exception of acetylsalicylic acid administered as an antiplatelet agent), hormone replacement therapy, and contraceptives.

A total of 83 subjects were enrolled in the study. Group 1 included 29 apparently healthy volunteers (10 men, 19 women). Median age in group 1 was 24 [23; 30] years. Median level of glycated hemoglobin (HbA1c) was 5.25 [5.1; 5.5%]. Group 2 included 27 patients (5 men, 22 women). Median age was 59 [56; 64] years; HbA1c, 8.7 [7.7; 9.96%]. Group 3 included 27 patients (19 men, 8 women). Median age was 64 [56; 68] years; HbA1c, 8 [7; 9.5%].

The study was carried out in parallel in two centers: Moscow Regional Research and Clinical Institute (MONIKI) (Moscow) and Almazov National Medical Research Center, Ministry of Health of the Russian Federation (Moscow).

The study of peripheral hemodynamics parameters. The study of perfusion was carried out using the method of incoherent optical fluctuation flowmetry (IOFF) implemented by a prototype device (AO Elatomskii Instrument Plant, Russia) [13, 14]. The design of the sensors of the device used in this study is shown in Fig. 1.

The IOFF method is based on the analysis of low-frequency fluctuations (0–10 Hz) of an optical signal backscattered from the tissue, emitted by an incoherent source, a light-emitting diode (LED). To implement the IOFF method in the device prototype, three LED radiation sources operating in the 560–580-nm wavelength range and one silicon photodiode were used in the optical sensor. The perfusion index calculated during signal processing is proportional to fluctuations of blood filling in the probed tissue volume per unit time and corresponds to the microcirculation index calculated by the LDF method. The tissue probing depth in this case is 2–3 mm, which is slightly greater than in LDF. Due to this, the signal backscattered from the tissue is recorded from a larger tissue volume than in LDF, into which, among other things, the deeper vascular plexuses of the dermis fall. A detailed description of the method can be found in [14].

Patients were asked to refrain from smoking at least 3 h before the study. The study was carried out in an air-conditioned room at an air temperature of 23–25°C after a 15-min adaptation of the subject to the temperature conditions of the room. At the time of measurement, the subject was in the supine position. A complete protocol for assessing hemodynamic parameters using a device prototype includes registration of baseline perfusion, blood pressure measurement, a 3-min pause, and functional tests (thermal and occlusive). The duration of the complete measurement cycle is 10 min. First, the measurement was carried out on the left side of the body, then on the right. In this publication, only the results of the assess-

(a) (b)

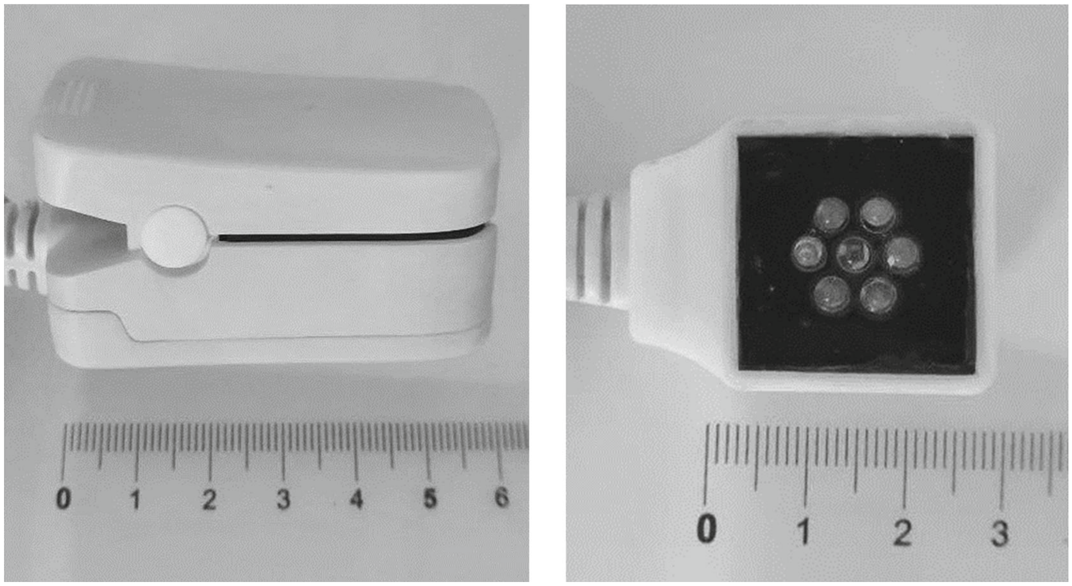

Fig. 1. Sensors of the device for recording perfusion parameters on the index finger (a) and the big toe (b).

ment of baseline perfusion parameters (baseline perfusion level—BP) are considered. Perfusion parameters were simultaneously recorded for 40 s on the index finger (BPh) and the big toe (BPf). The placement scheme of the device sensors on the pad of the index finger and the pad of the big toe is shown in Fig. 2. Since each subject was measured on both the left and right side of the body, the results will present an analysis of 58, 54, and 54 measurements in groups 1, 2, and 3, respectively.

Ultrasound duplex scanning of the lower limb vessels. All subjects underwent ultrasound duplex scanning (USDS) of the arteries of the lower extremities for the presence of hemodynamically significant stenoses. The type of blood flow (magistral, magistral altered, collateral) was analyzed in six arteries: common femoral artery, deep femoral artery, superficial femoral artery, popliteal artery, anterior tibial artery, and posterior tibial artery. When stenoses leading to impaired blood flow were detected according to the results of USDS (magistral altered or collateral type) in one or several vessels, a conclusion was made about the presence of hemodynamically significant stenoses of the lower limb arteries/artery.

Statistical data processing. Statistical data processing was performed using R Studio 1.4.1106 software (RStudio PBC, United States) using the R 4.1.0 programming language (R Foundation for Statistical Computing, Austria). During the analysis of quantitative variables, medians and quartiles (*Me* [*LQ*; *UQ*]) were calculated. To compare quantitative variables in the three groups, the Kruskal–Wallis test with a posteriori pairwise comparisons using the Dunn test with Bonferroni correction for multiple comparisons was used. Quantitative variables in two paired samples were compared using the Wilcoxon matched pairs test. Sensitivity and specificity analysis of quantitative signs in the detection of limbs with hemodynamically significant arterial lesions was performed using ROC analysis (*p*ROC package v. 1.18.0). Difference between groups was considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The results of perfusion measurements in three groups of subjects are presented in Table 1 and in Fig. 3.

In all three groups, the level of perfusion in the upper limb was significantly higher ($p < 0.001$, Wilcoxon test) than in the lower limb. There are examples of similar results in the literature [15, 16]. We can suggest the following series of physiological causes of this effect. Firstly, it is known that the density of the superficial and deep vascular plexuses on the skin of the palmar surface of the hand is higher than on the plantar surface of the foot by 70 and 20% for the superficial and deep plexuses, respectively [17]. Secondly, the thickness of the stratum corneum on the plantar surface of the lower extremities is twice as high as on the palmar surface of the upper extremities, which leads to the fact that a smaller volume of vascularized tissue falls into the probing area on the lower extremity due to the greater thickness of the stratum corneum [18].

The baseline perfusion level in the skin of the index finger was significantly lower in group 1 than in groups 2 ($p_{1-2} < 0.001$) and 3 ($p_{1-3} < 0.001$). No statistically significant differences were found between

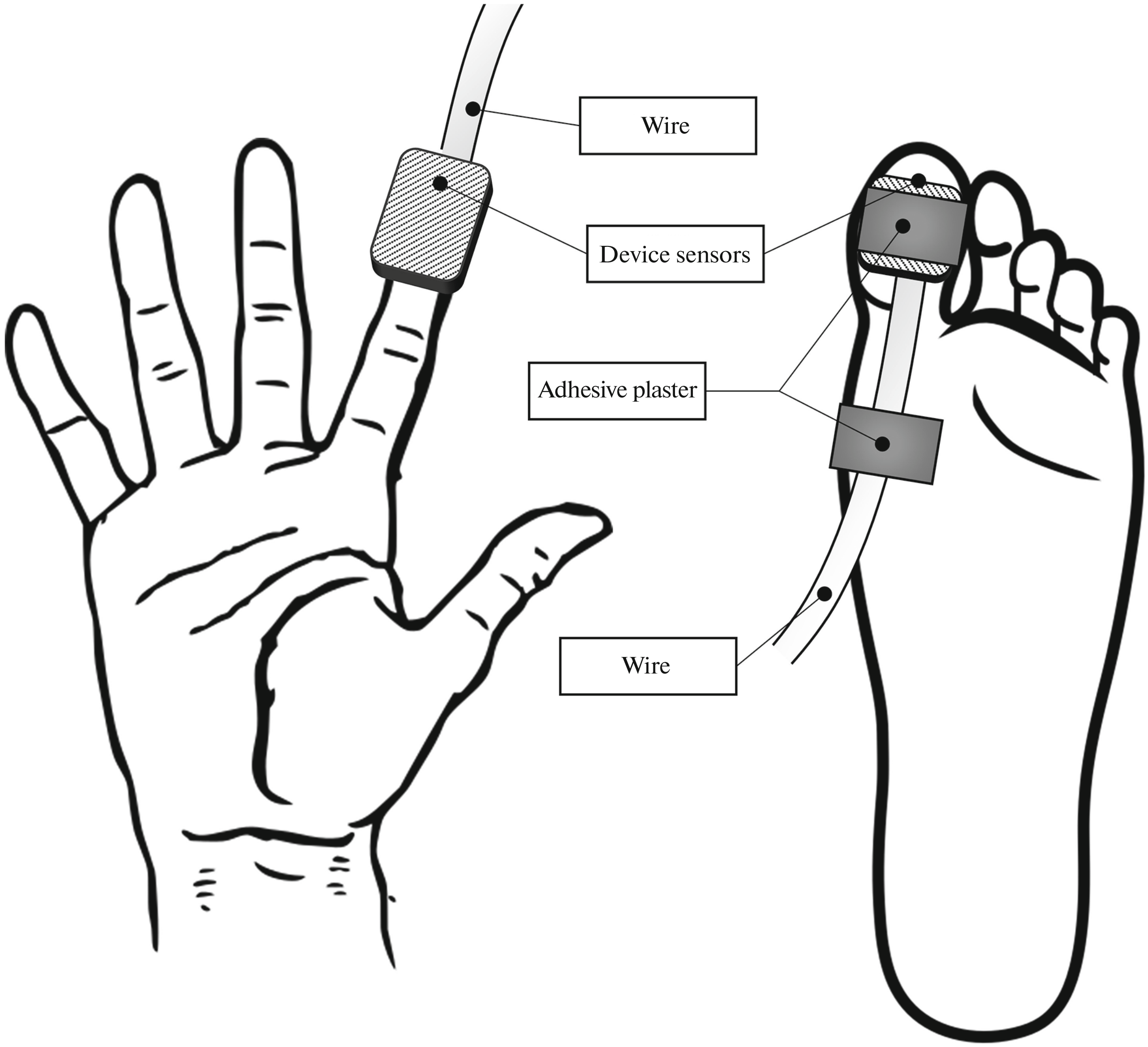

Fig. 2. Scheme of placement of the device sensors.

groups 2 and 3 ($p_{2-3} = 1$). Thus, a significantly higher level of perfusion was recorded in the palmar surface of the index finger in patients with DM than in healthy volunteers.

At the same time, a different picture was observed on the big toe. In group 2, the perfusion level was also significantly higher than in group 1 ($p_{1-2} = 0.006$); however, the perfusion level in group 3 was comparable to the values from group 1 ($p_{1-3} = 0.730$). In other words, in patients with "moderately severe" DM (group 2), there was a significant increase in the level of baseline perfusion both in the hands and feet compared with healthy volunteers, and in the group of patients with severe DM-associated lower limb damage (group 3), "pseudonormalization" of baseline perfusion on the toe was noted, the values were comparable to those in healthy volunteers.

The BPh/BPf ratio was analyzed (Table 1, Fig. 4). The parameter is calculated as the ratio of perfusion in the skin of the index finger to the perfusion in the skin of the big toe; the perfusion ratio is a dimensionless quantity. In the group of healthy volunteers, this parameter was 2.11 [1.22; 3.03]. In several patients with DM, abnormally high values of this parameter were detected, which were not found in healthy volunteers (group 1). This was associated with very low BPf values against the background of increased BPh values. Note that the BPh/BPf ratio in patients with diabetic foot syndrome (group 3) was significantly higher than in groups 1 ($p_{1-3} < 0.001$) and 2 ($p_{2-3} < 0.001$).

Thus, when these three parameter values were analyzed, the following effect was found: the BPh parameter significantly differed in group 1 from groups 2 and 3; the BPf value significantly differed in group 2 from

Table 1. Baseline perfusion results

Parameter	Group 1, ($n = 58$), *Me* [*LQ*; *UQ*]	Group 2, ($n = 54$), *Me* [*LQ*; *UQ*]	Group 3, ($n = 54$), *Me* [*LQ*; *UQ*]	*p* value (Kruskal–Wallis test)	*p* value (Dunn's test with Bonferroni correction)
Baseline perfusion on the index finger (BPh), p.u.	11.5 [5.4; 16.8]	17.4 [13.2; 24.8]	18.4 [13.2; 23.6]	$\mathbf{p < 0.001}$	$\mathbf{p_{1-2} < 0.001}$ $\mathbf{p_{1-3} < 0.001}$ $p_{2-3} = 1$
Baseline perfusion on the big toe (BPf), p.u.	4.4 [2.3; 8.8]*	7.9 [5.4; 14.6]*	3.9 [1; 9.9]*	$\mathbf{p < 0.001}$	$\mathbf{p_{1-2} = 0.006}$ $p_{1-3} = 0.73$ $\mathbf{p_{2-3} < 0.001}$
BPh/BPf ratio	2.11 [1.22; 3.03]	1.91 [1.18; 3.92]	4.29 [1.8; 12.84]	$\mathbf{p < 0.001}$	$p_{1-2} = 1$ $\mathbf{p_{1-3} < 0.001}$ $\mathbf{p_{2-3} < 0.001}$

* Comparison with BPh; $p < 0.001$ (Wilcoxon test), $p < 0.05$ values are in bold.

groups 1 and 3, and the BPh/BPf ratio significantly differed in group 3 from groups 1 and 2.

A significantly higher level of perfusion on the skin of the index finger was noted in patients with DM (groups 2 and 3) than in healthy volunteers. Higher perfusion values were also recorded on the skin of the big toe in group 2 than in the group of healthy volunteers. Higher perfusion values in the skin in patients from groups 2 and 3 may be due to both the influence of the underlying disease and age-related changes. Healthy volunteers from group 1 were significantly younger than patients from groups 2 and 3. It is known that the level of baseline perfusion may increase with age [19]. However, in patients with diabetic foot syndrome (group 3), the level of baseline perfusion in the feet was significantly lower than in sex- and age-matched patients with diabetes mellitus (group 2) and was comparable to that in healthy young volunteers. Such a phenomenon of pseudonormalization of foot perfusion in group 3 may be due to damage to the lower extremity main arteries.

To test this measurement hypothesis, group 3 was divided into two subgroups, 3a and 3b. Subgroup 3a ($n = 18$) included measurements made on the limbs without hemodynamically significant blood flow disorders; subgroup 3b ($n = 36$) included measurements made on the legs with hemodynamically significant stenosis as shown by the results of USDS. In this analysis, one measurement was excluded from group 2,

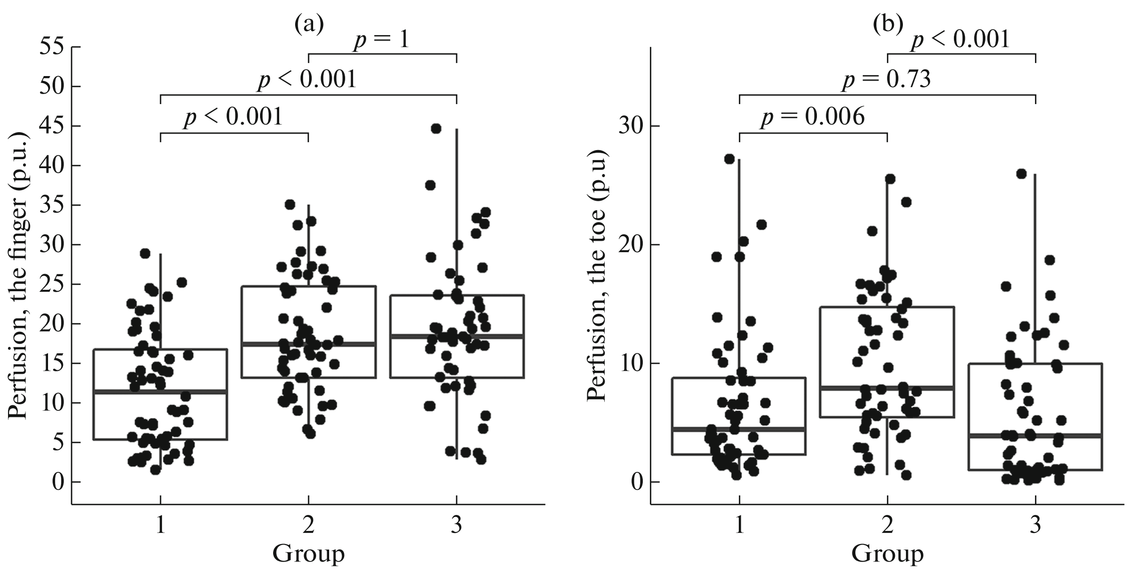

Fig. 3. Comparison of baseline perfusion recorded on the finger (a) and on the toe (b) in three groups.

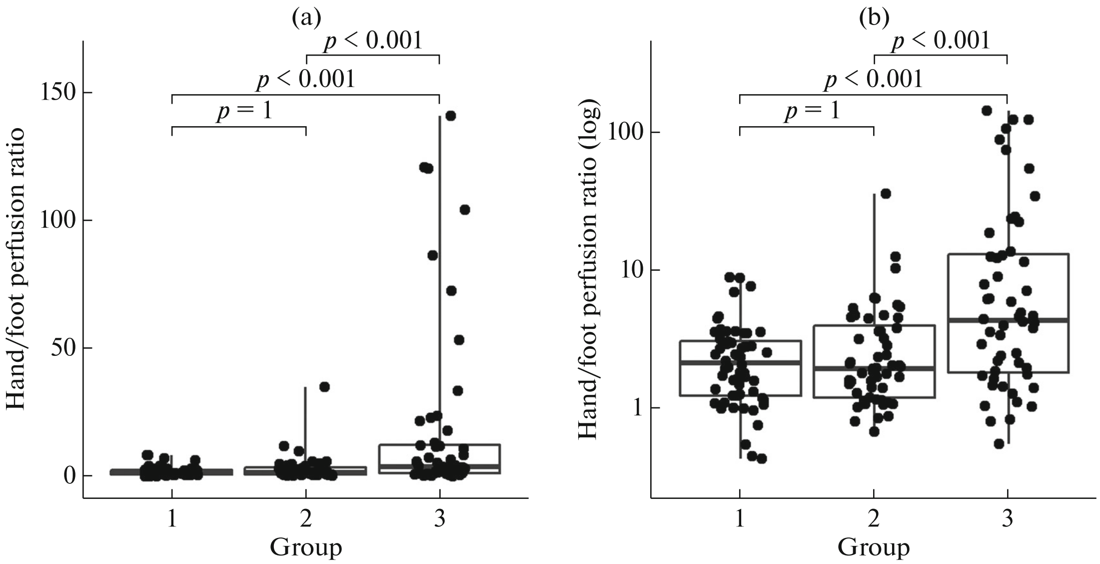

Fig. 4. Comparison in three groups of the ratio of the level of perfusion recorded on the finger to the level of perfusion recorded on the toe. (a) Graph in standard coordinates; (b) graph in logarithmic coordinates.

because the patient had hemodynamically significant blood flow disorders in this limb.

Comparison of the parameter values of baseline perfusion with regard for the above-described division of patients is given in Table 2. The presence of hemodynamically significant stenoses in patients with diabetic foot (subgroup 3b) leads to the fact that BPf is significantly decreased. That is the reason why BPf in group 3 "mimicked" normal values and did not differ from BPf in group 1. The decrease in foot perfusion in the lower extremity artery disease is pathophysiologically justified and, according to the literature, can be detected using various instrumental methods [12, 20–22]. It is seen from Table 2 that in subgroup 3b, the BPh/BPf ratio assumed anomalously high values compared to the measurements in other groups.

In order to assess whether the calculation of the BPh/BPf ratio provides additional information compared to BPf assessment, ROC analysis was carried out for all 166 measurements (Fig. 5). The purpose of the analysis was to assess the diagnostic potential of the BPf parameter and the BPh/BPf ratio in identifying limbs with hemodynamically significant stenoses.

Based on the results of the ROC analysis, it was shown that the calculation of the BPh/BPf ratio allows us to expand the possibility of detecting hemodynamically significant stenoses compared to the analysis of the BPf parameter. The area under the ROC curve for BPf was 0.808 (0.729; 0.887); for the BPh/BPf ratio,

Table 2. The results of the assessment of the baseline level of perfusion, depending on the presence of hemodynamic disorders according to the results of ultrasound duplex scanning (USDS)

Parameter	Group 2 (n = 53), *Me* [*LQ*; *UQ*]	Subgroup 3a (n = 18), *Me* [*LQ*; *UQ*]	Subgroup 3b (n = 18), *Me* [*LQ*; *UQ*]	p value (Kruskal-Wallis test)	p value (Dunn's test with Bonferroni correction)
Baseline perfusion on the index finger (BPh), p.u.	17.4 [13.2; 25]	18.2 [11.2; 26.6]	18.4 [14.9; 23.1]	0.842	–
Baseline perfusion on the big toe (BPf), p.u.	8 [5.6; 14.8]*	10.9 [7; 14.2]*	1.7 [0.8; 4]*	**<0.001**	$p_{2-3a} = 1$ $\mathbf{p_{2-3b} < 0.001}$ $\mathbf{p_{3a-3b} < 0.001}$
BPh/BPf ratio	1.9 [1.17; 3.67]	1.65 [1.07; 3.97]	6.57 [3.57; 23.86]	**<0.001**	$p_{2-3a} = 1$ $\mathbf{p_{2-3b} < 0.001}$ $\mathbf{p_{3a-3b} < 0.001}$

See Table 1 for designations.

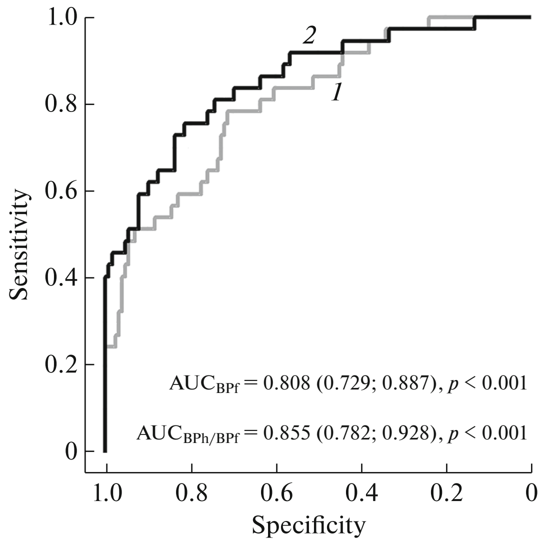

Fig. 5. The results of ROC analysis to detect damage to the lower extremity arteries using the BPf (*1*) and BPh/BPf parameters (*2*). BP is the baseline perfusion level (of the hand (BPh) and foot (BPf)).

this parameter increased to 0.855 (0.782; 0.928). Thus, the BPh/BPf ratio has a higher diagnostic potential in detecting limbs with hemodynamically significant stenoses than BPf. This is due to the fact that the frequency of false-positive detection of extremities with hemodynamically significant stenoses decreases among those examined from the first group. In healthy individuals, the so-called "spastic" type of microcirculation is not infrequently found, which is characterized by a systemic increase in vascular tone at rest (vasospasm) and, as a result, a decrease in perfusion both in the upper and lower extremities. Therefore, healthy subjects with a "spastic" type of microcirculation according to the results of the assessment of solely BPf can be falsely classified as individuals with hemodynamically significant stenoses. However, the BPh/BPf ratio in such subjects does not assume pathological values, since both the BPf and BPh parameters decrease in systemic vasospasm, which allows one to classify the subjects correctly.

ROC analysis showed that an increase in the BPh/BPf ratio to more than 3.7 with a sensitivity of 75.7% and a specificity of 81.4% can detect limbs with hemodynamically significant stenoses. At the same time, abnormally high BPh/BPf ratio values (more than 12.5) were found exclusively in the limbs with impaired arterial blood flow, the specificity of detecting hemodynamically significant stenoses in these cases was 100%. Thus, the assessment of the BPh/BPf ratio may be promising as a simple screening method for detecting hemodynamically significant stenoses; this approach is more revealing than the assessment of BPf.

CONCLUSIONS

It has been shown that in healthy volunteers and in patients with DM without hemodynamically significant stenoses of the lower extremity arteries, the level of baseline perfusion on the finger is higher than on the toe (palmar and plantar surfaces, respectively). An increase in the baseline perfusion level was observed against the background of diabetes mellitus, compared with the control group.

The presence of arterial blood flow disorders in the great vessels of the lower extremities causes a significant decrease in the level of toe perfusion.

Low baseline perfusion values on the toe may indicate the presence of hemodynamically significant stenoses of the lower extremity arteries. The calculation of the finger to toe perfusion ratio increases the informativeness of identifying patients with hemodynamically significant stenoses, since it improves the accuracy of diagnosis due to the correct classification of healthy individuals with low baseline perfusion both on the hand and on the foot ("spastic" type of blood flow).

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COMPLIANCE WITH ETHCAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the biomedical ethics principles formulated in the 1964 Helsinki Declaration and its later amendments and approved by the Independent Ethics Committee (IEC) of the Moscow Regional Research and Clinical Institute (MONIKI) (Moscow) (protocol no. 13 of November 7, 2019) and the Ethics Committee of the Almazov National Medical Research Center, Ministry of Health of the Russian Federation (Moscow) (extract no. 27112019, meeting no. 11–19 of November 11, 2019).

Conflict of interest. JSC "Elatma Instrument-Making Enterprise" sponsored the examination of patients and healthy volunteers and also provided a prototype of the device for scientific research. The company did not take part in data processing, description of the results, and was not involved in any of the stages of writing the text of this article. The authors declare that they have no conflict of interest.

Informed consent. Each study participant provided a voluntary written informed consent signed by him after explaining to him the potential risks and benefits, as well as the nature of the upcoming study.

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